

Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing

Andrea L. Gold,¹ Margaret A. Sheridan,² Matthew Peverill,³ Daniel S. Busso,⁴ Hilary K. Lambert,³ Sonia Alves,⁴ Daniel S. Pine,¹ and Katie A. McLaughlin³

¹National Institutes of Health, Bethesda, MD; ²The University of North Carolina at Chapel Hill, Chapel Hill, NC; ³University of Washington, Seattle, WA; ⁴Harvard Graduate School of Education, Cambridge, MA, USA

Background: Alterations in gray matter development represent a potential pathway through which childhood abuse is associated with psychopathology. Several prior studies find reduced volume and thickness of prefrontal (PFC) and temporal cortex regions in abused compared with nonabused adolescents, although most prior research is based on adults and volume-based measures. This study tests the hypothesis that child abuse, independent of parental education, predicts reduced cortical thickness in prefrontal and temporal cortices as well as reduced gray matter volume (GMV) in subcortical regions during adolescence. **Methods:** Structural MRI scans were obtained from 21 adolescents exposed to physical and/or sexual abuse and 37 nonabused adolescents (ages 13–20). Abuse was operationalized using dichotomous and continuous measures. We examined associations between abuse and brain structure in several a priori-defined regions, controlling for parental education, age, sex, race, and total brain volume for subcortical GMV. Significance was evaluated at $p < .05$ with a false discovery rate correction. **Results:** Child abuse exposure and severity were associated with reduced thickness in ventromedial prefrontal cortex (PFC), right lateral orbitofrontal cortex, right inferior frontal gyrus, bilateral parahippocampal gyrus (PHG), left temporal pole, and bilateral inferior, right middle, and right superior temporal gyri. Neither abuse measure predicted cortical surface area or subcortical GMV. Bilateral PHG thickness was inversely related to externalizing symptoms. **Conclusions:** Child abuse, an experience characterized by a high degree of threat, is associated with reduced cortical thickness in ventromedial and ventrolateral PFC and medial and lateral temporal cortex in adolescence. Reduced PHG thickness may be a mediator linking abuse with externalizing psychopathology, although prospective research is needed to evaluate this possibility. **Keywords:** Abuse; childhood adversity; ventromedial prefrontal cortex; temporal cortex; cortical thickness.

Introduction

Child abuse is associated with elevated risk for a wide range of internalizing and externalizing psychopathology in children and adolescents (McLaughlin et al., 2012). Alterations in gray matter (GM) development represent a potential pathway through which childhood abuse is associated with psychopathology. However, few studies examine whether maltreatment-related differences in brain structure are associated with psychopathology. Thus, additional work comparing brain structure in adolescents with high and low levels of abuse may inform neurodevelopmental models connecting childhood maltreatment to psychopathology.

Existing research reports associations of child maltreatment with prefrontal and temporal cortex structure, although inconsistencies exist, as summarized in Table S1. Notably, a recent meta-analysis based largely on adult participants linked maltreatment to reduced GM volume in ventral expanses of the prefrontal cortex (PFC) and superior temporal gyrus (STG), extending to the amygdala, insula, parahippocampal gyrus (PHG), and middle temporal gyrus (MTG) (Lim, Radua, & Rubia, 2014). Some additional studies implicate hippocampal

perturbations (Edmiston et al., 2011; Hanson et al., 2015; Morey, Haswell, Hooper, & De Bellis, 2016), whereas other studies do not (De Brito et al., 2013; Hanson et al., 2010; Kelly et al., 2015; Whittle et al., 2013). In general, the most consistent findings arise in ventromedial PFC (vmPFC), dorsolateral PFC, and lateral temporal cortex (De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010; Kelly et al., 2013, 2015, 2016).

Most of these studies assess cortical volume, a composite of thickness, surface area, and folding. As such, structural findings could reflect any combination of perturbed thickness, surface area, or gyrification (Mechelli, Price, Friston, & Ashburner, 2005). Cortical thickness and surface area reflect distinct factors, show unique developmental trajectories, and relate to distinct features of brain structure (Raznahan et al., 2011; Wierenga, Langen, Oranje, & Durston, 2014). Studies considering cortical thickness, surface area, and volume may be more sensitive to individual differences than studies considering only volume (Hutton, Draganski, Ashburner, & Weiskopf, 2009; Wallace et al., 2015). Cortical thickness and surface area are associated with child/adolescent mental disorders, including anxiety, depression, conduct disorder, and attention-deficit/hyperactivity disorder (ADHD) (Ducharme et al., 2014; Fairchild et al., 2015;

Conflict of interest statement: No conflicts declared.

Foland-Ross et al., 2015; McLaughlin, Sheridan, Winter, et al., 2014). Thus, studies of cortical thickness and surface area in youth exposed to abuse may help elucidate associations of childhood abuse with psychopathology.

Additional issues in prior research on child maltreatment and neural structure include inadequate controls for confounding variables, age of assessment of neural structure, and sample composition. First, deprivation related to low socioeconomic status (SES), which is associated with both maltreatment and brain structure, has rarely been controlled for in studies of maltreatment. SES is associated with cortical structure, but the specific pattern appears to differ from experiences involving a high degree of threat, such as abuse. Lower SES is associated with global surface area reductions throughout prefrontal, parietal, temporal, and occipital cortices (Noble et al., 2015), and reduced volume in association cortex that interacts with age, particularly in the PFC (Noble, Houston, Kan, & Sowell, 2012). In contrast, abuse is associated with more focal differences in the prefrontal and temporal cortices (Table S1). Second, most existing studies are based on adults who retrospectively report on maltreatment exposure when they were children (Lim et al., 2014; Teicher, Anderson, & Polcari, 2012). Given substantial age-related variation in neural structure and challenges disentangling early and later experiences in studies of adults, understanding the association of maltreatment with neural development requires assessment of neural structure in children and adolescents with maltreatment histories. The marked increase in both internalizing and externalizing psychopathologies in adolescence (Costello, Copeland, & Angold, 2011) further emphasizes the need for pediatric studies of brain morphometry in abused and nonabused youth. Finally, of the handful of morphometry studies focused on youth, many are community samples that were not recruited on the basis of maltreatment exposure (Edmiston et al., 2011; Whittle et al., 2013), resulting in a restricted range of maltreatment severity.

To our knowledge, only two research groups have examined cortical thickness in adolescents exposed to maltreatment (Kelly et al., 2013; Whittle et al., 2013), and in one of these studies, adolescents were not recruited based on maltreatment exposure and had low levels of maltreatment (Whittle et al., 2013). One research group (Kelly et al., 2013, 2016) reported on overlapping samples in two studies comparing maltreated and nonmaltreated adolescents, who did not differ on SES. They observed differences in vmPFC/OFC thickness, but not surface area or gyrification. Whittle et al. (2013) statistically controlled for SES in a community sample with relatively low maltreatment exposure, but did not find maltreatment-related vmPFC/OFC differences. Given scant research on neural structure with

children and adolescents exposed to maltreatment, there is a critical need for replication across independent research groups and samples that both use cortical thickness measures and control for other adverse environmental factors, such as low SES.

Independent lines of maltreatment and psychopathology research on neural structure implicate medial and lateral temporal and prefrontal cortices (Lim et al., 2014; Noordermeer, Luman, & Oosterlaan, 2016; Shang et al., 2014; Woon & Hedges, 2008) generating interest in the inter-relationships among the three variables. Although few studies directly test whether brain structure mediates the effects of maltreatment on psychopathology, there are some initial positive findings for both internalizing and externalizing disorders in volume-based studies. For example, hippocampal and PFC volume reductions have been linked to risk for later internalizing psychopathology following childhood maltreatment (Gorka, Hanson, Radtke, & Hariri, 2014; Rao et al., 2010). Maltreatment-related GMV reductions in the hippocampus, parahippocampus, and fusiform gyrus predicted severity of substance use relapse in a recent study (Van Dam, Rando, Potenza, Tuit, & Sinha, 2014). In the current cross-sectional study, we examined whether brain regions showing maltreatment-related differences also relate to psychopathology in adolescence.

This study compared cortical thickness, surface area, and subcortical GM volume (GMV) in adolescents with and without physical and/or sexual abuse, while controlling for SES. We hypothesized that abuse would be associated with reduced cortical thickness in lateral and medial PFC and temporal cortex. We also tested associations with GMV in subcortical regions involved in emotional processing, and predicted reduced volume of the amygdala, but not hippocampus, given recent meta-analytic findings (Lim et al., 2014). Finally, for regions showing significant associations with abuse, we tested the secondary hypotheses that symptoms of internalizing and externalizing psychopathology would be related to cortical thickness and surface area.

Methods

Participants

Participants included 58 adolescents aged 13–20 years (mean = 16.97 years, $SD = 1.45$ years; 60.3% female) who underwent MRI scanning at the Harvard Center for Brain Science. Participants were recruited from the community as part of a larger study ($N = 168$) of child maltreatment and emotional reactivity to stress (McLaughlin, Alves, & Sheridan, 2014; McLaughlin, Sheridan, Alves, & Mendes, 2014). A subsample of the adolescents reported on here were followed longitudinally in an effort to predict future psychopathology using neural structure; those prospective, longitudinal data, and mediation analyses are reported on elsewhere (Busso et al., in revision). The abused group comprised 21 adolescents with exposure to physical and/or sexual abuse, and the nonabused group included 37 adolescents with no abuse

exposure. For both groups, exclusion criteria included MRI contraindications, current substance dependence, current use of psychiatric medications (except stimulants discontinued 24 hr prior to scanning), pervasive developmental disorder, and presence of active safety concerns. All female participants were postmenarchal. Groups did not differ in age, sex, IQ, or parental education, but abused participants were more likely to be nonwhite. Table 1 reports sample characteristics.

The Institutional Review Board at Harvard University and Boston Children's Hospital approved all study procedures. After receiving complete description of the study, parents provided informed consent and adolescents provided assent.

Child abuse

Child abuse was assessed in two ways: a dichotomous measure of abuse exposure and a continuous measure of abuse severity. Both abuse measures were tested in all a priori-defined regions described below. Abuse was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997) and the Childhood Experiences of Care & Abuse interview (Bifulco, Brown, Lillie, & Jarvis, 1997). The CTQ is a self-report measure that assesses the frequency of childhood physical, sexual, and emotional abuse. The CECA is an interview-based measure, which assesses physical and sexual abuse, along with multiple aspects of caregiving experiences. Participants were classified as abused if they endorsed physical or sexual abuse during the CECA interview or had a score exceeding a validated threshold on the CTQ physical or sexual abuse subscales (Walker et al., 1999). The inclusion criteria for the abused group requiring exposure to physical and/or sexual abuse was based on the DSM-5 definition of trauma exposure, an experience involving threats

to one's physical integrity or the physical integrity of others or sexual violation (American Psychiatric Association, 2013).

Abuse severity was calculated as the sum of the CTQ physical and sexual abuse subscale items. As expected, higher abuse severity (CTQ score) was observed in abused versus nonabused adolescents ($\beta = .74$, $p < .001$), which remained significant after controlling for parental education, race, age, and sex ($\beta = .75$, $p < .001$). Primary analyses tested associations between neural structure and abuse severity across the full sample, as done in prior studies (Edmiston et al., 2011; Teicher et al., 2012; Whittle et al., 2013). Continuous associations within the abused group only ($N = 21$) restrict the range of the severity scale by examining only the most severe cases and ignoring cases at the low end of the scale and have limited statistical power, but are reported for thoroughness.

Covariates

We examined associations of child abuse exposure and severity with brain structure while adjusting for race, age, sex, and parental education, given that these factors have been associated with neural structure. See Table 1 for details.

Psychopathology

Lifetime and past-year psychiatric disorders were assessed via the Diagnostic Interview Schedule for Children Version IV (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC-IV measured symptoms of internalizing (separation anxiety disorder, social phobia, specific phobia, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, and major depression) and externalizing disorders (conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity

Table 1 Sample characteristics by abuse exposure

Characteristic	Abused ($N = 21$) Mean \pm SD	Nonabused ($N = 37$) Mean \pm SD	t	p
Age (years)	16.73 \pm 1.52	17.11 \pm 1.42	-0.95	.35
IQ (WASI total score)	100.33 \pm 15.81	101.06 \pm 15.13	-0.17	.87
Abuse severity	34.05 \pm 10.46	17.03 \pm 2.33	7.35	<.001
Internalizing symptoms ^a	26.71 \pm 13.07	15.27 \pm 8.81	3.98	<.001
Externalizing symptoms ^a	19.67 \pm 9.70	9.76 \pm 7.12	4.46	<.001
CTQ abuse subscale scores				
Physical abuse	10.57 \pm 4.65	5.24 \pm .72	5.21	<.001
Sexual abuse	10.33 \pm 6.18	5.08 \pm 0.49	3.89	<.001
	n (%)	n (%)	χ^2	p
Female	13 (61.90%)	22 (59.46%)	0.03	.86
Parental education ^b				
High school or less	4 (19.05%)	5 (13.51%)	3.79	.29
Some college	7 (33.33%)	7 (18.92%)		
College degree	4 (19.05%)	16 (43.24%)		
Graduate school	6 (28.57%)	9 (24.32%)		
Race/ethnicity ^c				
White	2 (9.52%)	14 (37.84%)	12.97	.01
Black	8 (38.10%)	9 (24.32%)		
Latino	5 (23.81%)	7 (18.92%)		
Asian/Pacific islander	0 (0%)	5 (13.51%)		
Other/biracial	6 (28.57%)	2 (5.41%)		

^aInternalizing and externalizing symptoms assessed with the Diagnostic Interview Schedule for Children Version IV (DISC-IV).

^bFor use as a covariate, parental education was dichotomized as 'less than college degree' (11 abused, 12 nonabused) versus 'college degree or higher education' (10 abused, 25 nonabused), and did not differ based on maltreatment exposure ($\chi^2 = 2.23$, $p = .114$).

^cRace was also dichotomized for use as a covariate (i.e. white [2 abused, 14 nonabused] vs. nonwhite [19 abused, 23 nonabused], $\chi^2 = 5.38$, $p = .02$).

CTQ, Childhood Trauma Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence.

disorder). Both internalizing and externalizing symptoms were elevated in the abused participants (Table 1).

Image acquisition and processing

Anatomical MRI scans were acquired on a 3T Siemens Trio scanner with a 32-channel head coil (see Appendix S1 for acquisition parameters). Standard procedures, including cortical surface reconstruction, cortical thickness estimation, and cortical and subcortical segmentation, were conducted with the FreeSurfer image analysis suite (Version 5.3, <http://surfer.nmr.mgh.harvard.edu>). Technical details of these procedures are described in Appendix S1.

Statistical analysis

We tested our hypotheses regarding relationships between child abuse and brain morphometry using three structural brain measures: cortical thickness, cortical surface area, and subcortical GMV. Cortical thickness and surface area differences were tested primarily using region-of-interest (ROI) analyses, followed by an exploratory whole-brain-corrected vertex-wise analysis for thickness (see Supplemental Methods and Results for details). A priori-defined cortical ROIs were selected in medial and lateral PFC and temporal cortex regions associated with abuse exposure (Table S1). ROIs were derived using FreeSurfer automated parcellation procedures for 13 regions, as described in Appendix S1 and listed in Table 2. GMV differences were tested in the following subcortical ROIs generated by FreeSurfer automated segmentation, separately by hemisphere: hippocampus, amygdala, thalamus, caudate, putamen, pallidum, and nucleus accumbens area.

Multiple regression analyses tested associations with abuse exposure (dichotomous) and abuse severity (continuous), separately, in each ROI. All analyses controlled for parental education, race, age, and sex; subcortical GMV analyses

additionally controlled for intracranial volume (ICV). In regions showing significant associations with either abuse measure, follow-up analyses assessed relationships between brain morphometry and internalizing and externalizing symptoms, controlling for age and sex (and ICV for subcortical regions).

To control for multiple comparisons, a false discovery rate (FDR) correction was applied to the cortical thickness, surface area, and subcortical GMV analyses, separately ($\alpha = .05$).

Results

Cortical thickness and child abuse

Associations of abuse exposure and severity with cortical thickness are presented in Table 2. Abuse exposure was associated with reduced cortical thickness in ventromedial PFC, bilateral orbitofrontal cortex (OFC), right inferior frontal gyrus (IFG), left temporal pole, bilateral parahippocampal gyrus (PHG), bilateral inferior temporal gyrus, right middle temporal gyrus, and right superior temporal gyrus. Similarly, abuse severity across the full sample was inversely related to cortical thickness in these regions except the left lateral OFC (Figure 1). Associations with abuse severity were nonsignificant when tested in the abused group only.

Cortical surface area and child abuse

Cortical surface area was not associated with abuse exposure or abuse severity in any of the ROIs (all FDR-corrected $p > .70$).

Table 2 Associations between child abuse and cortical thickness

Cortical thickness ROI ^a	Abuse exposure (Dichotomous)		Abuse severity (Continuous)	
	β	<i>p</i>	β	<i>p</i>
Ventromedial PFC	-.48*	.00015	-.38*	.003
Left lateral OFC	-.31*	.025	-.23	.087
Right lateral OFC	-.36*	.007	-.32*	.014
Left inferior frontal gyrus	-.26	.066	-.24	.09
Right inferior frontal gyrus	-.51*	.00021	-.46*	.001
Anterior cingulate cortex	-.16	.251	-.20	.14
Posterior cingulate cortex	-.19	.18	-.25	.073
Left middle frontal gyrus	-.19	.16	-.06	.66
Right middle frontal gyrus	-.23	.11	-.15	.274
Medial superior frontal gyrus	-.29	.036	-.22	.10
Left insular cortex	-.12	.41	-.05	.71
Right insular cortex	-.05	.76	-.02	.89
Left temporal pole	-.35*	.012	-.40*	.003
Right temporal pole	-.05	.73	-.14	.34
Left parahippocampal gyrus	-.33*	.009	-.32*	.011
Right parahippocampal gyrus	-.44*	.001	-.34*	.01
Left inferior temporal gyrus	-.38*	.005	-.35*	.01
Right inferior temporal gyrus	-.43*	.001	-.42*	.001
Left middle temporal gyrus	-.25	.064	-.22	.096
Right middle temporal gyrus	-.41*	.003	-.34*	.015
Left superior temporal gyrus	-.26	.061	-.28	.035
Right superior temporal gyrus	-.32*	.018	-.36*	.007

^aMultiple regression analyses tested associations with abuse exposure and abuse severity in separate models, adjusting for parental education, age, sex, and race.

*FDR-corrected $p < .05$, two-tailed.

OFC, orbitofrontal cortex; PFC, prefrontal cortex; ROI, region-of-interest.

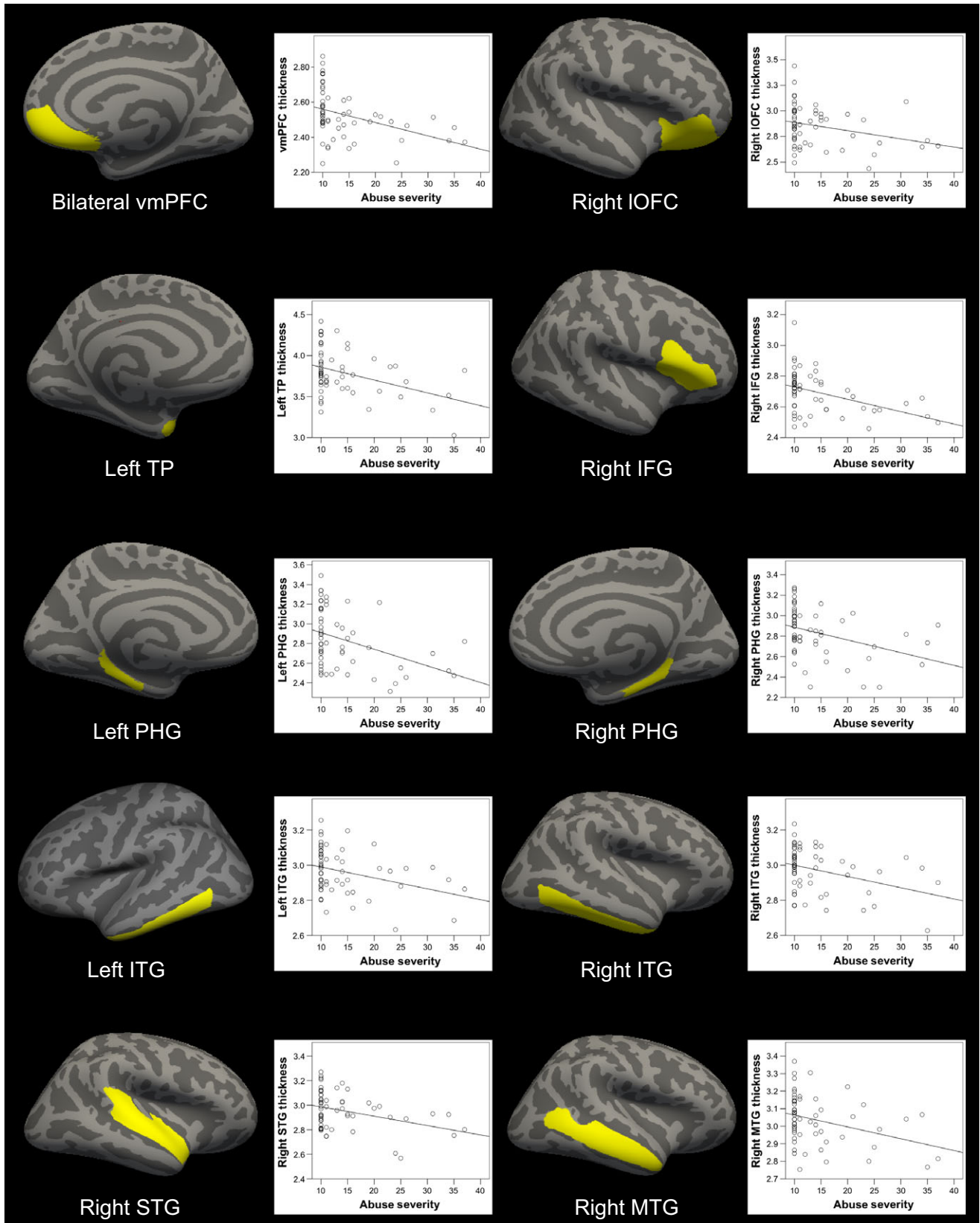


Figure 1 Cortical thickness ROIs showing associations with child abuse severity. Abuse severity was significantly associated with cortical thickness in prefrontal cortex and temporal cortex ROIs, after adjusting for parental education, race, sex, and age. The vmPFC, left temporal pole, and right and left PHG are shown on the medial surface of an inflated brain, and the right lateral OFC, right IFG, right and left ITG, right STG, and right MTG are shown on the lateral surface. Scatterplots of abuse severity and ROI thickness are presented. IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; LOFC, lateral orbitofrontal cortex; MTG, middle temporal gyrus; PHG, parahippocampal gyrus; R, right; ROI, region-of-interest; STG, superior temporal gyrus; TP, temporal pole; vmPFC, ventromedial prefrontal cortex

Subcortical GMV and child abuse

Neither abuse exposure nor abuse severity was significantly associated with regional GMV in any of the subcortical ROIs (all FDR-corrected $p > .90$).

Cortical thickness and psychopathology

In regions that significantly differed among abuse and nonabused adolescents, we examined the associations of cortical thickness with internalizing and externalizing psychopathology. Cortical thickness was not associated with internalizing symptoms in these regions (all FDR-corrected $p > .33$). In contrast, cortical thickness in the left PHG ($\beta = -.36$, $p = .007$, FDR-corrected $p = .05$) and right PHG ($\beta = -.35$, $p = .009$, FDR-corrected $p = .05$) was inversely related to externalizing symptoms (Figure 2).

Follow-up analyses regressing externalizing psychopathology on both abuse exposure and PHG thickness revealed a significant association with maltreatment (left PHG: $\beta = .41$, $p = .002$; right PHG: $\beta = .39$, $p = .004$) but not PHG thickness (left: $\beta = -.04$, $p = .79$; right: $\beta = -.07$, $p = .59$). To the extent that mediation is possible in this cross-sectional dataset, abuse appears to be mediating the relationship between PHG thickness and externalizing psychopathology. However, the field is in

general agreement that tests of statistical mediation should not be conducted in cross-sectional studies, such as this one, due to substantial issues with interpretation (Maxwell & Cole, 2007).

Discussion

This study generated two main results. First, abuse exposure and severity predicted reduced thickness in both lateral and medial prefrontal and temporal cortical regions, independent of parental education. These regions comprised ventromedial and ventrolateral PFC, PHG, and lateral temporal cortex. Of note, findings were specific to cortical thickness; abuse did not predict cortical surface area or subcortical GMV. Second, for the PHG, reduced thickness was associated with higher levels of externalizing psychopathology.

We observed reduced thickness of the vmPFC and lateral OFC in abused compared with nonabused adolescents. This region is the most consistently associated with maltreatment in previous research (De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010; Kelly et al., 2015; Lim et al., 2014). However, unlike most prior studies that relied on measures of cortical volume, this study shows that OFC differences are specific to cortical thickness, replicating findings from prior studies in a sample of adolescents with verified maltreatment exposure

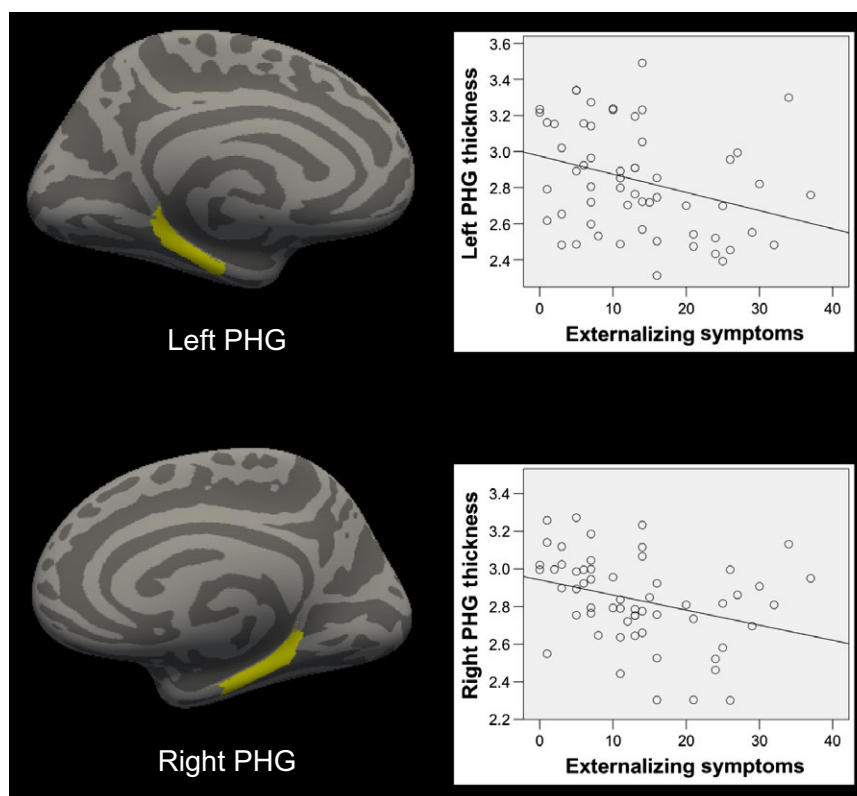


Figure 2 Cortical thickness ROIs showing associations with externalizing psychopathology. Inverse relationships between cortical thickness in the left and right PHG and externalizing symptoms are plotted. Externalizing symptoms were inversely associated with cortical thickness in the left and right PHG, which are shown on the medial surface of an inflated brain. Scatterplots of externalizing psychopathology and ROI thickness are presented. PHG, parahippocampal gyrus; ROI, region-of-interest

(Kelly et al., 2013, 2016). Thus, the current findings reflect an important contribution to the maltreatment literature as the first independent replication of prior findings of reduced OFC thickness in abused adolescents. This positive replication is particularly noteworthy given the cultural and contextual differences across the UK and US samples reported by Kelly and colleagues and our group.

Altered OFC structure in adolescence following maltreatment exposure is consistent with translational research in rodents and nonhuman primates showing that early-life stress influences PFC development (Arnsten, 2009). One of multiple psychological processes supported by the vmPFC/OFC involves the recall of fear extinction memory. The vmPFC promotes the maintenance of fear extinction in both rodents and humans (Milad & Quirk, 2012). In humans, the vmPFC is activated during extinction recall (Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004), and vmPFC/OFC thickness is positively associated with extinction memory (Hartley, Fischl, & Phelps, 2011; Milad et al., 2005). Our findings thus point to the importance of examining extinction recall in future studies examining associations among maltreatment, perturbed brain structure, and adolescent psychopathology. Indeed, structural perturbations in the OFC/vmPFC are linked not only to maltreatment but also to mental illness across a range of internalizing and externalizing disorders (Fairchild et al., 2015; McLaughlin, Sheridan, Winter, et al., 2014; Price & Drevets, 2010). However, OFC/vmPFC thickness was not associated with internalizing or externalizing psychopathology in the current study. This may be due to small sample size or the restricted range of psychopathology in this sample. Future research with larger samples is needed to examine medial and lateral OFC thickness in adolescents with a broader range of psychiatric symptoms.

Abuse also predicted thickness in lateral PFC and both medial and lateral temporal cortex. These regions are implicated in specific forms of emotion regulation. The lateral PFC and temporal cortices support explicit or effortful forms of emotion regulation, such as cognitive reappraisal of emotion (Buhle et al., 2014; Kohn et al., 2014), and the lateral temporal cortex is additionally involved in emotional face processing (Phan, Wager, Taylor, & Liberzon, 2002; Sabatinelli et al., 2011). Thus, reduced cortical thickness in these regions could relate to disruptions in multiple forms of emotional regulation beyond just extinction recall. Consistent with this possibility, in an fMRI study using some of the same participants examined in the current report (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015), we observed increased dorsolateral and dorsomedial PFC activation in abused relative to nonabused adolescents during cognitive reappraisal. Thus, the current and prior findings link childhood abuse to both reduced brain structure and altered patterns of PFC

recruitment during emotion regulation. Reduced brain structure in the context of increased brain activation could reflect reduced neural efficiency or excitotoxicity. The current findings suggest the need to examine these issues in greater depth with regard to child maltreatment and PFC structure and function.

A particularly noteworthy result involved PHG thickness and its association with externalizing psychopathology. This is consistent with prior studies linking reduced structure in the PHG and other temporal lobe regions with conduct disorder (Huebner et al., 2008), antisocial behavior (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2013), and ADHD (Schweren et al., 2015). Although research typically does not emphasize the role of the PHG in emotion, the PHG is anatomically connected to both the hippocampus and the OFC and has significant input to the hippocampus (Witter, Wouterlood, Naber, & Van Haeften, 2000), supporting its role in memory as well as emotion processing and regulation. Taken together, in light of these associations, future longitudinal research might examine the role of the PHG as a potential mediator linking childhood abuse with elevated risk of externalizing disorders.

Unlike cortical thickness, abuse did not predict differences in cortical surface area. These findings are consistent with the only prior two studies of cortical thickness and surface area in overlapping samples of maltreated and nonmaltreated adolescents, which found perturbations in the PFC for thickness but not surface area (Kelly et al., 2013, 2016). Similar findings of reduced thickness but comparable surface area have been observed in studies of neurodevelopmental disorders, such as autism (Wallace et al., 2015). As shown in Table S1, however, maltreatment studies predominantly employ volume-based cortical measures and the recent meta-analysis by Lim et al. (2014) utilized volume-based methods. Given that volume conflates thickness and surface area, volume-based methods may obscure important information about the specificity of cortical thinning following maltreatment. Although each measure is highly heritable, cortical thickness and surface area appear to be genetically independent (Panizzon et al., 2009). Moreover, cortical thickness and surface area are differentially influenced by development (Raznahan et al., 2011; Wierenga et al., 2014). For example, cortical surface area follows a curvilinear developmental trajectory, increasing during early adolescence before decreasing through middle adulthood (Schnack et al., 2015). In contrast, cortical thickness declines steadily during childhood and adolescence (Ducharme et al., 2015; Schnack et al., 2015). Distinct developmental trajectories might partially explain differential associations of abuse exposure with cortical thickness, but not surface area, in adolescence. Future research might evaluate longitudinal relationships across development that maltreatment shows with distinct surface-based measures.

Similar to cortical surface area, no abuse-related differences were detected in the GMV of subcortical regions. Although some prior pediatric studies showed volumetric differences in the amygdala and hippocampus, findings are inconsistent across studies (Table S1). A recent meta-analysis of childhood maltreatment found GM volume differences in the amygdala, but not the hippocampus (Lim et al., 2014). However, the meta-analysis examined childhood maltreatment in pediatric and adult studies and most participants were adults. Earlier meta-analyses of pediatric studies did not find hippocampal or amygdala volume differences associated with childhood maltreatment or PTSD in youths (Karl et al., 2006; Woon & Hedges, 2008), although maltreated individuals both with and without psychiatric diagnoses, notably PTSD, were included. As few abused adolescents in the current sample met criteria for PTSD, the lack of amygdala differences could reflect sample features. Future research is needed to compare and contrast abused adolescents with and without PTSD.

Limitations

The study findings should be considered in light of six key limitations. First, the sample size was small, particularly in the abused group. Structural neuroimaging studies with larger samples of maltreated children are needed, as well as meta-analyses of pediatric studies. Second, this sample had low levels of psychopathology, which may have restricted the ability to detect associations between psychopathology and brain structure. Third, we used parental education as a measure of SES and grouped all parents with less than a college education together, including parents who had pursued some form of higher education following high school. This may have obscured more profound risk for deprivation in parents with very low educational attainment, such as having a high-school education or less. We did not have data on actual exposure to deprivation. Although we measured family income, 20 participants had missing data, resulting in limited statistical power to index SES using family income. Future neuroscience research on childhood abuse should assess SES as a multi-factor construct, incorporating measures of parental education, family income, and cognitive enrichment. Fourth, although the abused and nonabused adolescents were matched on age, measures of pubertal development were not obtained. Fifth, given that our sample was based on a strict definition of physical and/or sexual abuse, our findings cannot be generalized to the population of adolescents exposed to other forms of childhood maltreatment, such as neglect or emotional abuse.

Finally, this study utilized a cross-sectional design in which brain structure and psychopathology were measured concurrently. Prospective, longitudinal research is needed to assess whether structural brain differences in adolescence mediate or moderate elevated rates of both externalizing and internalizing psychopathology at follow-up, both in later adolescence and adulthood.

Conclusion

Exposure to childhood abuse was associated with reduced cortical thickness in the ventromedial and ventrolateral PFC and temporal cortex in adolescence. These associations were observed using both dichotomous and continuous measures of abuse and were independent of low SES. Higher levels of externalizing psychopathology were associated with reduced thickness of the PHG. Future prospective research may examine cortical thickness measures to investigate whether atypical brain development influences associations of child abuse with downstream psychopathology outcomes.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of pediatric structural MRI studies examining associations with maltreatment exposure.

Appendix S1. Supplemental methods and results.

Figure S1. Whole-brain vertexwise analysis of cortical thickness associated with abuse severity, unadjusted for covariates.

Acknowledgements

This research was supported by grants from the National Institutes of Health (K01-MH092526 and K01-MH092555) and a Child Health Young Investigator Award from the Charles H. Hood Foundation. These funders provided support for all data collection and analysis. In addition, this research was supported, in part, by the Intramural Research Program of the National Institutes of Health. The authors declare that, except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

Correspondence

Katie A. McLaughlin, University of Washington, 3939 University Way NE, Seattle, WA 98105, USA; Email: mclaughk@uw.edu

Key points

- Alterations in gray matter development represent a potential pathway through which childhood abuse is associated with psychopathology.
- Prior research, mostly based on adults and volume-based measures, finds reduced volume and thickness of prefrontal (PFC) and temporal cortex regions in abused compared to nonabused adolescents.
- This study found that child abuse is associated with reduced cortical thickness, but not surface area, in ventromedial and ventrolateral PFC and temporal cortex in adolescence.
- Atypical cortical development, such as reduced PHG thickness, may link abuse exposure with externalizing psychopathology, although prospective research in adolescence is needed to evaluate this possibility.

References

- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, DC: Author.
- Arnsten, A.F.T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*, 410–422.
- Bernstein, D.P., Ahluvalia, T., Pogge, D., & Handelsman, L. (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 340–348.
- Bifulco, A., Brown, G.W., Lillie, A., & Jarvis, J. (1997). Memories of childhood neglect and abuse: Corroboration in a series of sisters. *Journal of Child Psychology and Psychiatry*, *38*, 365–374.
- Buhle, J.T., Silvers, J.A., Wager, T.D., Lopez, R., Onyemekwu, C., Kober, H., ... & Ochsner, K.N. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex*, *24*, 2981–2990.
- Busso, D., McLaughlin, K.A., Brueck, S., Peverill, M., Gold, A.L. & Sheridan, M.A. (in revision). Child abuse, neural structure, and adolescent psychopathology: A longitudinal study.
- Costello, E.J., Copeland, W., & Angold, A. (2011). Trends in psychopathology across the adolescent years: What changes when children become adolescents, and when adolescents become adults? *Journal of Child Psychology and Psychiatry*, *52*, 1015–1025.
- De Brito, S.A., Viding, E., Sebastian, C.L., Kelly, P.A., Mechelli, A., Maris, H., & McCrory, E.J. (2013). Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. *Journal of Child Psychology and Psychiatry*, *54*, 105–112.
- Ducharme, S., Albaugh, M.D., Hudziak, J.J., Botteron, K.N., Nguyen, T.-V., Truong, C., ... & Karama, S. (2014). Anxious/depressed symptoms are linked to right ventromedial prefrontal cortical thickness maturation in healthy children and young adults. *Cerebral Cortex*, *24*, 2941–2950.
- Ducharme, S., Albaugh, M.D., Nguyen, T.-V., Hudziak, J.J., Mateos-Pérez, J.M., Labbe, A., ... & Karama, S. (2015). Trajectories of cortical thickness maturation in normal brain development - The importance of quality control procedures. *NeuroImage*, *125*, 267–279.
- Edmiston, E.E., Wang, F., Mazure, C.M., Guiney, J., Sinha, R., Mayes, L.C., & Blumberg, H.P. (2011). Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Archives of Pediatrics and Adolescent Medicine*, *165*, 1069–1077.
- Ermer, E., Cope, L.M., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2013). Aberrant paralimbic gray matter in incarcerated male adolescents with psychopathic traits. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*, 94–103.e3.
- Fairchild, G., Toschi, N., Hagan, C.C., Goodyer, I.M., Calder, A.J., & Passamonti, L. (2015). Cortical thickness, surface area, and folding alterations in male youths with conduct disorder and varying levels of callous-unemotional traits. *NeuroImage. Clinical*, *8*, 253–260.
- Foland-Ross, L.C., Sacchet, M.D., Prasad, G., Gilbert, B., Thompson, P.M., & Gotlib, I.H. (2015). Cortical thickness predicts the first onset of major depression in adolescence. *International Journal of Developmental Neuroscience*, *46*, 125–131.
- Gorka, A.X., Hanson, J.L., Radtke, S.R., & Hariri, A.R. (2014). Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. *Biology of Mood and Anxiety Disorders*, *4*, 12.
- Hanson, J.L., Chung, M.K., Avants, B.B., Shirtcliff, E.A., Gee, J.C., Davidson, R.J., & Pollak, S.D. (2010). Early stress is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk. *Journal of Neuroscience*, *30*, 7466–7472.
- Hanson, J.L., Nacewicz, B.M., Sutterer, M.J., Cayo, A.A., Schaefer, S.M., Rudolph, K.D., ... & Davidson, R.J. (2015). Behavioral problems after early life stress: Contributions of the hippocampus and amygdala. *Biological Psychiatry*, *77*, 314–323.
- Hartley, C.A., Fischl, B., & Phelps, E.A. (2011). Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cerebral Cortex*, *21*, 1954–1962.
- Huebner, T., Vloet, T.D., Marx, I., Konrad, K., Fink, G.R., Herpertz, S.C., & Herpertz-Dahlmann, B. (2008). Morphometric brain abnormalities in boys with conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 540–547.
- Hutton, C., Draganski, B., Ashburner, J., & Weiskopf, N. (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *NeuroImage*, *48*, 371–380.
- Karl, A., Schaefer, M., Malta, L.S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience and Biobehavioral Reviews*, *30*, 1004–1031.
- Kelly, P.A., Viding, E., Puetz, V.B., Palmer, A.L., Mechelli, A., Pingault, J.-B., ... & McCrory, E.J. (2015). Sex differences in socioemotional functioning, attentional bias, and gray matter volume in maltreated children: A multilevel investigation. *Development and Psychopathology*, *27*(4 Pt 2), 1591–1609.
- Kelly, P.A., Viding, E., Puetz, V.B., Palmer, A.L., Samuel, S., ... & McCrory, E.J. (2016). The sexually dimorphic impact of

- maltreatment on cortical thickness, surface area and gyri-fication. *Journal of Neural Transmission*, 123, 1069–1083.
- Kelly, P.A., Viding, E., Wallace, G.L., Schaer, M., De Brito, S.A., Robustelli, B., & McCrory, E.J. (2013). Cortical thickness, surface area, and gyri-fication abnormalities in children exposed to maltreatment: Neural markers of vulnerability? *Biological Psychiatry*, 74, 845–852.
- Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., & Habel, U. (2014). Neural network of cognitive emotion regulation—an ALE meta-analysis and MACM analysis. *NeuroImage*, 87, 345–355.
- Lim, L., Radua, J., & Rubia, K. (2014). Gray matter abnormalities in childhood maltreatment: A voxel-wise meta-analysis. *American Journal of Psychiatry*, 171, 854–863.
- Maxwell, S.E., & Cole, D.A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*, 12, 23–44.
- McLaughlin, K.A., Alves, S., & Sheridan, M.A. (2014). Vagal regulation and internalizing psychopathology among adolescents exposed to childhood adversity. *Developmental Psychobiology*, 56, 1036–1051.
- McLaughlin, K.A., Greif Green, J., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., & Kessler, R.C. (2012). Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. *Archives of General Psychiatry*, 69, 1151–1160.
- McLaughlin, K.A., Peeverill, M., Gold, A.L., Alves, S., & Sheridan, M.A. (2015). Child maltreatment and neural systems underlying emotion regulation. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 753–762.
- McLaughlin, K.A., Sheridan, M.A., Alves, S., & Mendes, W.B. (2014). Child maltreatment and autonomic nervous system reactivity: Identifying dysregulated stress reactivity patterns by using the biopsychosocial model of challenge and threat. *Psychosomatic Medicine*, 76, 538–546.
- McLaughlin, K.A., Sheridan, M.A., Winter, W., Fox, N.A., Zeanah, C.H., & Nelson, C.A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 76, 629–638.
- Mechelli, A., Price, C.J., Friston, K.J., & Ashburner, J. (2005). Voxel-based morphometry of the human brain: Methods and applications. *Current Medical Imaging Reviews*, 1, 105–113.
- Milad, M.R., Quinn, B.T., Pitman, R.K., Orr, S.P., Fischl, B., & Rauch, S.L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 10706–10711.
- Milad, M.R., & Quirk, G.J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology*, 63, 129–151.
- Milad, M.R., Wright, C.I., Orr, S.P., Pitman, R.K., Quirk, G.J., & Rauch, S.L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry*, 62, 446–454.
- Morey, R.A., Haswell, C.C., Hooper, S.R., & De Bellis, M.D. (2016). Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. *Neuropsychopharmacology*, 41, 791–801.
- Noble, K.G., Houston, S.M., Brito, N.H., Bartsch, H., Kan, E., Kuperman, J.M., ... & Sowell, E.R. (2015). Family income, parental education and brain structure in children and adolescents. *Nature Neuroscience*, 18, 773–778.
- Noble, K.G., Houston, S.M., Kan, E., & Sowell, E.R. (2012). Neural correlates of socioeconomic status in the developing human brain. *Developmental Science*, 15, 516–527.
- Noordermeer, S.D.S., Luman, M., & Oosterlaan, J. (2016). A systematic review and meta-analysis of neuroimaging in oppositional defiant disorder (ODD) and conduct disorder (CD) taking attention-deficit hyperactivity disorder (ADHD) into account. *Neuropsychology Review*, 26, 44–72.
- Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., ... & Kremen, W.S. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebral Cortex*, 19, 2728–2735.
- Phan, K.L., Wager, T., Taylor, S.F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, 16, 331–348.
- Phelps, E.A., Delgado, M.R., Nearing, K.I., & LeDoux, J.E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, 43, 897–905.
- Price, J.L., & Drevets, W.C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology*, 35, 192–216.
- Rao, U., Chen, L.-A., Bidesi, A.S., Shad, M.U., Thomas, M.A., & Hammen, C.L. (2010). Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biological Psychiatry*, 67, 357–364.
- Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G.L., Greenstein, D., ... & Giedd, J.N. (2011). How does your cortex grow? *Journal of Neuroscience*, 31, 7174–7177.
- Sabatinelli, D., Fortune, E.E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W.T., ... & Jeffries, J. (2011). Emotional perception: Meta-analyses of face and natural scene processing. *NeuroImage*, 54, 2524–2533.
- Schnack, H.G., van Haren, N.E.M., Brouwer, R.M., Evans, A., Durston, S., Boomsma, D.I., ... & Hulshoff Pol, H.E. (2015). Changes in thickness and surface area of the human cortex and their relationship with intelligence. *Cerebral Cortex*, 25, 1608–1617.
- Schweren, L.J.S., Hartman, C.A., Heslenfeld, D.J., van der Meer, D., Franke, B., Oosterlaan, J., ... & Hoekstra, P.J. (2015). Thinner medial temporal cortex in adolescents with attention-deficit/hyperactivity disorder and the effects of stimulants. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 660–667.
- Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K., & Schwab-Stone, M.E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 28–38.
- Shang, J., Fu, Y., Ren, Z., Zhang, T., Du, M., Gong, Q., & Lui, S. (2014). The common traits of the ACC and PFC in anxiety disorders in the DSM-5: Meta-analysis of voxel-based morphometry studies. *PLoS One*, 9, e93432, doi: 10.1371/journal.pone.0093432
- Teicher, M.H., Anderson, C.M., & Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences of the United States of America*, 109, E563–E572.
- Van Dam, N.T., Rando, K., Potenza, M.N., Tuit, K., & Sinha, R. (2014). Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry*, 71, 917–925.
- Walker, E.A., Unutzer, J., Rutter, C., Gelfand, A., Saunders, K., VonKorff, M., ... & Katon, W. (1999). Costs of health care use by women HMO members with a history of childhood abuse and neglect. *Archives of General Psychiatry*, 56, 609–613.
- Wallace, G.L., Eisenberg, I.W., Robustelli, B., Dankner, N., Kenworthy, L., Giedd, J.N., & Martin, A. (2015). Longitudinal cortical development during adolescence and young adulthood in autism spectrum disorder: Increased cortical thinning but comparable surface area changes. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 464–469.

- Whittle, S., Dennison, M., Vijayakumar, N., Simmons, J.G., Yücel, M., Lubman, D.I., . . . & Allen, N.B. (2013). Childhood maltreatment and psychopathology affect brain development during adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*, 940–952.e1.
- Wierenga, L.M., Langen, M., Oranje, B., & Durston, S. (2014). Unique developmental trajectories of cortical thickness and surface area. *NeuroImage*, *87*, 120–126.
- Witter, M.P., Wouterlood, F.G., Naber, P.A., & Van Haeften, T. (2000). Anatomical organization of the parahippocampal-hippocampal network. *Annals of the New York Academy of Sciences*, *911*, 1–24.
- Woon, F.L., & Hedges, D.W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. *Hippocampus*, *18*, 729–736.

Accepted for publication: 22 June 2016