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ORIGINAL ARTICLE

Grey matter volume and thickness abnormalities in young people with a history of childhood abuse

L. Lim[1]*†, H. Hart[1]†, M. Mehta[2], A. Worker[2], A. Simmons[2], K. Mirza[1] and K. Rubia[1]

[1] *Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK*
[2] *Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK*

Background. Childhood abuse is associated with abnormalities in brain structure and function. Few studies have investigated abuse-related brain abnormalities in medication-naïve, drug-free youth that also controlled for psychiatric comorbidities by inclusion of a psychiatric control group, which is crucial to disentangle the effects of abuse from those associated with the psychiatric conditions.

Methods. Cortical volume (CV), cortical thickness (CT) and surface area (SA) were measured in 22 age- and gender-matched medication-naïve youth (aged 13–20) exposed to childhood abuse, 19 psychiatric controls matched for psychiatric diagnoses and 27 healthy controls. Both region-of-interest (ROI) and whole-brain analyses were conducted.

Results. For the ROI analysis, the childhood abuse group compared with healthy controls only, had significantly reduced CV in bilateral cerebellum and reduced CT in left insula and right lateral orbitofrontal cortex (OFC). At the whole-brain level, relative to healthy controls, the childhood abuse group showed significantly reduced CV in left lingual, pericalcarine, precuneus and superior parietal gyri, and reduced CT in left pre-/postcentral and paracentral regions, which furthermore correlated with greater abuse severity. They also had increased CV in left inferior and middle temporal gyri relative to healthy controls. Abnormalities in the precuneus, temporal and precentral regions were abuse-specific relative to psychiatric controls, albeit at a more lenient level. Groups did not differ in SA.

Conclusions. Childhood abuse is associated with widespread structural abnormalities in OFC–insular, cerebellar, occipital, parietal and temporal regions, which likely underlie the abnormal affective, motivational and cognitive functions typically observed in this population.

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Key words: Brain abnormalities, childhood adversity, childhood maltreatment, cortical thickness, cortical volume, early-life stress, surface area.

Introduction

Brain development is a complex process regulated by genes and sculpted by environmental experiences (Lenroot & Giedd, 2008). Although experiential influences affect brain structure and function throughout the lifespan, childhood experience is particularly crucial with early stress adversely affecting the nature and trajectory of normal brain development (Pechtel & Pizzagalli, 2011).

Childhood maltreatment, which includes physical, sexual and emotional abuse and neglect, is common in the UK with paediatric prevalence rates of 7–10% (NSPCC, 2011). It has been associated with a host of adverse consequences, such as low IQ, abnormal error processing (Lim *et al.* 2015), impaired attention, inhibition, emotion and reward processing (Pechtel & Pizzagalli, 2011; Hart & Rubia, 2012; De Bellis & Zisk, 2014). Large-scale epidemiological studies found that childhood maltreatment is significantly associated with first onsets of various psychiatric disorders, such as depression and post-traumatic stress disorder (PTSD) (Green *et al.* 2010).

The psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of neural underpinnings (Bremner & Vermetten, 2001). Structural MRI studies show that, relative to non-maltreated controls, individuals exposed to childhood maltreatment have grey matter volume (GMV) abnormalities in several relatively late-developing brain regions, such as the orbitofrontal cortex (OFC) (Hanson *et al.* 2010; Thomaes *et al.* 2010; Edmiston *et al.* 2011; De Brito *et al.* 2013; Hodel *et al.* 2015), insula (Edmiston *et al.* 2011; Dannlowski *et al.* 2012; Lim *et al.* 2014), temporal lobes (Bremner *et al.*

* Address for correspondence: Dr L. Lim, Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, De Crespigny Park, London SE5 8AF, UK.

(Email: lena.lim@kcl.ac.uk)

† Dr Lim and Dr Hart share first authorship

1997; De Bellis *et al.* 2002; Tomoda *et al.* 2011) and cerebellum (De Bellis & Kuchibhatla, 2006; Bauer *et al.* 2009; Walsh *et al.* 2014). Volumetric abnormalities in subcortical regions such as the hippocampus and amygdala have been mainly observed in adults but not children/adolescents exposed to childhood maltreatment (Woon & Hedges, 2008). Recent studies also reported reduced visual cortex GMV in childhood maltreatment (Tomoda *et al*. 2009; 2012; Edmiston *et al*. 2011). Several reviews of childhood maltreatment have consistently reported structural deficits in several stress-susceptible brain regions including the OFC, limbic, insula and cerebellar regions (McCrory *et al.* 2011*a*; Hart & Rubia, 2012; Lim *et al.* 2014; Nemeroff, 2016; Teicher *et al.* 2016), with the late-developing OFC and cerebellum being particularly vulnerable to the effects of early stress (Hanson *et al.* 2010; Pechtel & Pizzagalli, 2011), and the insula is known to be involved in regulating the glucocorticoid effect (Fornari *et al.* 2012). Our meta-analysis also showed that childhood maltreatment is associated with GMV reduction in OFC–limbic–temporal regions and inferior frontal cortices that mediate top–down affect and cognitive control, respectively; and with GMV reduction in pre-/postcentral gyri that mediate sensory functions (Lim *et al.* 2014).

Cortical volume (CV) is determined by two separable cortical indices, cortical thickness (CT) and surface area (SA), which are genetically (Panizzon *et al.* 2009) and phenotypically (Winkler *et al.* 2010) independent with differing developmental trajectories (Panizzon *et al.* 2009). Studies examining CT, SA and CV may be more sensitive to individual differences than considering volume alone (Hutton *et al.* 2009). However, as most of the earlier structural studies on childhood maltreatment examined abuse-related volumetric abnormalities, examining group differences in volume in the current study thus allows for comparison with the existing literature. Volume measurements are also useful for subcortical structures where CT/SA measurements are unavailable. Therefore, it is important to explore these brain measures to better understand the structural correlates of childhood maltreatment.

To date, few studies on childhood maltreatment examined whole-brain differences in CV, CT and SA within the same sample. Compared with healthy controls, maltreated young people had significantly reduced CT in right OFC (Kelly *et al*. 2013; 2016; Gold *et al*. 2016), and reduced SA in left middle temporal and lingual regions (Kelly *et al.* 2013). Children who experienced psychosocial deprivation exhibited widespread CT reductions in lateral OFC, precuneus, insula, parietal and lingual gyri, which were furthermore associated with inattention and impulsivity (McLaughlin *et al.* 2014). In adults, childhood sexual abuse was associated with reduced CT in left somatosensory cortex, while emotional abuse was associated with reduced CT in bilateral precuneus and left somatosensory cortex (Heim *et al.* 2013). Individuals exposed to domestic violence during childhood had reduced CT in bilateral lingual (Tomoda *et al.* 2012).

Given that childhood maltreatment is associated with the development of psychiatric complications (Sugaya *et al.* 2012; Herrenkohl *et al.* 2013; MacMillan *et al.* 2013), it is crucial to control for these in order to disentangle the effects of maltreatment from the psychiatric comorbidities (McCrory *et al.* 2011*a*; Hart & Rubia, 2012; Lim *et al.* 2014). Only two prior structural studies in childhood maltreatment controlled for psychiatric disorders. However, they examined CV alone in specific disorders, such as psychosis (Sheffield *et al.* 2013) and depression (Chaney *et al.* 2014), which limits the generalizability of their findings to other psychiatric comorbidities. The majority of patients in the two studies were also on psychotropic medications (e.g. chlorpromazine, SSRIs), which are known to affect brain structure and function (Murphy, 2010).

Therefore, the aim of this study was to control for the limitations of earlier studies by conducting both region-of-interest (ROI) and whole-brain structural (CV, CT, SA) analyses in medication-naïve, drug-free youth exposed to documented childhood physical abuse and in healthy controls. To assess the specificity of the association with childhood abuse, we included a third group of psychiatric controls that was matched with the abuse group on psychiatric comorbidities. Sexual abuse was excluded because it has different effects on brain structure (Heim *et al.* 2013) and different behavioural and psychiatric consequences (Teicher *et al.* 1997; Weierich & Nock, 2008; Lopez-Castroman *et al.* 2013; Lewis *et al.* 2016). For instance, both childhood physical abuse and neglect, but not sexual abuse, were associated with alterations in regional corpus callosum size (Teicher *et al.* 1997) and with GMV reduction in a distributed corticostriatal–limbic system (Edmiston *et al.* 2011). Furthermore, childhood sexual abuse is associated with experiences unique to sexual victimization relative to other abuse experiences; for example, traumatic sexualization, stigmatization, attributions of responsibility as well as feelings of guilt and shame may impact sexual abuse victims differently than victims of other abuse experiences (Finkelhor & Browne, 1985; Feiring *et al.* 1996). For these reasons, and in order to obtain a more homogenous group, we only included youth exposed to childhood physical abuse. Nevertheless, it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Claussen & Crittenden, 1991; Edwards *et al.* 2003) since psychological maltreatment would be present in *almost all* cases of physical maltreatment (Claussen & Crittenden, 1991).

Since childhood maltreatment is consistently associated with structural deficits in several stress-susceptible brain regions including the OFC, limbic, insula and cerebellar regions (McCrory *et al.* 2011*a*; Hart & Rubia, 2012; Lim *et al.* 2014; Nemeroff, 2016; Teicher *et al.* 2016), we hypothesized that the abuse group, relative to both healthy and psychiatric controls, would have structural abnormalities particularly in the OFC, insula and cerebellum. We also investigated abnormalities outside our priori defined ROIs with a whole-brain analysis.

Methods and materials

Participants

Seventy (23 abuse, 20 psychiatric controls, 27 healthy controls) right-handed, medication-naïve, drug-free and age- and gender-matched youth (aged 13–20) were assessed by a child psychiatrist (KM) using the Development and Well-Being Assessment (DAWBA) (Goodman *et al.* 2000), which was designed to generate International Classification of Diseases, 10th Edition (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) psychiatric diagnoses. The Strengths and Difficulties Questionnaires (SDQ) (Goodman, 1997) and Beck's Depression Inventory (BDI) (Beck *et al.* 1988) were also used to provide symptom scores on psychopathology. IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) was used to measure the severity of childhood physical, sexual and emotional abuse, and physical and emotional neglect. Socioeconomic status (SES) was measured by two non-sensitive items (on housing tenure and room occupancy) from the Family Affluence Scale (FAS) (Currie *et al.* 1997).

Exclusion criteria for all participants were childhood sexual abuse, drug abuse, learning disability, neurological abnormalities, epilepsy, IQ < 70 and MRI contraindications. Urine screening for recent drug use was conducted with 10-panel urine drug test integrated cups (T-Cup; http://www.testfield.co.uk). All participants or their guardians, if they were under the age of 18, provided written informed consent to participate in the study. The study was approved by the National Research Ethics Service Committee London – Fulham.

The 23 youth who experienced physical abuse before the age of 12 were first recruited through social services and psychiatric clinics. They or their guardians were first asked to provide signed permission to contact their social services for written confirmation of official records of physical abuse. The Childhood Experience of Care and Abuse (CECA) interview (Bifulco *et al.* 1994) was used to corroborate the CTQ and provide information on the age of onset and duration of abuse. The participants scored ⩾ 13 (i.e. the cut-off for severe/extreme physical abuse) (Bernstein & Fink, 1998) on the CTQ physical abuse subscale and information from the CECA interview and the CTQ were consistent with the official records. The common psychiatric comorbidities included PTSD, depression, anxiety and conduct disorder (Table 1). One participant was excluded due to MRI motion artefacts, leaving a final sample of 22 participants.

The 20 psychiatric patients that were matched with the abuse group on psychiatric comorbidities but with no history of childhood maltreatment (scoring below the cut-offs for the respective CTQ subscales) (Bernstein & Fink, 1998) were recruited through psychiatric clinics and social services (Table 1). PTSD patients experienced non-abuse-related trauma (e.g. witnessed a murder, experienced a car accident or experienced the death of a loved one). One participant was excluded due to motion artefacts, leaving a final sample of 19 patients.

The 27 healthy controls with no history of psychiatric illness and childhood maltreatment (scoring below the same cut-offs as above) were recruited through advertisements in the same geographic areas of South London to ensure similar SES (Table 1).

MRI acquisition and analysis

The MRI acquisition procedures are described in the online Supplementary Materials.

Image preprocessing and analyses were carried out using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvest.edu). After preprocessing (online supplementary materials), whole-brain between-group differences in CV, CT and SA were investigated within the QDEC surface-based group analysis. For each hemisphere, the General Linear Model was computed vertex-by-vertex for analysis of each cortical morphometric measure (CV, CT and SA), with group as a between-subjects factor and IQ, age and a total brain measure (total brain volume for CV, mean CT for CT and total SA for SA) included as covariates. Although there were no significant group differences in age, it was included given the relatively wide age range of the current sample. Cortical maps were smoothed with a full width at half maximum Gaussian kernel of 10 mm. Between-group differences were corrected for multiple comparisons with a Monte Carlo z-field simulation at $p < 0.05$ (two-tailed).

Table 1. *Demographic characteristics of 22 young people exposed to childhood abuse, 19 psychiatric controls and 27 healthy controls*

	Childhood abuse ($N=22$)		Psychiatric controls ($N=19$)		Healthy controls ($N=27$)		Analysis		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	F (2,65)	p (corr.)	Between groups
Age (years) (age range: 13–20)	17.6	2.31	16.8	2.59	17.5	1.63	0.80	N.S.	–
Socioeconomic status	2.77	0.69	2.94	0.66	3.22	0.75	2.53	N.S.	–
IQ	89.5	12.5	93.5	12.8	105.4	10.1	12.3	<0.001	CA, PC < HC
Strengths and difficulties questionnaire									
Emotional problems	4.68	2.72	4.89	2.98	1.92	1.61	10.7	<0.001	CA, PC > HC
Conduct problems	4.36	1.99	2.21	2.20	1.68	1.60	12.4	<0.001	CA > PC, HC
Hyperactivity	5.41	2.34	4.68	2.65	2.84	2.14	7.4	0.001	CA, PC > HC
Peer problems	3.77	1.51	2.53	1.95	1.16	1.72	13.4	<0.001	CA > PC, HC
Prosocial	7.36	1.76	8.58	1.78	8.08	1.41	2.87	N.S.	–
Total difficulties score	18.2	6.05	14.3	6.31	7.60	5.73	18.9	<0.001	CA, PC > HC
Beck's Depression Inventory	16.4	10.4	19.4	10.2	5.92	6.09	8.17	0.001	CA, PC > HC
Childhood trauma questionnaire									
Physical abuse	20.9	4.97	6.00	1.45	5.52	0.94	126.6	<0.001	CA > PC, HC
Emotional abuse	17.9	4.30	7.00	1.86	6.04	1.13	98.1	<0.001	CA > PC, HC
Sexual abuse	5.14	0.64	5.15	1.07	5.11	0.42	1.49	N.S.	–
Physical neglect	14.1	4.97	6.63	3.69	5.59	1.22	40.4	<0.001	CA > PC, HC
Emotional neglect	18.3	3.84	8.79	3.69	7.93	3.35	53.0	<0.001	CA > PC, HC
Age at onset of (physical) abuse (years)	4.00	2.76	–	–	–	–	–	–	–
Duration of (physical) abuse (years)	8.27	3.12	–	–	–	–	–	–	–
	N	%	N	%	N	%	χ^2	p	Between groups
Gender (males)	15	68	9	47	21	77	4.67	N.S.	CA *v.* HC ($\chi^2=0.57$, N.S.); CA *v.* PC ($\chi^2=1.82$, N.S.); HC *v.* PC ($\chi^2=4.55$, $p=0.03$)
Ethnicity							7.98	N.S.	–
Caucasian	10	45	3	16	13	48			
Afro-Caribbean	9	41	10	52	12	44			
Others (Asian/mixed)	3	14	6	32	2	8			
Psychiatric diagnosis:									
PTSD	13	59	12	63	–				
Depression	6	27	6	32	–				
Anxiety disorders	5	23	5	26	–				
Social phobia	1	5	1	5	–				
ADHD	1	5	1	5					
ODD/CD/Other disruptive behaviours	5	23	4	21	–				

CA, childhood abuse group; PC, psychiatric controls; HC, healthy controls; corr, Bonferroni corrected; ADHD, attention deficit hyperactivity disorder; PTSD, post-traumatic stress disorder; ODD, oppositional defiant disorder; CD, conduct disorder; N.S., non-significant.

For group differences in the hypothesized ROIs (i.e. OFC, insula, cerebellum), analysis of variance with group (abuse *v.* healthy controls; abuse *v.* psychiatric controls) as a between-subject factor and covariates outlined above were used on the cortical measures of these regions generated during the automated segmentation and parcellation process (Fischl *et al.* 2004). Given that a limited number of studies have aimed at specifying surface-based brain indices in relation to abuse exposure (Kelly *et al.* 2016), the stringent

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Bonferroni multiple comparisons correction was not applied in this analysis to limit potential type II errors.

Tests for normality were conducted in SPSS using the Kolmogorov–Smirnov and Shapiro–Wilk tests. None of the volume measurement distributions deviated significantly from normality.

Finally, we also conducted three preliminary analyses. First, we explored if gender influenced the impact of maltreatment on brain measures at the whole-brain level in QDEC with age, IQ and a total brain measure included as covariates. Second, the significant clusters were extracted for exploratory Pearson correlational analysis with the clinical measures *within* each group and with the abuse measures within the abuse group only. Lastly, we explored if the groups differed on hippocampus volume (online Supplementary Materials).

Results

Subject characteristics

The groups did not differ significantly on age, gender, ethnicity nor SES ($p > 0.05$), but differed on IQ ($p < 0.001$), which was expected as this is typical for the population (Mills *et al.* 2011; Young & Widom, 2014; Geoffroy *et al.* 2016) (Table 1). Although we selected participants with severe childhood physical abuse, they also experienced severe emotional abuse and neglect (Table 1), which typically co-occur with physical abuse; hence, we consider this group representative of the childhood abuse population (Edwards *et al.* 2003; Trickett *et al.* 2011).

ROI analysis

Relative to healthy controls only, the abuse group showed significantly reduced CV in left [$F(1,44) = 4.68$, $p = 0.03$] and right [$F(1,44) = 5.33$, $p = 0.02$] cerebellum, and reduced CT in left insula [$F(1,44) = 6.06$, $p = 0.02$] and right lateral OFC [$F(1,44) = 4.30$, $p = 0.04$]. The abuse and psychiatric groups did not differ significantly (Table 2). There were no significant group differences on hippocampus volume (online Supplementary Materials).

Whole-brain analysis

Cortical volume

Compared with healthy controls, the abuse group had significantly reduced CV in a left-hemispheric posterior cluster comprising lingual, pericalcarine, precuneus, cuneus, isthmus cingulate and superior parietal gyri (Table 3, Fig. 1; cluster-corrected $p < 0.05$). They had larger CV in two left-hemispheric clusters: inferior temporal gyrus, along with middle temporal and inferior parietal gyri (Table 3, Fig. 2; cluster-corrected $p < 0.05$). Two of these regional differences, reduced CV in left precuneus ($t = -2.36$, $p < 0.05$) and larger CV in left middle temporal gyrus ($t = 2.38$, $p < 0.05$), were also significant relative to psychiatric controls at an uncorrected level; suggesting that the CV abnormalities in these two regions could be abuse-specific. Healthy and psychiatric controls did not differ significantly from each other. There was no significant maltreatment by gender interaction.

Cortical thickness

The abuse group had significantly reduced CT in left precentral, postcentral and paracentral gyri (Table 4, Fig. 3; cluster-corrected $p < 0.05$) relative to healthy controls, and significantly reduced left precentral CT ($t = -2.18$, $p < 0.05$) relative to psychiatric controls at an uncorrected level, suggesting that the precentral deficit could be abuse-specific. Healthy and psychiatric controls did not differ significantly from each other. There was no significant maltreatment by gender interaction.

Surface area

There were no significant group differences or maltreatment by gender interaction in SA.

Correlational analysis

The significant clusters were correlated with the SDQ and abuse measures within each group, controlling for IQ and age. Lower CV in the lingual–pericalcarine–precuneus cluster was significantly associated with higher CTQ physical abuse ($r = -0.45$, $p < 0.05$) and total score ($r = -0.46$, $p < 0.05$) in the abuse group, and with higher SDQ total score ($r = -0.49$, $p < 0.05$) and peer problems ($r = -0.56$, $p < 0.05$) in the healthy controls. Reduced CT in the pre-/postcentral cluster was also significantly associated with higher CTQ total score ($r = -0.46$, $p < 0.05$) in the abuse group.

Discussion

To our knowledge, this is the first structural study on childhood abuse that examined group differences in CV, CT and SA within the same sample in a group of medication-naïve, drug-free youth that also controlled for psychiatric comorbidities by inclusion of a psychiatric control group. Both are crucial to elucidate the effects of abuse independent from effects associated with psychiatric comorbid conditions or medication and drug abuse (McCrory *et al.* 2011*a*; Hart & Rubia, 2012; Lim *et al.* 2014).

For the ROI, the abuse group had significantly reduced CV in bilateral cerebellum and reduced CT

Table 2. *Group differences in the cortical measures of the regions of interest among 22 young people exposed to childhood abuse, 19 psychiatric controls and 27 healthy controls*

	Childhood abuse ($N = 22$)		Psychiatric controls ($N = 19$)		Healthy controls ($N = 27$)		CA *v.* HC comparisons			CA *v.* PC comparisons		
Brain regions	Mean	S.D.	Mean	S.D.	Mean	S.D.	$F(1,44)$	p Value		$F(1,36)$	p Value	
Cerebellum												
Left CV	54 314	5158	56 358	6854	57 463	4992	4.68	0.03	CA < HC	0.24	N.S.	–
Right CV	55 308	5038	55 408	6799	58 392	4318	5.33	0.02	CA < HC	1.27	N.S.	–
Insula												
Left CV	6959	812	6806	762	7025	708	0.53	N.S.	–	0.11	N.S.	–
Left CT	3.13	0.13	3.19	0.17	3.23	0.14	6.06	0.02	CA < HC	0.28	N.S.	–
Left SA	2154	279	2083	223	2121	174	0.51	N.S.	–	0.02	N.S.	–
Right CV	7101	922	7041	1020	7200	766	0.19	N.S.	–	0.17	N.S.	–
Right CT	3.12	0.12	3.21	0.15	3.17	0.15	2.02	N.S.	–	3.19	N.S.	–
Right SA	2221	280	2168	340	2228	234	0.29	N.S.	–	0.36	N.S.	–
Lateral OFC												
Left CV	8556	998	8464	1099	8649	903	0.20	N.S.	–	0.15	N.S.	–
Left CT	2.79	0.14	2.86	0.23	2.83	0.18	0.69	N.S.	–	0.22	N.S.	–
Left SA	2624	319	2562	324	2636	287	0.35	N.S.	–	0.86	N.S.	–
Right CV	8673	1222	8489	1117	8609	696	0.17	N.S.	–	0.18	N.S.	–
Right CT	2.80	0.17	2.90	0.15	2.91	0.20	4.30	0.04	CA < HC	2.55	N.S.	–
Right SA	2747	358	2565	368	2624	252	1.74	N.S.	–	1.79	N.S.	–

CA, childhood abuse group; HC, healthy controls; PC, psychiatric controls; OFC, orbitofrontal cortex; CV, cortical volume (mm^3); CT, cortical thickness (mm); SA, surface area (mm^2); N.S., non-significant; S.D., standard deviation.

Table 3. *Regions with significant group differences in cortical volume among 22 young people exposed to childhood abuse, 19 psychiatric controls and 27 healthy controls*

Comparison	Brain regions	Talairach coordinates (x,y,z)	Brodmann's area	t value	p value	Cluster size (mm^3)
CA < HC	Left pericalcarine/precuneus/cuneus/isthmus cingulate/lingual/superior parietal gyrus	−19.0, −72.7, 10.4	18/17/19/29/7	−3.16[a]	0.003	3368.05
CA < PC	Left precuneus	−11.4, −64.2, 23.8	31	−2.36[b]	0.02	220.11
CA > HC	Left inferior temporal gyrus	−48.1, −23.9, −23.4	20	2.99[a]	0.02	1301.33
	Left middle temporal/inferior parietal gyrus	−48.0, −58.1, 5.5	21/39	2.82[a]	0.03	1231.88
CA > PC	Left middle temporal gyrus	−54.5, −45.5, −1.5	21	2.38[b]	0.02	188.29

CA, childhood abuse group; HC, healthy controls; PC, psychiatric controls.

[a] The t value at which the test statistic is significant at $p < 0.05$, corrected for multiple comparisons with a Monte Carlo z-field simulation.

[b] The t value at which the test statistic is significant at $p < 0.05$, uncorrected for multiple comparisons.

in left insula and right lateral OFC, compared with healthy controls only. At the whole-brain level, relative to healthy controls, the abuse group showed significantly reduced CV in a cluster comprising left lingual, pericalcarine, precuneus and superior parietal regions, along with reduced CT in left pre-/postcentral and paracentral regions, which were furthermore significantly associated with greater abuse severity. Lower lingual–pericalcarine–precuneus CV was associated with greater SDQ total score and peer problems in the healthy controls, thereby suggesting possibly detrimental effects particularly in terms of peer problems,

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Fig. 1. Significant cortical volume cluster projected onto the inflated surface of the left hemisphere in (*a*) medial and (*b*) tilted anterior views. The significant cluster shows reduced cortical volume in the childhood abuse group compared with healthy controls, and survived cluster correction for multiple comparisons using Monte Carlo simulation, $p < 0.05$.

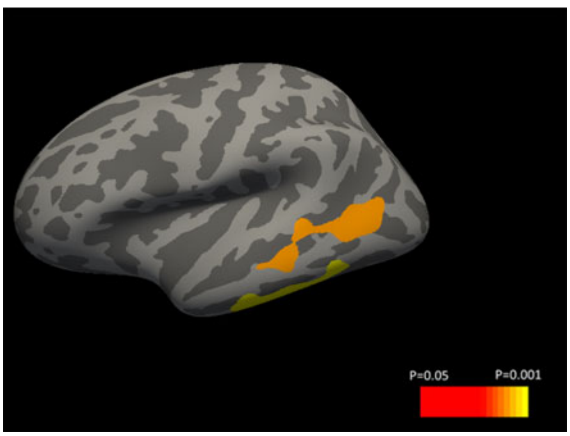

Fig. 2. Significant cortical volume clusters projected onto the inflated surface of the left hemisphere in lateral view. The significant clusters show increased cortical volume in the childhood abuse group compared with healthy controls, and survived cluster correction for multiple comparisons using Monte Carlo simulation, $p < 0.05$.

at least in the general healthy population. The abuse group also had increased CV in left inferior and middle temporal regions compared with healthy controls. Abnormalities in the precuneus, middle temporal and precentral regions were abuse-specific relative to psychiatric controls, albeit at a more lenient level.

The OFC receives strong inputs from the limbic system and is involved in emotion regulation, social behaviour and reward-related decision making (Rempel-Clower, 2007). It also receives inputs from the visual and somatosensory regions, and the lateral OFC is activated when viewing aversive pictures (Nitschke *et al.* 2006) and experiencing unpleasant touch (Rolls *et al.* 2003). The current finding of a thinner right lateral OFC is consistent with previous studies that found thinner right (lateral) OFC in children who experienced severe early-life deprivation and childhood abuse (Kelly *et al.* 2013; McLaughlin *et al.* 2014; Gold *et al.* 2016), and extends findings of our meta-analysis (Lim *et al.* 2014) and other volumetric studies that found significantly reduced OFC CV in children (Hanson *et al.* 2010; Edmiston *et al.* 2011; De Brito *et al.* 2013; Hodel *et al.* 2015) and adults (Thomaes *et al.* 2010) exposed to childhood maltreatment.

The insula plays a key role in interoceptive awareness and emotion regulation (Goldin *et al.* 2008) and together with the somatosensory, motor and prefrontal cortices, forms part of the neural circuitry of pain (Tracey & Mantyh, 2007). It is also part of the salience network that detects threat (Pichon *et al.* 2012), where it integrates information about salience into perceptual decisions about pain (Wiech *et al.* 2010). Previous structural studies have found thinner insula in children who experienced severe early-life derivation (McLaughlin *et al.* 2014), as well as reduced insula CV in children (Edmiston *et al.* 2011) and adults (Dannlowski *et al.* 2012) exposed to physical abuse and childhood maltreatment, respectively.

The cerebellum is vulnerable to the effects of early stress (Pechtel & Pizzagalli, 2011). It plays a crucial role in emotion processing and fear conditioning via its connection with limbic structures and the hypothalamic–pituitary–adrenal axis (Schutter & van Honk, 2005), and is a key region in many cognitive processes, particularly attention and timing functions (Stoodley & Schmahmann, 2009; Arnsten & Rubia, 2012). Cerebellar deficit has also been reported in previous studies of childhood abuse (De Bellis & Kuchibhatla, 2006; Bauer *et al.* 2009; Edmiston *et al.* 2011), and may possibly underlie the affective and cognitive deficits in this population.

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Table 4. *Regions with significant group differences in cortical thickness among 22 young people exposed to childhood abuse, 19 psychiatric controls and 27 healthy controls*

Comparison	Brain regions	Talairach coordinates (*x*,*y*,*z*)	Brodmann's area	*t* value	*p* value	Cluster size (mm)
CA < HC	Left precentral/postcentral/ paracentral	−38.8, −13.0, 55.4	4/1/2/3	-3.05^a	0.004	1029.25
CA < PC	Left precentral	−28.6, −22.7, 60.9	4	-2.18^b	0.04	207.44

CA, childhood abuse group; HC, healthy controls; PC, psychiatric controls.
[a] The t value at which the test statistic is significant at $p < 0.05$, corrected for multiple comparisons with a Monte Carlo z-field simulation.
[b] The t value at which the test statistic is significant at $p < 0.05$, uncorrected for multiple comparisons.

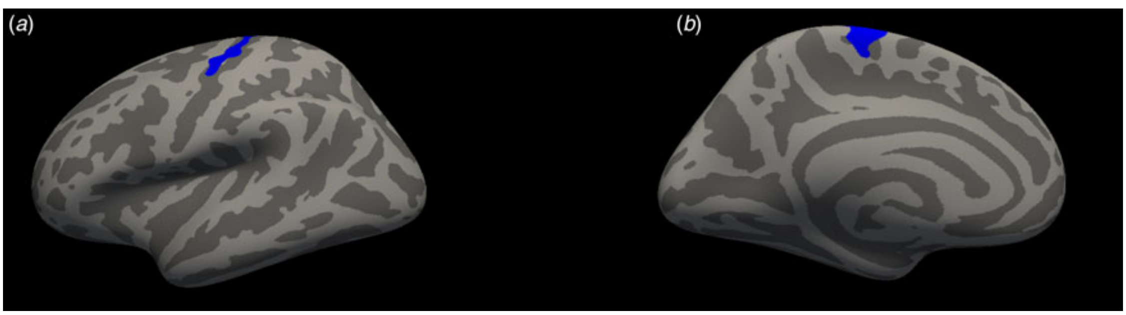

Fig. 3. Significant cortical thickness cluster projected onto the inflated surface of the left hemisphere in (*a*) lateral and (*b*) medial views. The significant cluster shows reduced cortical thickness in the childhood abuse group compared with healthy controls, and survived cluster correction for multiple comparisons using Monte Carlo simulation, $p < 0.05$.

Childhood maltreatment has been associated with abnormal development of the sensory systems that relay adverse sensory experiences. For instance, studies reported reduced lingual CV in women who experienced childhood sexual and physical abuse (Tomoda *et al.* 2009), reduced lingual CT in children who experienced psychosocial deprivation (McLaughlin *et al.* 2014) and in young adults who witnessed domestic violence during childhood (Tomoda *et al.* 2012), as well as reduced lingual SA in maltreated children (Kelly *et al.* 2013). Women exposed to childhood sexual and emotional abuse also had reduced CT in left somatosensory cortex (Heim *et al.* 2013). Thus, the current findings of reduced left lingual CV and motor–somatosensory CT in the abuse group are consistent with these earlier studies and our meta-analysis finding of a smaller left motor–somatosensory CV in childhood maltreatment (Lim *et al.* 2014). Together, these findings support the suggestion that the sensory systems that process and interpret adverse sensory inputs may be altered by the abuse experience, reflecting an adaptive response of the developing brain to protect the child from highly hostile environmental conditions by gating sensory experiences and processing related to the abuse (Heim *et al.* 2013). Given that painful stimulation decreases blood flow in the somatosensory cortex (Tommerdahl *et al.* 1996), severe and painful punishments during the critical time of synapse formation and development in childhood may possibly reduce the number of synapses leading to a thinner somatosensory cortex. Moreover, the association between abuse and deficits in the sensory regions is further underpinned by the current findings of significant negative correlations between them.

The finding of a possibly abuse-specific reduced precuneus CV corroborates earlier findings of a negative association between precuneus CV and abuse severity (Dannlowski *et al.* 2012), as well as reduced CT (Heim *et al.* 2013; McLaughlin *et al.* 2014) and network centrality of the precuneus (Teicher *et al.* 2014) in individuals exposed to childhood maltreatment. The precuneus plays a critical role in self-referential processing (Cavanna & Trimble, 2006). Childhood maltreatment has been associated with an increase in negative self-associations, which are postulated to further enhance negative bias when engaged in new situations, leading to the development and maintenance of affective disorders after exposure to childhood maltreatment (van Harmelen *et al.* 2010). Hence, the abuse-specific deficit in the precuneus may possibly be related to

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disturbances in self-referential processing in victims of childhood abuse, making them more vulnerable to the development and maintenance of psychopathology.

The possibly abuse-specific increased middle temporal CV is also novel. The middle temporal lobe is involved in moral function and intention attributions, and its dysfunction is often implicated in violent psychopathy (Sommer *et al.* 2010; Fumagalli & Priori, 2012). Boys with callous-unemotional conduct problems had greater middle temporal CV than healthy controls (De Brito *et al.* 2009), while thicker middle temporal cortex correlated with higher concurrent psychopathic traits and psychopathic tendencies in adolescents (Yang *et al.* 2015). Thus, the abuse-specific increase in middle temporal CV may possibly serve as a biomarker for the development of psychopathic propensity in later life.

The OFC–limbic–cerebellar structural deficits may possibly underlie the neuropsychological deficits in emotion and reward processing (Pine *et al.* 2005; Weller & Fisher, 2013) and attention (Pollak *et al.* 2010) observed in childhood maltreatment. This relationship is further supported by findings of fMRI studies of childhood maltreatment of abnormal OFC–limbic–cerebellar activation during emotion processing. For instance, increased activation in the insula (McCrory *et al.* 2011*b*; Garrett *et al.* 2012) and cerebellum (McCrory *et al.* 2013) relative to controls to angry faces has been reported in maltreated children; together with lower OFC activation to angry faces in severely deprived children (Tottenham *et al.* 2011) and healthy adults exposed to childhood physical abuse (Taylor *et al.* 2006), suggesting a deficit in their emotion-regulation abilities.

Finally, although there were no significant differences in the ROIs between the abuse group and psychiatric controls or between the psychiatric and healthy controls, the brain measurements of the psychiatric controls were in between those of the abuse group and healthy controls. This suggests that the abuse group, by nature of the abuse experience *and* the psychiatric comorbidities, was more adversely impaired than the psychiatric controls.

Among the strengths of this study are that all participants were medication-naïve and drug-free, and their abuse experience was carefully assessed and corroborated by social service records. We also included a psychiatric control group to determine the specificity of childhood abuse in our findings. The inclusion of a childhood abuse group without any psychiatric disorders would have provided a more robust means of determining abuse-specific abnormalities; however, such a 'pure' group would not be representative of the general childhood abuse populations, as large-scale epidemiological and longitudinal studies have consistently reported that childhood maltreatment is linked developmentally to psychiatric disorders (Sugaya *et al.* 2012; Herrenkohl *et al.* 2013; MacMillan *et al.* 2013), and a meta-analysis further reported a causal relationship between non-sexual childhood maltreatment and a range of mental disorders (Norman *et al.* 2012). It is unclear to what extent pubertal development, malnutrition, prenatal drug exposure and presence of current life stressors may have influenced the findings. The SES measure used is limited, as it does not provide information on parents' income and education; however, youth often have difficulties in reporting this information (Currie *et al.* 1997). Although we recruited participants exposed to childhood physical abuse, it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards *et al.* 2003; Trickett *et al.* 2011).

In summary, using medication-naïve, drug-free, carefully assessed age- and gender-matched groups of youth exposed to childhood abuse and psychiatric controls matched on psychiatric comorbidities, we found that childhood abuse is associated with widespread structural abnormalities in the OFC–limbic, cerebellar, parietal, temporal and sensory regions; which likely underlie the abnormal affective, motivational and cognitive functions typically observed in this population.

Supplementary Material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717002392

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