

Paper

Examining the common and specific grey matter abnormalities in childhood maltreatment and peer victimisation

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Background

Early-life interpersonal stress, particularly childhood maltreatment, is associated with neurobiological abnormalities. However, few studies have investigated the neural effects of peer victimisation.

Aims

This study examines common and specific associations between childhood maltreatment, peer victimisation and brain structural alterations in youths.

Method

Grey matter volume (GMV) and cortical thickness data were collected from 105 age- and gender-matched youths (age range: 17–21 years). Region-of-interest and whole-brain analyses were conducted.

Results

For the region-of-interest analyses, the childhood maltreatment group had smaller GMV than controls in left inferior frontal gyrus, bilateral anterior insula, postcentral and lingual regions, which were associated with greater emotional abuse, along with smaller insular GMV than the peer victimisation group, who had smaller left lingual and postcentral GMV than controls. At the whole-brain level, both childhood maltreatment and peer victimisation groups had smaller GMV than controls in a cluster comprising left post/precentral, inferior frontal gyrus, insula, superior parietal and supramarginal gyri. The peer victimisation group alone had increased cortical thickness in a cluster

comprising left superior frontal, anterior cingulate and medial orbitofrontal gyri, which was related to greater cyberbullying.

Conclusions

Early-life interpersonal stress is associated with common structural alterations of the inferior frontal-limbic, sensory and lingual regions involved in cognitive control, emotion and sensory processing. The findings of childhood-maltreatment-related reduced anterior insular GMV and peer-victimisation-related increased cortical thickness in the left medial prefrontal-anterior cingulate cluster underscore the distinctive negative effects of childhood maltreatment and peer victimisation, and suggest that peer victimisation, particularly cyberbullying, could be as detrimental as childhood maltreatment.

Keywords

Childhood experience; trauma; imaging; neuroanatomy; social deprivation.

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Childhood maltreatment

There is an increasing interest in understanding the effects of early adverse developmental experiences. Childhood maltreatment, which includes physical, sexual and emotional abuse and neglect, is common worldwide, with paediatric prevalence rates of 13–36%.¹ It has been associated with a host of adverse consequences, including abnormal error processing² and impaired attention, inhibition, emotion and reward processing.^{3,4} Large-scale epidemiological studies found that childhood maltreatment is significantly associated with first onsets of various psychiatric disorders, including mood, anxiety and substance use disorders.⁵ The psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of neural underpinnings.⁶

Several structural magnetic resonance imaging (MRI) studies found that childhood maltreatment is associated with grey matter volume (GMV) abnormalities, particularly in the inferior frontal gyrus (IFG)⁷ and limbic regions,⁸ as well as the somatosensory and visual regions.^{9,10} Meta-analytical studies showed that childhood maltreatment is associated with GMV reductions in prefrontal cortex (PFC)-limbic¹¹ and ventrolateral PFC-limbic-temporal and somatosensory regions that are known to mediate cognitive control, emotion and sensory processing, which are typically compromised in this population.¹² Furthermore, recent large-scale

transdiagnostic studies have found that childhood maltreatment is linked to inferior frontal GMV reductions,¹³ whereas emotional childhood trauma is associated with GMV alterations in the PFC-limbic and sensory networks.¹⁴

Maltreated young people also had reduced cortical thickness in the frontal-limbic and sensory^{15,16} regions. In adults, reduced left somatosensory cortical thickness was associated with childhood sexual and emotional abuse,¹⁷ whereas individuals exposed to domestic violence during childhood had reduced cortical thickness in bilateral lingual gyri.¹⁰

Peer victimisation

Peers are important for a child's social development, but they can also be a substantial source of interpersonal stress during childhood. Peer victimisation is characterised by repetitive aggressive behaviour engaged in by an individual or peer group, with the intention to cause harm to the victim.¹⁸ It can take several forms, including overt confrontation between the perpetrator and the victim, as well as relational aggression, reputational aggression and ostracism. Peer victimisation is a serious global issue, with paediatric prevalence rate of 30%.¹⁹ Several large-scale prospective studies reported that peer victimisation has deleterious developmental and mental health outcomes, including poor school performance and

development of psychiatric disorders such as anxiety and depression.²⁰ Cohort studies in the UK and USA even found that peer victimisation in childhood had worse long-term adverse effects on young adults' mental health than childhood maltreatment.²¹

The field of early-life stress has made much progress in documenting the neurobiological effects of childhood maltreatment, but research investigating neural alterations in peer victimisation is relatively limited. Peer victimisation has been associated with decreased medial orbitofrontal cortex (OFC)²² GMV and increased fusiform cortical thickness.²³ However, it remains unclear if the structural abnormalities observed were specifically associated with peer victimisation, given that childhood maltreatment and peer victimisation have additive effects on mental health outcomes and maltreated children are at increased risk of subsequent victimisation by peers, possibly via altered neurocognitive functioning.²⁴ Therefore, it is imperative that studies examine peer victimisation in the absence of prior exposure to childhood maltreatment from carers.

MAOA gene

Although childhood trauma is an important risk factor for several psychiatric disorders, it does not invariably lead to dysfunction. It is recognised that genetic differences influence the likelihood that trauma exposure will result in psychopathology. The monoamine oxidase type A (*MAOA*) gene, which selectively metabolises serotonin, norepinephrine and dopamine,²⁵ has emerged as an important genetic factor in relation to psychopathology. The *MAOA* influences the regulation of the hypothalamic-pituitary-adrenal axis response to stress, which may occur through the hippocampus and other limbic areas. Corticosteroids have a profound effect on cells in the hippocampus through hippocampal glucocorticoid receptors, where chronic stress can cause hippocampal atrophy.²⁶ Furthermore, stress interacts with the *MAOA* gene, resulting in differences in hippocampal activation and functional connectivity with other limbic regions during emotional tasks.²⁷

Therefore, the aim of this study was to examine the common and specific neural effects of childhood interpersonal stress from carers (childhood maltreatment) and peers (peer victimisation), by conducting both region-of-interest (ROI) and whole-brain structural (GMV, cortical thickness) analyses on a community sample of healthy youths free from psychopathology, drug misuse and medications. Given that childhood maltreatment is associated with GMV deficits in inferior frontal-limbic and sensory regions,^{11,12} we hypothesised that the childhood maltreatment group, and the peer victimisation group to a lesser extent, would have structural abnormalities particularly in the IFG, insula, postcentral and lingual regions. We also explored the interactional effects of exposure to childhood interpersonal stress (childhood maltreatment and peer victimisation) and *MAOA* genotype on the hippocampus, the most stress-sensitive structure in the brain.

Method

Participants

Potential participants were recruited from the community via advertisement in social clubs and organisations and on social media. Exclusion criteria were childhood sexual abuse, drug abuse, psychotropic medications, neurological abnormalities, brain injuries, intellectual disabilities and a history of or current psychiatric disorders. We first conducted a thorough pre-screening interview via phone to assess the inclusion/exclusion criteria and severity of the early-life stressful experiences by using the Childhood Trauma Questionnaire (CTQ),²⁸ Revised-Peer Experiences Questionnaire (RPEQ)²⁹ and European

Cyberbullying Intervention Project Questionnaire (ECIPQ).³⁰ Inclusion criteria for the childhood maltreatment group were non-sexual maltreatment from carers before the age of 13 years, scoring above the cut-off for moderate severity on at least one of the CTQ subscales, but no experience of peer bullying. Inclusion criteria for the peer victimisation group were frequently bullied by peers before the age of 13 years, scoring at least 'a few times'/'once a month' on the RPEQ and ECIPQ, but no history of maltreatment from carers (scoring below the cut-offs for none/low severity on all the CTQ subscales). The control group should not have any experience of maltreatment from carers and victimisation from peers (scoring below the same cut-offs as above). Interested volunteers that were deemed suitable were next invited to participate in the study, and those who were unsuitable were notified and their information deleted immediately during this stage. A total of 108 youths (35 in the childhood maltreatment group, 35 in the peer victimisation group and 38 controls; age range: 17–21 years) participated in the study.

All participants and their guardians provided written informed consent and were reimbursed. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the Nanyang Technological University (NTU)'s Institutional Review Board (approval number IRB-2018-01-025) and all MRI scans were reviewed by a neuroradiologist.

Study design and procedure

The study consisted of a face-to-face interview and an MRI session that took place either on the same day or on different days within a 1-week period. During the interview session, all participants completed the following: DSM-5 Level-1 Cross-Cutting Symptom Measure and the KSADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version) interviews for psychopathology, Strengths and Difficulties Questionnaires (SDQ),³¹ Beck Depression Inventory (BDI),³² Beck Anxiety Inventory (BAI)³³ and the Negative and Positive Affect Scale (NAPAS).³⁴ The Childhood Experience of Care and Abuse (CECA) interview³⁵ was used to corroborate the CTQ. IQ was assessed with the Wechsler Abbreviated Scale of Intelligence.³⁶ Socioeconomic status was measured with six items (on parental educational level, housing size and type) from the Family Affluence Scale.³⁷ Lastly, recent stressful life events (RSLEs) was assessed with common stressors adapted from the Life Event Questionnaire for Adolescents,³⁸ where participants rated the 12-month incidence and distress level of each stressor. A total RSLE score was calculated by summing the number of items that were rated as quite or very stressful. In the present study, the internal consistency of the questionnaires ranged from 0.88 to 0.93.

Imaging acquisition and processing

All participants underwent high-resolution T1-weighted MRI on a 3T Siemens MAGNETOM Prisma (Siemens Healthcare GmbH, Germany) at NTU, with a 64-channel head coil and a MPRAGE sequence (repetition time 2200 ms, echo time 2.28 ms, T1 = 994 ms, 208 slices, isotropic voxel size 1 mm³, flip angle 8° and field of view 260 mm).

Images were first visually inspected for artefacts and structural abnormalities. Next, GMV and cortical thickness analyses were conducted with voxel-based morphometry and surface-based morphometry, respectively, using the standard fully automated processing pipelines with default parameters in the Computational Anatomy Toolbox (CAT12.8 for Windows; www.neuro.uni-jena.de/cat/) implemented in SPM12 version 7771 (Statistical

Parametric Mapping for Windows; Wellcome Centre for Human Neuroimaging, London, UK; <https://www.fil.ion.ucl.ac.uk/spm>). After pre-processing, all scans were passed through the automated image quality check protocol in the CAT12 toolbox, and only participants with a minimum weighted average score of B+ in the quality reports were included.³⁹ Finally, the scans were smoothed with a smoothing Gaussian kernel of 8 mm full width at half maximum (FWHM) for GMV data and 15 mm FWHM for cortical thickness data. The Neuromorphometrics (GMV) and DK40 (cortical thickness) atlases in CAT12 were used for anatomical labelling and ROI extraction. Prior research confirmed that CAT12 accurately measures cortical thickness and can be considered a fast and reliable alternative to FreeSurfer.⁴⁰

A general linear model was computed for each morphometric measure (GMV and cortical thickness), with group as a between-participant factor, controlling for RSLE (and total intracranial volume (TIV) for GMV analysis). A cluster threshold of $P < 0.05$ family-wise error (FWE) correction for multiple comparisons was used for the analyses.

Statistical analysis

Statistical analyses were carried out with Statistical Package for the Social Sciences (SPSS) version 26 (for Windows; SPSS Inc., Chicago, IL, USA). Demographic and clinical data were analysed with ANOVA and *post hoc t*-tests adjusted for multiple comparisons, whereas χ^2 -test and Fisher's exact test were used for categorical demographic variables. Pearson correlations were used to explore associations between brain metrics and psychological measures within each group. As the ROIs examined were defined *a priori* and identified independently based on earlier studies, no adjustment for multiple comparisons was made.

MAOA genotyping

DNA was extracted from buccal samples, using the routinely available QIAamp Fast DNA Tissue Kit. After laboratory quality control procedures to evaluate DNA integrity and concentration, all samples were genotyped with the Sequenom Mass ARRAY[®] primer extension assay. All single nucleotide polymorphism genotyping assays were designed with the Sequenom MassARRAY[®] genotyping platform, as previously described.⁴¹

Individuals were stratified and compared based on homozygous major allele carriers for the ten common assayable MAOA single nucleotide polymorphisms (*rs2235186*, *rs3788862*, *rs3027407*, *rs1465107*, *rs5953210*, *rs2072743*, *rs1137070*, *rs979606*, *rs6323*, *rs3027400*). Exploratory gene×environment analysis was conducted on the bilateral hippocampal GMV, using ANOVA with group (childhood stress: childhood maltreatment and peer victimisation versus controls) and MAOA genotype as between-participant factors, in SPSS version 26.

Results

Participant characteristics

All participants self-reported no history of or current psychiatric disorders, and the information was further corroborated with the DSM-5 Level-1 Cross-Cutting Symptom Measure and the SADS interviews. They also reported no head trauma injuries or loss of consciousness, and had not committed any bullying acts currently or in the past. One participant from the childhood maltreatment group and two participants from the control group had to be excluded because of MRI motion artefacts; they were hence excluded from all analyses. The final sample consisted of 105 participants (34 in the childhood maltreatment group, 35 in the peer victimisation group and 36 controls).

The three groups did not differ significantly in age, gender, IQ, ethnicity and socioeconomic status (Table 1). As expected, the childhood maltreatment and peer victimisation groups scored significantly higher than controls on the BDI, BAI, NAPAS negative affect scale, RSLEs and SDQ emotional and total difficulties ($P < 0.01$), but lower than controls on the NAPAS positive affect scale ($P < 0.001$); nevertheless, their depression and anxiety scores were still within normative range below the cut-offs for moderate severity on the BDI and BAI, respectively. The childhood maltreatment and peer victimisation groups did not differ from each other, except on SDQ peer problems, where the peer victimisation group had the highest score (Table 1). RSLE score was used as a covariate in all subsequent analyses to avoid confounding the effects of early-life stress with recent stressors.

ROI analysis

GMV

Relative to controls, the childhood maltreatment group had significantly reduced GMV in left postcentral ($F(1,66) = 6.72$, $P = 0.012$), IFG ($F(1,66) = 4.09$, $P = 0.047$), anterior insula ($F(1,66) = 4.05$, $P = 0.048$) and bilateral lingual (left: $F(1,66) = 4.07$, $P = 0.048$; right: $F(1,66) = 3.95$, $P = 0.049$) regions, as well as marginally smaller GMV in right anterior insula ($F(1,66) = 3.53$, $P = 0.065$) and postcentral ($F(1,66) = 3.70$, $P = 0.059$) regions (Table 2).

Compared with controls, the peer victimisation group exhibited significantly smaller left lingual GMV ($F(1,67) = 4.48$, $P = 0.038$) and marginally smaller right IFG ($F(1,67) = 3.63$, $P = 0.061$) and left postcentral ($F(1,67) = 3.68$, $P = 0.059$) GMV. The peer victimisation group had marginally larger bilateral (right: $F(1,65) = 3.89$, $P = 0.050$; left: $F(1,65) = 3.63$, $P = 0.061$) anterior insula GMV than the childhood maltreatment group, thereby suggesting that the reduced anterior insula GMV may be abuse-related whereas the reduced left lingual and postcentral GMV may be related to exposure to early-life interpersonal stress from carers or peers (Table 2).

Cortical thickness

Relative to controls, the childhood maltreatment group had significantly reduced left lingual cortical thickness ($F(1,67) = 6.07$, $P = 0.016$), whereas the peer victimisation group had significantly increased cortical thickness in right insula ($F(1,68) = 5.20$, $P = 0.026$) and marginally increased in the left IFG ($F(1,68) = 3.87$, $P = 0.050$) (Table 2).

Whole-brain analysis

GMV

The childhood maltreatment group had significantly reduced GMV in a cluster comprising left post/precentral, IFG, insula, superior parietal and supramarginal gyri relative to controls ($P = 0.018$, FWE-corrected) (Table 3, Fig. 1). Mean GMV values of the significant cluster were next extracted for comparison with the peer victimisation group, using analysis of covariance with RSLEs and TIV as covariates. The peer victimisation group also had significantly reduced GMV relative to controls ($F(1,67) = 12.3$, $P = 0.001$) only, which was furthermore related to higher ECIPQ cyberbullying score ($r = -0.36$, $P = 0.036$, 95% CI -0.67 to -0.03) within the peer victimisation group.

Cortical thickness

The peer victimisation group had significantly increased cortical thickness in a cluster comprising the left superior frontal, (rostral) anterior cingulate (ACC) and medial OFC relative to the childhood maltreatment group ($P = 0.011$, FWE-corrected) (Table 4, Fig. 2).

Table 1 Demographic characteristics of 34 youths exposed to childhood maltreatment, 35 youths exposed to peer victimisation and 36 controls

Characteristic	Childhood maltreatment group (<i>n</i> = 34)		Peer victimisation group (<i>n</i> = 35)		Control group (<i>n</i> = 36)		Analysis ^{a,b}		
	Mean	s.d.	Mean	s.d.	Mean	s.d.	<i>F</i> (2,102)	<i>P</i> -value	Group comparisons
Age (years) ^c	19.9	1.60	20.1	1.64	20.1	1.64	0.14	Not significant	–
IQ	104.3	10.3	102.8	8.34	102	7.27	0.61	Not significant	–
Socioeconomic status ^d	14.8	4.11	16.7	3.86	16.1	3.31	2.52	Not significant	–
Recent stressful life events scale	1.25	1.05	1.36	1.37	0.31	0.68	10.1	<0.001	Peer victimisation, childhood maltreatment > controls
Beck Depression Inventory	8.97	7.01	9.88	8.94	3.09	3.69	9.92	<0.001	Peer victimisation, childhood maltreatment > controls
Beck Anxiety Inventory	8.13	8.52	9.03	10.2	2.31	3.45	7.36	0.001	Peer victimisation, childhood maltreatment > controls
Negative and Positive Affect Scale									
Negative affect	11.8	4.04	12.4	5.84	8.14	2.76	9.46	<0.001	Peer victimisation, childhood maltreatment > controls
Positive affect	17.5	4.72	17.9	4.57	23.1	3.20	19.2	<0.001	Peer victimisation, childhood maltreatment < controls
Strengths and Difficulties Questionnaire									
Emotional problems	4.03	2.02	3.94	2.47	2.17	1.54	9.00	<0.001	Peer victimisation, childhood maltreatment > controls
Conduct problems	1.81	1.55	1.85	1.48	1.17	1.10	2.58	(0.08)	–
Hyperactivity	4.06	2.34	3.42	2.37	2.69	2.26	2.95	(0.06)	–
Peer problems	2.28	1.63	3.03	1.70	1.57	1.36	7.37	0.001	Peer victimisation > controls, childhood maltreatment < controls
Prosocial	7.53	1.92	7.88	1.80	8.54	1.48	2.96	(0.06)	Childhood maltreatment < controls
Externalising	5.87	3.37	5.27	3.22	3.86	2.96	3.58	0.032	Childhood maltreatment > controls
Internalising	6.31	2.89	6.97	3.34	3.74	2.48	11.7	<0.001	Peer victimisation, childhood maltreatment > controls
Total difficulties score	12.2	5.31	12.2	5.75	7.60	4.35	9.14	<0.001	Peer victimisation, childhood maltreatment > controls
Childhood Trauma Questionnaire									Severity classification
Physical abuse	14.4	3.99	6.76	1.52	5.23	0.55	134.2	<0.001	Childhood maltreatment > peer victimisation, controls
Emotional abuse	17.6	3.45	8.18	2.21	5.71	0.96	223.6	<0.001	Childhood maltreatment > peer victimisation, controls
Physical neglect	9.97	2.56	6.52	2.09	5.60	1.06	44.4	<0.001	Childhood maltreatment > peer victimisation, controls
Emotional neglect	17.4	3.30	9.79	3.41	6.63	2.16	112.0	<0.001	Childhood maltreatment > peer victimisation, controls
CTQ total ^e	59.3	8.54	31.2	6.78	23.2	3.43	278.6	<0.001	Childhood maltreatment > peer victimisation, controls
Revised Peer Experience Questionnaire									
Relational victimisation	1.44	1.78	8.79	2.55	0.43	0.78	206.7	<0.001	Peer victimisation > childhood maltreatment, controls
Overt victimisation	1.22	2.03	10.7	4.83	0.06	0.24	126.5	<0.001	Peer victimisation > childhood maltreatment, controls
Reputational victimisation	1.41	2.34	9.33	2.27	0.14	0.49	234.1	<0.001	Peer victimisation > childhood maltreatment, controls
European Cyberbullying Intervention Project Questionnaire	1.47	2.90	10.5	7.21	0.66	1.06	49.3	<0.001	Peer victimisation > childhood maltreatment, controls
Gender (males)	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	χ^2	<i>P</i> -value	Group comparisons
Ethnicity ^f									
Chinese	30	88	27	77	35	97	0.81	Not significant	–
Malay	3	9	3	9	0	0	9.22	Not significant	–
Indian	1	3	5	14	1	3			

a. Tests adjusted for multiple comparisons.

b. The values in parentheses are marginally statistically significant.

c. The age range is 17–21 years.

d. The socioeconomic status total score ranges from 6 to 26, with higher values indicating higher status.

e. The total score is the sum of the physical abuse, emotional abuse, physical neglect and emotional neglect scores.

f. The Fisher's exact test was used.

This significant medial PFC (mPFC)-ACC cluster was next extracted for comparison with controls, using analysis of covariance with RSEs as a covariate. The peer victimisation group also had significantly increased cortical thickness relative to controls ($F(1,68) = 10.1, P = 0.002$), which was furthermore related to higher ECIPQ

cyberbullying score ($r = 0.34, P = 0.045, 95\% \text{ CI } 0.08\text{--}0.66$) within the peer victimisation group. There were no significant differences between childhood maltreatment and control groups. Hence, the observed atypical increased cortical thickness of the mPFC-ACC cluster may be related to exposure to peer bullying.

Table 2 Group differences in grey matter volume and cortical thickness of the regions of interest

Brain region	Peer victimisation group (n = 35)		Peer victimisation group (n = 35)		Control group (n = 36)		Group comparisons ^{a,b}									
	Mean	s.d.	Mean	s.d.	Mean	s.d.	Childhood maltreatment versus control		Peer victimisation versus control		Childhood maltreatment versus peer victimisation					
							F	P-value	F	P-value	F	P-value				
Inferior frontal gyrus																
Left GMV	3.51	0.30	3.57	0.39	3.66	0.45	4.09	0.047	Childhood maltreatment < controls	2.18	Not significant	–	0.39	Not significant	–	
Right GMV	3.55	0.37	3.57	0.38	3.72	0.56	2.42	Not significant	–	3.63	(0.061)	(Peer victimisation < controls)	0.01	Not significant	–	
Pars opercularis																
Left cortical thickness	3.09	0.11	3.14	0.14	3.09	0.13	0.01	Not significant	–	3.87	0.050	Peer victimisation > controls	2.73	Not significant	–	
Right cortical thickness	3.12	0.10	3.13	0.13	3.11	0.14	0.07	Not significant	–	1.65	Not significant	–	0.17	Not significant	–	
(Anterior) Insula																
Left GMV	4.74	0.37	4.94	0.58	4.92	0.47	4.05	0.048	Childhood maltreatment < controls	0.24	Not significant	–	3.63	(0.061)	(Childhood maltreatment < peer victimisation)	
Right GMV	4.86	0.40	5.08	0.64	5.04	0.49	3.53	(0.065)	(Childhood maltreatment < controls)	0.17	Not significant	–	3.89	0.050	Peer victimisation > childhood maltreatment	
Left cortical thickness ^c	3.72	0.24	3.76	0.22	3.78	0.20	0.23	Not significant	–	3.16	Not significant	–	0.98	Not significant	–	
Right cortical thickness	3.69	0.27	3.75	0.22	3.67	0.20	1.59	Not significant	–	5.20	0.026	Peer victimisation > controls	1.13	Not significant	–	
Postcentral gyrus																
Left GMV	10.0	0.96	10.3	1.01	10.7	0.92	6.72	0.012	Childhood maltreatment < controls	3.68	(0.059)	(Peer victimisation < controls)	1.34	Not significant	–	
Right GMV	9.10	0.82	9.41	1.09	9.65	1.00	3.70	(0.059)	(Childhood maltreatment < controls)	1.09	Not significant	–	2.06	Not significant	–	
Left cortical thickness	2.38	0.11	2.41	0.11	2.43	0.13	2.81	Not significant	–	0.09	Not significant	–	1.47	Not significant	–	
Right cortical thickness	2.38	0.11	2.40	0.11	2.42	0.14	0.78	Not significant	–	0.01	Not significant	–	0.61	Not significant	–	
Lingual gyrus																
Left GMV	6.79	0.73	6.94	0.63	7.07	0.78	4.07	0.048	Childhood maltreatment < controls	4.48	0.038	Peer victimisation < controls	0.86	Not significant	–	
Right GMV	7.34	0.81	7.50	0.87	7.63	0.84	3.95	0.049	Childhood maltreatment < controls	1.84	Not significant	–	0.63	Not significant	–	
Left cortical thickness	2.22	0.11	2.25	0.12	2.27	0.11	6.07	0.016	Childhood maltreatment < controls	1.00	Not significant	–	1.00	Not significant	–	
Right cortical thickness	2.26	0.14	2.27	0.13	2.28	0.12	0.78	Not significant	–	0.05	Not significant	–	0.29	Not significant	–	

GMV, grey matter volume.

a. Group differences in GMV were conducted with total intracranial volume and recent stressful life events (RSLE) score as covariates. Group differences in cortical thickness were conducted with RSLE score as a covariate.

b. The values in parentheses are marginally statistically significant.

c. Cortical thickness of the whole insula.

Table 3 Group differences in grey matter volume in the whole-brain analysis

Brain regions	Peak MNI coordinates (x, y, z)	Cluster size (voxels)	P-value of cluster (FWE-corrected)	Group comparisons ^{a,b}
Left postcentral/ Precentral/inferior frontal/ insula/superior parietal/supramarginal gyrus	-42, -11, 30 -62, 8, 6 -47, -14, 24	3685	0.018	Childhood maltreatment < controls

MNI, Montreal Neurological Institute, FWE, family-wise error.
a. Group differences in grey matter volume were conducted with total intracranial volume and recent stressful life events score as covariates.
b. The cluster was also found to be significantly reduced in the peer victimisation group relative to the control group only.

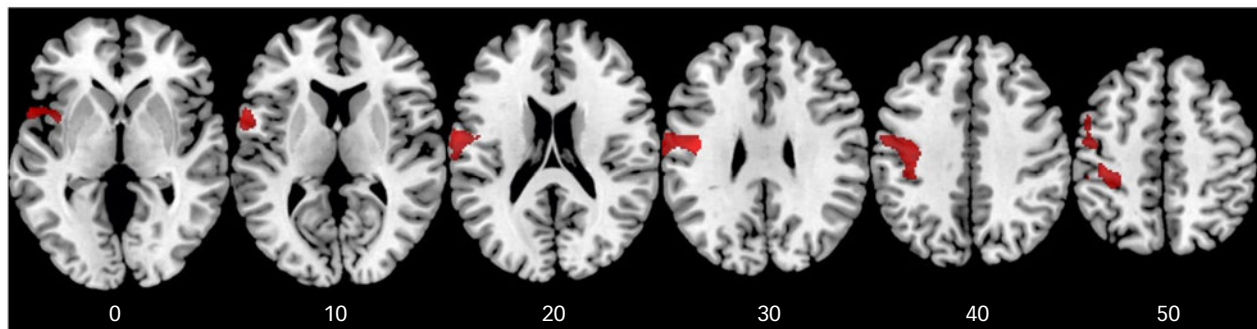


Fig. 1 Axial sections of grey matter volume reduction in the childhood maltreatment group compared with the control group (shown in red), as revealed by *F*-test ($P < 0.05$), family-wise error-corrected at the cluster level. The cluster was also significantly reduced in the peer victimisation group relative to the control group only. Axial slices are marked with the z-coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

Exploratory correlational analysis

For the childhood maltreatment group, higher CTQ emotional abuse score was significantly associated with reduced GMV in the bilateral insula (left: $r = -0.37$, $P = 0.034$, 95% CI -0.70 to -0.03 ; right: $r = -0.51$, $P = 0.002$, 95% CI -0.81 to -0.20), lingual (left: $r = -0.43$, $P = 0.011$, 95% CI -0.75 to -0.10 ; right: $r = -0.52$, $P = 0.002$, 95% CI -0.82 to -0.21), left IFG ($r = -0.40$, $P = 0.018$, 95% CI -0.73 to -0.07) and right postcentral ($r = -0.36$, $P = 0.037$, 95% CI -0.69 to -0.03) regions. Reduced right lingual GMV was also associated with higher CTQ emotional neglect ($r = -0.39$, $P = 0.024$, 95% CI -0.71 to -0.06) and total CTQ ($r = -0.37$, $P = 0.031$, 95% CI -0.70 to -0.04) scores.

Exploratory gene×environment analysis

There was a significant stress×MAOA effect on the bilateral hippocampal GMV (left: $P < 0.01$; right: $P < 0.05$), resulting from childhood stress-exposed youths without the homozygous major alleles having significantly smaller hippocampal GMV than childhood stress-exposed homozygous major allele carriers and childhood stress-unexposed controls without the homozygous major alleles (Table 5, Fig. 3).

Discussion

Both parent and peer relationships have been proposed to have an impact on the brain development of young people, yet little research has examined the common and specific neural effects associated with being maltreated by carers and bullied by peers. Moreover, given that childhood maltreatment and peer victimisation have additive effects on mental health outcomes,²⁵ it is imperative for studies to examine peer victimisation in the absence of exposure to adverse caregiving, and to examine childhood maltreatment in

the absence of exposure to peer bullying. To our knowledge, this is the first MRI study to do so in a sizable community youth sample free from psychopathology, medications and drug abuse and controlled for the number of RSLEs. This is crucial to elucidate the effects of early-life stress independently from confounding effects associated with recent stressors, psychiatric diagnosis, medications and drug abuse.¹²

For the ROI analysis, the childhood maltreatment group had reduced left IFG, bilateral anterior insula, postcentral and lingual GMV and left lingual cortical thickness relative to controls, as well as reduced bilateral anterior insula GMV relative to the peer victimisation group. The reduced GMV in bilateral anterior insula, lingual, left IFG and right postcentral regions were furthermore associated with higher emotional abuse, whereas the reduced right lingual GMV was associated with higher emotion neglect and total CTQ scores, within the childhood maltreatment group. The peer victimisation group exhibited reduced GMV in left lingual and postcentral regions, along with increased cortical thickness in left IFG and right insula relative to controls.

At the whole-brain level, both the childhood maltreatment and peer victimisation groups had smaller GMV than controls in a cluster comprising left post/precentral, IFG, insula, superior parietal and supramarginal gyri, which was furthermore related to greater cyberbullying within the peer victimisation group. Furthermore, the peer victimisation group had increased cortical thickness in a cluster comprising the left superior frontal, ACC and medial OFC relative to both childhood maltreatment and control groups, which was also related to greater cyberbullying. Hence, our findings suggest that the reduced anterior insula GMV and increased mPFC-ACC cortical thickness may be related to being maltreated by carers and bullied by peers, respectively, whereas the relatively widespread compromised GMV in inferior frontal-limbic, somatosensory and lingual regions may be related to exposure to early-life interpersonal stress. Finally, our

Table 4 Group differences in cortical thickness in the whole-brain analysis

Brain regions	Peak MNI coordinates (x, y, z)	Cluster size (vertices)	P-value of cluster (FWE-corrected)	Group comparisons ^{a,b}
Left superior frontal/rostral anterior cingulate/medial orbitofrontal gyrus	-9, 45, 2 -8, 29, 32 -7, 37, 34	366	0.011	Childhood maltreatment < peer victimisation

MNI, Montreal Neurological Institute; few, family-wise error.
a. Group differences in cortical thickness were conducted with recent stressful life events score as a covariate.
b. The cluster was also found to be significantly reduced in the control group relative to the peer victimisation group only.

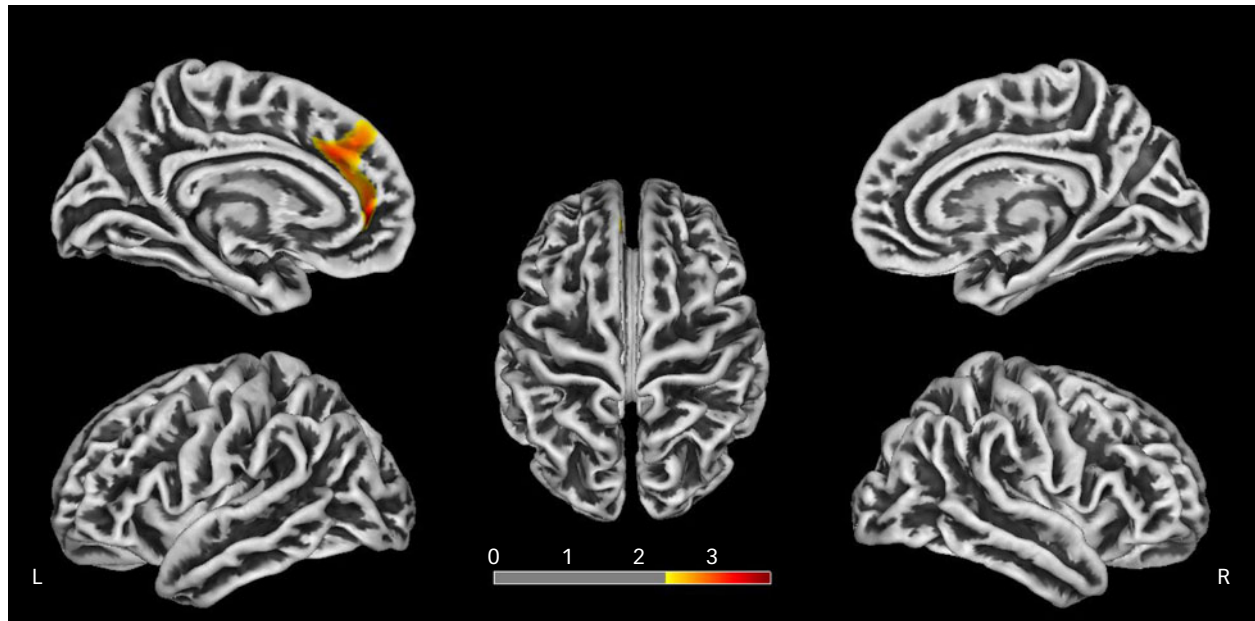


Fig. 2 Significant vertex-wise cortical thickness cluster superimposed on a template reconstruction of brain surface in Montreal Neurological Institute (MNI) space. The significant cluster shows reduced cortical thickness in the childhood maltreatment group compared with the peer victimisation group, as revealed by *F*-test ($P < 0.05$), family-wise error-corrected. The cluster was also significantly reduced in the control group relative to the peer victimisation group only. The colour bar represents *T* statistics.

exploratory childhood stress \times MAOA analysis on the bilateral hippocampal GMV suggests a protective effect of having homozygous major alleles, particularly in the presence of early-life interpersonal stress.

The IFG is a key area of cognitive control, mediating saliency detection, action selection, inhibition and sustained attention.⁴² It is also involved in interpersonal emotion regulation and implementing reappraisal strategies,⁴³ along with linguistic processing in the Broca's area, including processing emotional content of speech.⁴⁴ The IFG has been proposed as part of the trauma-disrupted network, where the left IFG, in particular, is implicated in processing aversive and trauma-related information.^{45,46} Adolescents exposed to verbal abuse showed hypersensitivity of left IFG to swear words,⁴⁵ whereas women with sexual abuse-related post-traumatic stress disorder exhibited left IFG overactivation to trauma-related words.⁴⁶ A meta-analysis further found that anger stimuli exhibited a greater association with left IFG activation compared with other emotions.⁴⁷ The current finding of reduced left IFG GMV is consistent with our meta-analysis¹² and previous studies in childhood maltreatment.⁷ The association of reduced left IFG with adverse caregiving experiences is further underpinned by the observed correlation with emotional abuse, which has a strong linguistic component.

The insula plays a key role in interoceptive awareness and emotion regulation, where the anterior insula, in particular, is involved in the processing of specific negative emotions including fear and disgust,⁴⁸ which are common in emotional abuse. Studies often implicate the insula in emotion regulation abnormalities in childhood maltreatment. Insula hyperresponsiveness to negative facial expressions has been observed in individuals exposed to childhood maltreatment relative to controls,³ whereas childhood maltreatment scores strongly correlated with insula responsiveness to fearful/angry faces in healthy adults.⁴⁹ The present finding of a possibly abuse-related reduced insula GMV is further supported by the significant correlation with emotional abuse within the childhood maltreatment group, and corroborates earlier findings of insula GMV deficit in childhood maltreatment.⁸ Recent large-scale transdiagnostic studies also underscore the involvement of left (anterior) insula abnormalities in childhood trauma, particularly emotional trauma.¹⁴

Childhood maltreatment has been associated with abnormal development of the sensory systems that relay adverse sensory experiences. Studies reported reduced lingual GMV in women who experienced childhood sexual and physical abuse⁹ and in adolescents exposed to severe childhood maltreatment,¹⁵ as well as reduced lingual cortical thickness in children who experienced

Table 5 Significant group by MAOA genotype on hippocampal grey matter volume

Group	MAOA genotype	Left hippocampal GMV				Right hippocampal GMV			
		Mean	s.d.	Group×MAOA ^a		Mean	s.d.	Group×MAOA ^a	
				F(1,101)	P-value			F(1,101)	P-value
Stress	<i>rs2235186</i>			7.33	0.008			6.80	0.011
	A/A allele	3.40	0.329			3.77	0.327		
Control	G-allele	3.20	0.239			3.57	0.271		
	A/A allele	3.28	0.220	7.15	0.009	3.65	0.260	6.74	0.011
G-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs3788862</i>			7.29	0.008			5.89	0.017
	A/A allele	3.39	0.319			3.77	0.324		
Control	G-allele	3.20	0.249			3.57	0.272		
	A/A allele	3.28	0.220	7.15	0.009	3.65	0.260	6.74	0.011
G-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs3027407</i>			7.15	0.009			6.74	0.011
	A/A allele	3.40	0.314			3.76	0.327		
Control	G-allele	3.20	0.243			3.58	0.274		
	A/A allele	3.28	0.220	7.15	0.009	3.65	0.260	6.74	0.011
G-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs1465107</i>			6.79	0.011			7.17	0.009
	A/A allele	3.39	0.319			3.77	0.324		
Control	G-allele	3.20	0.249			3.57	0.272		
	A/A allele	3.28	0.220	6.79	0.011	3.64	0.265	7.17	0.009
G-allele	3.38	0.238	3.77			0.291			
Stress	<i>rs5953210</i>			8.75	0.004			7.44	0.008
	G/G allele	3.39	0.319			3.77	0.324		
Control	A-allele	3.20	0.249			3.57	0.272		
	G/G allele	3.28	0.226	8.75	0.004	3.64	0.265	7.44	0.008
A-allele	3.37	0.233	3.77			0.291			
Stress	<i>rs2072743</i>			7.79	0.006			6.18	0.015
	T/T allele	3.42	0.314			3.79	0.323		
Control	C-allele	3.20	0.239			3.57	0.271		
	T/T allele	3.28	0.220	7.79	0.006	3.65	0.260	6.18	0.015
C-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs1137070</i>			9.24	0.003			7.75	0.006
	T/T allele	3.40	0.314			3.76	0.327		
Control	C-allele	3.19	0.250			3.57	0.273		
	T/T allele	3.28	0.220	9.24	0.003	3.65	0.260	7.75	0.006
C-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs979606</i>			9.24	0.003			7.75	0.006
	C/C allele	3.42	0.314			3.79	0.323		
Control	T-allele	3.19	0.245			3.56	0.269		
	C/C allele	3.28	0.220	9.24	0.003	3.65	0.260	7.75	0.006
T-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs6323</i>			8.75	0.004			7.44	0.008
	G/G allele	3.42	0.314			3.79	0.323		
Control	T-allele	3.19	0.245			3.56	0.269		
	G/G allele	3.28	0.220	8.75	0.004	3.65	0.260	7.44	0.008
T-allele	3.38	0.238	3.76			0.299			
Stress	<i>rs3027400</i>			8.75	0.004			7.44	0.008
	T/T allele	3.42	0.314			3.79	0.323		
Control	G-allele	3.20	0.239			3.57	0.271		
	T/T allele	3.28	0.220	8.75	0.004	3.65	0.260	7.44	0.008
G-allele	3.38	0.238	3.76			0.299			

MAOA, monoamine oxidase type A; GMV, grey matter volume.
a. Tests were not adjusted for multiple comparisons.

psychosocial deprivation¹⁶ and in young adults who witnessed domestic violence during childhood.¹⁰ Reduced left somatosensory GMV in childhood maltreatment has also been reported in meta-analysis¹² and recent large-scale transdiagnostic studies.¹³ Thus, the current findings of reduced lingual and somatosensory GMV in maltreated individuals relative to controls, which were furthermore correlated with higher emotional abuse with the childhood maltreatment group, are consistent with earlier studies. Importantly, the peer victimisation group also exhibited similar deficits in left lingual (albeit at a marginal level in left somatosensory) GMV relative to controls. Thus, our findings underscore the detrimental effects of peer victimisation and suggest that the sensory systems that process and interpret adverse sensory inputs may be

altered by early traumatic interpersonal experiences from carers or peers.

Our exploratory stress×MAOA analysis on the bilateral hippocampal GMV suggests a 'protective' effect of having homozygous major alleles, particularly in the presence of early-life interpersonal stress. Childhood stress, moderated by genetic vulnerability, is associated with reduced hippocampal GMV and increased vulnerability to depression.⁵¹ Additionally, stress interacts with the MAOA gene, resulting in differences in hippocampal activation and functional connectivity with other limbic regions during emotional tasks,²⁷ where hippocampal deactivation may lead to disinhibition of the hypothalamic-pituitary-adrenal axis and the initiation of stress hormone release under stress. Together, this novel but preliminary evidence

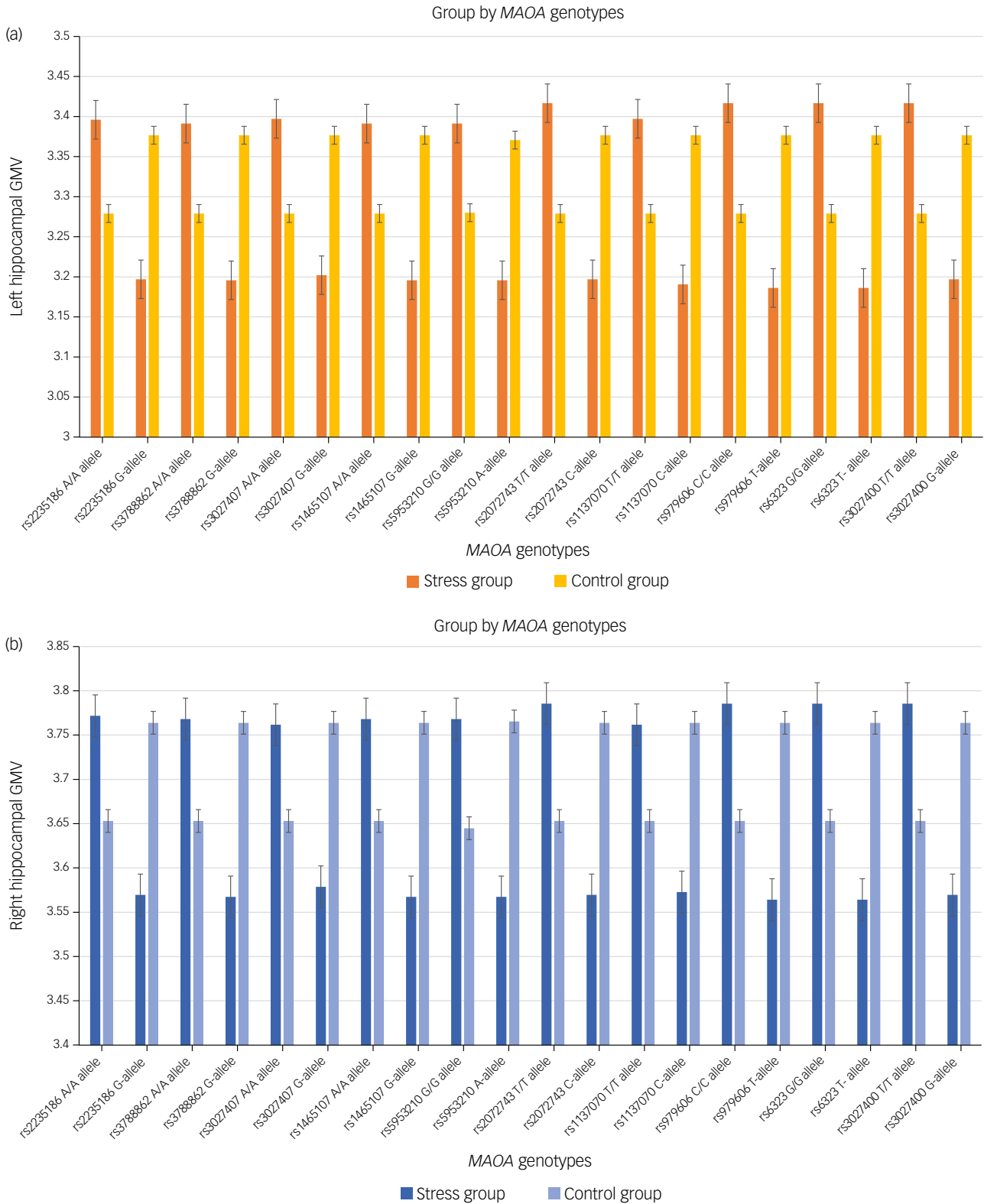


Fig. 3 Significant gene×environment interaction effects between group (childhood stress exposed versus unexposed controls) and MAOA genotype on grey matter volume of (a) left hippocampus and (b) right hippocampus, $P < 0.05$. GMV, grey matter volume; MAOA, monoamine oxidase type A.

suggests that in healthy adolescents, vulnerability to hippocampus alterations may be driven by reduced ‘genetic protection’ in the presence of childhood trauma, which could have implications for targeted prevention of mood disorders.

Finally, although the childhood maltreatment and peer victimisation groups had comparable levels of depression, anxiety, negative affect and SDQ difficulties scores (which were still within normative ranges), they exhibited common and distinct structural


abnormalities. Both the childhood maltreatment and peer victimisation groups exhibited early-life stress related reduced GMV in inferior frontal-limbic, somatosensory and lingual regions, whereas abnormalities in anterior insula GMV are likely to be abuse-related. The peer victimisation group had increased cortical thickness in mPFC-ACC regions relative to the childhood maltreatment and control groups, which may possibly reflect a delayed maturation of the regions and the associated emotion processing capabilities. Only one study had investigated whole-brain cortical thickness abnormalities in peer victimisation, and found that children who were frequently victimised by peers had thicker left fusiform gyrus, which could be related to the development of social anxiety disorder, given the role of the fusiform in processing threatening faces.²³ Furthermore, studies observed increased activity in the rostral and dorsal ACC in chronically peer-victimised and rejection-sensitive adolescents in response to online peer rejection, which was associated with higher levels of internalising symptoms and distress,^{51,52} whereas spending more time with friends reduced ACC response to social exclusion.⁵³ Being rejected based on one's profile pictures also resulted in increased activity in the mPFC.⁵⁴ Adolescents are particularly sensitive to peer rejection, and this is further exacerbated by social media. Cyberbullying has more detrimental effects on adolescent mental health than traditional bullying, and it may be more dangerous as it has an increased potential for a large audience (i.e. the entire virtual world), anonymity and it is not limited to a specific location/time (e.g. during school hours). Given the involvement of the mPFC and ACC regions in appraisal and expression of fear or anxiety, we speculate that the observed thicker mPFC-ACC cluster, which was furthermore correlated with greater cyberbullying, may reflect a delayed maturation of the regions linked to the adolescents' heightened emotional sensitivity to online peer rejection/bullying, and the ensuing immature emotion processing capabilities may increase their risk of developing psychopathology later on.

Strengths and limitations

Among the strengths of this study are that all participants were free from psychopathology, medications and drug abuse; their current stressors were assessed and controlled for; and the early adverse experiences were carefully corroborated by interviews (e.g. CECA). The generalisability of the results may be restricted to the 'more resilient' portion of community youths who did not have any psychiatric disorders despite been exposed to harsh treatment by carers or peers during childhood. Nonetheless, the current findings underscore that early-stress exposed individuals do show neural alterations compared with the early-stress-unexposed controls, even in the absence of psychopathology. Future studies with larger samples should build on the current findings and examine the neural effects of peer victimisation, particularly cyberbullying, in youths. The study is cross-sectional and the findings are still correlational. The gene×environment analysis was exploratory given the sample size and should be interpreted with caution. It is also unclear to what extent malnutrition, levels of social support and duration of early-life stress may have influenced the findings. Finally, the differences in MRI measurements observed may possibly be related to, rather than as direct evidence of, underlying brain structural abnormalities.

In conclusion, early-life interpersonal stress from carers and peers is commonly associated with structural alterations of the inferior frontal-limbic, somatosensory and visual regions that are known to mediate cognitive control, emotion and sensory processing. In addition, childhood maltreatment and peer victimisation may be specifically associated with reduced anterior insula GMV and increased mPFC-ACC cortical thickness, respectively. The

peer-victimisation-related thicker mPFC-ACC cluster, which was furthermore correlated with greater cyberbullying, may suggest a delayed maturation of the regions linked to the adolescents' heightened emotional sensitivity, particularly to online peer rejection/bullying. Our findings underscore the negative effects of being bullied by peers, which is no less detrimental than being maltreated by carers, and the need for future studies to explicitly examine how cyberbullying may affect brain development and increase risk of developing psychopathology in young people.

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Data availability

The data that support the findings of this study are available from the corresponding author, L.L., upon reasonable request.

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Author contributions

L.L. conceived and designed the study, recruited the participants and acquired the data. L.L. and C.C.K. analysed the data. L.L. wrote the manuscript, and both authors reviewed the manuscript.

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Declaration of interest

None.

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