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The effects of childhood maltreatment on cortical thickness and gray matter volume: a coordinate-based meta-analysis

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Review Article

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Abstract

Childhood maltreatment has been suggested to have an adverse impact on neurodevelopment, including microstructural brain abnormalities. Existing neuroimaging findings remain inconsistent and heterogeneous. We aim to explore the most prominent and robust cortical thickness (CTh) and gray matter volume (GMV) alterations associated with childhood maltreatment. A systematic search on relevant studies was conducted through September 2022. The whole-brain coordinate-based meta-analysis (CBMA) on CTh and GMV studies were conducted using the seed-based *d* mapping (SDM) software. Meta-regression analysis was subsequently applied to investigate potential associations between clinical variables and structural changes. A total of 45 studies were eligible for inclusion, including 11 datasets on CTh and 39 datasets on GMV, consisting of 2550 participants exposed to childhood maltreatment and 3739 unexposed comparison subjects. Individuals with childhood maltreatment exhibited overlapped deficits in the median cingulate/paracingulate gyri simultaneously revealed by both CTh and GM studies. Regional cortical thinning in the right anterior cingulate/paracingulate gyri and the left middle frontal gyrus, as well as GMV reductions in the left supplementary motor area (SMA) was also identified. No greater regions were found for either CTh or GMV. In addition, several neural morphology changes were associated with the average age of the maltreated individuals. The median cingulate/paracingulate gyri morphology might serve as the most robust neuroimaging feature of childhood maltreatment. The effects of early-life trauma on the human brain predominantly involved in cognitive functions, socio-affective functioning and stress regulation. This current meta-analysis enhanced the understanding of neuropathological changes induced by childhood maltreatment.

Introduction

Childhood maltreatment, which mainly includes physical, sexual and emotional abuse and neglect, is common worldwide with pediatric prevalence rates of 13–36% (Lim, Howells, Radua, & Rubia, 2020). These adverse early-life experiences involved bio-psycho-social mediators and moderators (Sideli et al., 2020), and have been suggested to be closely related with cognitive decline, attention impairment, emotional dysregulation, and reward anticipation disorder (Hart et al., 2018; Lim et al., 2016), and may even increase the risks of suffering from mental illness, such as posttraumatic stress disorder (PTSD) (Daniels, Lamke, Gaebler, Walter, and Scheel, 2013), major depressive disorder (MDD) (Goltermann *et al.* 2022; Guo *et al.* 2022; Haidl *et al.* 2021), borderline personality disorder (Herzog, Kube, & Fassbinder, 2022), schizophrenia (Cancel, Dallel, Zine, El-Hage, & Fakra, 2019; D'Andrea et al., 2022; Sideli et al., 2020), substance abuse (Hughes et al., 2017), eating disorders (Cascino et al., 2022; Luo et al., 2020), as well as functional somatic and visceral pain syndromes (Chandan et al., 2020). Neurobiology changes of the brain might underlie the occurrence of the above symptoms. The human brain is a highly plastic organ, regulated by genes, but also shaped by environmental factors (Lim, Radua, & Rubia, 2014). Translational animal model also disclosed certain effects of early life adversity on neurodevelopment, indicating the susceptibility of brain structure (Aksić et al., 2013; Penninck et al., 2021; Waters & Gould, 2022). Early interventions were meaningful for preventing the psychosocial impairment of childhood maltreatment. For example, previous evidence has proven that non-pharmacological treatments such as enhancing exercise were effective both in reducing mortality and treating depressive symptoms related with childhood maltreatment (Belvederi Murri et al., 2018; Recchia et al., 2023). Understanding the effects of early environmental adversity on the developing brain and providing perspectives for early interventions were of great importance.

Emerging evidence suggests that early-life adversities alter trajectories of neurodevelopment to affect sensory systems, network architecture and circuit (Teicher, Samson, Anderson, & Ohashi, 2016), on the neural basis of changing the number of neurons, glial cells, dendrites, and synapses, myelination, and influencing neurotransmitter and growth factor activity (Praag, Kempermann, & Gage, 2000). Advances in neuroimaging techniques such as magnetic resonance imaging (MRI) have made it possible to detect neurobiological characteristics in childhood maltreatment-exposed individuals with noninvasive ways. One of the most prominent neuroanatomical differences between maltreated individuals and unexposed controls was microstructural abnormalities in gray matter (GM), including cortical thickness (CTh) and GM volume (GMV) (Hakamata, Suzuki, Kobashikawa, & Hori, 2022; Teicher et al., 2016). Neural plasticity due to childhood experience is significant, with GM being less heritable and more susceptible to early-life stress than white matter (WM) (Lim et al., 2014). Moreover, the surface-based morphometry (SBM) approach served as a vital supplement of voxel-based morphometry (VBM) in the investigation of GM, has unique advantages in exploring the pathological mechanism of neurodevelopmental disorders (Winkler et al., 2010). CTh is considered a heritable and relatively stable structural brain characteristic distinct from GMV (Panizzon et al., 2009). Its measurement avoids part of the volume effect which may lead to inaccurate estimation of brain volume, and it provides a direct quantitative indicator (mm), rather than a qualitative indicator of cortical morphology (Fischl, 2012). As the cerebral cortex develops rapidly during childhood, detailed measurement of CTh can provide key information about cortical maturation with regional changes in development process (Li et al., 2020; Winkler et al., 2010).

Most neuroimaging studies have utilized a region of interest (ROI) analysis approach, primarily estimating within the brain area chosen in advance (Lim et al., 2014). The prefrontal cortex (PFC), hippocampus and amygdala were most frequently assessed in childhood maltreatment (Paquola, Bennett, & Lagopoulos, 2016), which might miss some important information about other brain regions. By comparison, a whole-brain approach can explore alterations throughout the brain to avoid selection bias (Hakamata et al., 2022). A lately published large sample study performed whole-brain vertex-wise SBM in adolescent and adult females with interpersonal violence exposure, and found CTh in the median cingulate cortex was negatively related to early-life trauma in both age groups (Ross, Sartin-Tarm, Letkiewicz, Crombie, & Cisler, 2021). GMV studies achieved by VBM were more widely used, and brain areas involved with memory processing, socio-affective regulation, and executive control, such as the PFC, superior temporal gyrus (STG), hippocampus, anterior cingulate cortex (ACC), and limbic system were frequently reported (Cancel et al., 2019; Lim et al., 2014; Pollok et al., 2022). Functional MRI (fMRI) and diffusion tensor imaging (DTI) studies have yielded similar and complex findings (Hakamata et al., 2022; Lim et al., 2020; Teicher et al., 2016), further confirms the multi-dimensional effects of childhood trauma on the brain development. Disturbance of above regions were also considered to have strong associations with the development of a psychiatric illness. Besides, alterations of the brain morphology and disturbances in neural activities might also occur in healthy people without any psychiatric disorders but exposed to childhood maltreatment (Everaerd et al., 2016; Fan et al., 2022; Lu et al., 2013; Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009a). Therefore, understanding how maltreatment would affect brain microstructures is of crucial significance to prevent, preempt or treat the mental health consequences of early-life abuse and neglect.

Up to now, existing neuroimaging findings of childhood maltreatment were largely inconsistent. The inconsistency of investigation outcomes might be related with the heterogenous cohort demographics, definition of childhood trauma, data collection approaches, and analytical methods. In order to solve the heterogeneity of findings from distinct studies, the coordinate-based meta-analysis (CBMA) emerged as powerful means to comprehensively synthesize the neuroimaging discoveries that were found in a variety of research (Albajes-Eizagirre & Radua, 2018). This method is also able to distinguish between false results and replicable results, and summarize and integrate large amounts of data across studies (Muller et al., 2018). Therefore, the CBMA program is capable of alleviating the impact of research heterogeneity, determining reliable results, and discovering the potential impact of demographic characteristics on neuroimaging. A recent meta-analysis of effects of early-life adversities on GM was conducted using coordinate-based anatomical likelihood estimation (ALE). This study revealed the impacts of early-life trauma on GMV lied in the right hippocampus and amygdala and the left inferior frontal gyrus, age-specific effects for the right amygdala and hippocampus in children and adolescents, and maltreatment-specific effects for the right ACC in adults (Pollok et al., 2022). However, it is a pity that this work failed to include SBM analysis as the number of studies of CTh was insufficient than recommended for ALE ($n < 17$) (Eickhoff et al., 2016). Unlike ALE, the requirements for sample size are less strict for the seed-based *d* mapping (SDM) software (minimum of 10 datasets) (Hu et al., 2020; Muller et al., 2018; Radua & Mataix-Cols, 2009), and the algorithm also considers null results in a meta-analysis. A range of neuropsychiatric studies have applied this approach in the investigations of CTh and VBM (Li et al., 2020, 2022; Shen et al., 2022; Wang et al., 2019; Zhao et al., 2022; Zhu et al., 2022). By utilizing the SDM methods, one meta-analysis of VBM revealed that individuals exposed to childhood maltreatment exhibited decreased GMV in orbitofrontal cortex (OFC) limbic-temporal regions and inferior frontal cortex that mediate top-down affect and cognitive control, respectively; and in the left sensorimotor cortex that mediates sensory functions (Lim et al., 2014). Another meta-analysis focusing on adults with childhood trauma experience demonstrated the most robust findings of the whole-brain VBM were reductions of GM in the right dorsolateral PFC and right hippocampus (Paquola et al., 2016). These findings extended our knowledge of the effects of childhood maltreatment on microstructural brain abnormalities. However, these two studies both performed about seven years ago. As far as we are concerned, an updated and comprehensive meta-analysis containing both SBM and VBM studies is in need.

The purpose of this current CBMA is to identify the most noticeable and robust CTh and GMV alterations in individuals with a history of childhood trauma. The potential associations between clinical characteristics (average age, IQ, onset age of childhood maltreatment, as well as duration of maltreatment) and reported structural alterations were also explored by employing the meta-regression method. Additionally, we also intended to perform sub-group analyses of different age groups (youths *v.* adults). According to previous structural MRI (sMRI) studies (Maier et al., 2020; Opel et al., 2016; Paquola et al., 2016;

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Pollok et al., 2022), we assumed that individuals with childhood maltreatment experience would exhibit anatomical alterations in core brain areas such as the cingulate cortex and frontal gyrus.

Methods

Search strategy and selection criteria

The protocol of this present CBMA has been recorded in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) (registration number: CRD42022342543). This meta-analysis was implemented in accordance with the Preferred Reporting Standards for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & Group, 2009a, 2009b). Relevant literatures were obtained from the PubMed and Web of Science databases published (or 'in press') until 30 September 2022. We applied ('childhood maltreatment' or 'childhood trauma' or 'child abuse' or 'early stress' or 'early-life trauma' or 'childhood adversities') and ('cortical thickness' or 'cortical thinning' or 'thickness' or 'FreeSurfer' or 'VBM' or 'voxel-based morphometry' or 'voxel-wise' or 'morphometry' or 'gray matter') as the keywords in this present meta-analysis. In addition, in order to prevent omission, the reference lists of the included articles were manually reviewed.

Study selection strategy

We included studies that meet these specifications: (1) original research written in English and published in journals with peer review; (2) applied the SBM or VBM approach to explore CTh or GMV differences; (3) provided a comparison between individuals with and without childhood maltreatment experience or reporting the main effects of childhood maltreatment regarding CTh or GMV alterations in whole-brain assessments; (4) provided the coordinates of significant clusters in Montreal Neurological Institute (MNI) or Talairach space; (5) used a statistical threshold. The exclusion standards were as below: (1) case reports, reviews, meta-analyses, and theoretical papers; (2) there was no straight comparison between groups or no main effect of childhood maltreatment was reported; (3) limited to ROI analysis; (4) the peak coordinates were not available.

Quality evaluation and data acquisition

Following rules for neuroimaging meta-analyses promoted by Müller and colleagues (Muller et al., 2018), two authors (W.Y. and S.J.) independently searched the literatures, evaluated the quality of the retrieved articles, recorded and cross-checked the data from qualified studies. The following data were extracted for each research: first author, cohort size, demographics (age, gender, IQ), onset age of childhood maltreatment, duration of maltreatment, maltreatment types, and comorbid disorders. The data for SDM estimation was also collected, including the coordinates of primary findings and effect size values (e.g. t statistics, Z score, and p value).

SDM meta-analysis

We performed the meta-analysis applying the SDM program v5.15 (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019; Radua & Mataix-Cols, 2009) (http://www.sdmproject.com) to compare regional CTh and GMV alterations in individuals with a history of childhood maltreatment compared to those unexposed comparison subjects. A recent mask created by FreeSurfer was utilized to achieve the meta-analysis of CTh investigations (Li et al., 2020). Our present analyses were conducted in terms of the standardized SDM tutorial and previous meta-analytic studies.

The SDM algorithm does not simply evaluate the probability of the peak, but uses the effect size, combines the notified peak coordinates obtained from the dataset with the statistical parameters, and reestablishes the traditional map of the effect size between groups (Radua et al., 2012). The details of the SDM procedures have been described elsewhere (Li et al., 2022; Qiu & Wang, 2021; Tian et al., 2020; Zhao et al., 2022; Zhu et al., 2022), and we summarized as below: (1) The peak coordinates from each dataset were obtained at the t statistic level (Z- or p values for substantial clusters were switched to t statistics utilizing the SDM online converter); (2) the peak coordinates for each study were regenerated using a standard MNI map of the effect size of variances in CTh or GMV by means of an anisotropic Gaussian kernel (Radua et al., 2014). The default 20 mm full width at half maximum and GMV templates were employed to control false positive findings. The cortical mask was utilized for CTh studies while the GM mask was used for VBM studies; (3) the SDM approach conducted a random-effects evaluation to create the mean map, merging the data from all involved research and displaying both positive and negative variances on the identical map. Along with Radua et al. (Radua et al. 2012), an uncorrected p value of 0.005 when employing the SDM program is equal to a corrected p value of 0.025. The default thresholds were applied here: uncorrected p value < 0.005, peak height threshold $Z = 1.00$, and cluster size threshold = 10 voxels. The BrainNet Viewer program (Xia, Wang, & He, 2013) (https://www.nitrc.org/projects/bnv/) implemented in MATLAB was employed to display the CTh findings. The GMV results were displayed using the MRIcron program which is attached to the SDM software.

Jackknife sensitivity analysis

A systematic whole-brain voxel-based jackknife sensitivity examination was then performed to assess the robustness and repeatability of the results. This procedure involved with repeating the primary evaluation n times (n = the number of datasets included), removing one research at a time to detect whether the results persisted detectable. The finding is considered highly reliable if a brain region is preserved in a significant way after applying jackknife sensitivity in all or most research groups (Radua & Mataix-Cols, 2009; Tang et al., 2022).

Subgroup meta-analysis

The pooled meta-analysis of all included research was first conducted. Subsequently, in order to investigate the typical effects of childhood maltreatment on GM morphology for a more rigorous perspective, we re-ran the meta-analysis in studies containing only healthy participants with childhood trauma experience, together with studies which reported the main effect of childhood maltreatment. Then, we intended to perform subgroup meta-analyses of samples including only adults or youths who had childhood maltreatment experience to provide a more comprehensive perspective.

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Meta-regression analysis

To explore potential correlations between the average age, IQ, onset age of childhood maltreatment, as well as duration of maltreatment, the meta-regression analysis was further performed. In line with previous meta-analyses and SDM developers' guidelines, the potential effect of relevant sociodemographic and clinical variables is examined by means of simple linear regression, weighted by the squared root of the sample size and restricted to only predict possible SDM values (i.e. from −1 to 1) in the observed range of values of the variable (Radua & Mataix-Cols, 2009). The probability cut-off was restricted to $p < 0.0005$ so as to reduce the detection of spurious relations. The meta-regression analyses were also conducted in the subgroups. These procedures were only carried out in regions recognized in the primary impact.

Results

Sample characteristics of the included studies

A total of 295 records were identified through database searches. Forty-five studies were eligible for inclusion, of which eight were CTh studies based on SBM (Bounoua, Miglin, Spielberg, & Sadeh, 2020; Cascino et al., 2022; Corbo et al., 2014; Jaworska et al., 2014; Kelly et al., 2013, 2016; Lim et al., 2018; Ross et al., 2021), 34 were GMV studies based on VBM (Benedetti et al., 2012; Brito et al., 2013; Carballedo et al., 2012; Carrion et al., 2009; Chaney et al., 2014; Dam, Rando, Potenza, Tuit, & Sinha, 2014; Daniels et al., 2019; Duarte et al., 2016; Everaerd et al., 2016; Fan et al., 2022; Grabe et al., 2016; Harmelen et al., 2010; Kelly et al., 2015; Kuhn et al., 2016; Labudda et al., 2013; Liao et al., 2013; Lu et al., 2013, 2018, 2019; Maier et al., 2020; Mielke et al., 2016, 2018; Opel et al., 2016, 2019; Rinne-Albers et al., 2017; Sheffield, Williams, Woodward, & Heckers, 2013; Thomaes et al., 2010; Tomoda et al., 2009a, 2009b, 2011; Tomoda, Polcari, Anderson, & Teicher, 2012; Walsh et al., 2014; Wang et al., 2021; Yang et al., 2017), and 3 conducted both SBM and VBM analyses (Gao et al., 2022; Lim & Khor, 2022; Rinne-Albers et al., 2020). Among the VBM studies, two study both included two subgroups (Carballedo et al., 2012; Everaerd et al., 2016). Thus, these two researches contained two datasets, respectively. Finally, our sample consisted of 2550 individuals exposed to childhood maltreatment and 3739 unexposed comparison subjects, along with 120 coordinates derived from 50 datasets. The diagram of the categorization and characteristics of the research studies were illustrated in Fig. 1. Table 1 shows the detailed medical and demographic information of all involved studies.

Pooled meta-analysis

Individuals with childhood maltreatment experience exhibited significantly decreased CTh in three clusters compared with unexposed controls, including the right median cingulate/paracingulate gyri, the right anterior cingulate/paracingulate gyri, and the left middle frontal gyrus (Fig. 2, Table 2). Similarly, meta-analysis of VBM studies revealed significant GMV reductions lied in the left supplementary motor area (SMA), and the breakdown results also demonstrated right median cingulate/paracingulate gyri, left median cingulate/paracingulate gyri, and some other adjacent brain areas (Fig. 3, Table 3). No increased CTh or GMV were found in the maltreated individuals.

Jackknife sensitivity analysis

The jackknife sensitivity analyses of the whole brain detected the CTh thinning in the right median cingulate/paracingulate gyri and the left middle frontal gyrus were replicated throughout all but one combination of the datasets, while the reduced CTh in the right anterior cingulate/paracingulate maintained within 9 of 11 datasets (Table 2). Besides, decreased GMV in the left SMA were repeatable in 37 of 39 datasets. These indicated that the results were highly reliable and reproducible.

Subgroup meta-analysis

Considering the SBM literatures were not enough, and VBM studies in pure healthy (without comorbidities) participants with childhood maltreatment experience were also insufficient (minimum of 10 datasets recommended for SDM meta-analyses) (Hu et al., 2020; Muller et al., 2018), only VBM studies containing healthy participants with childhood trauma experience together with studies which reported the main effect of childhood maltreatment were included ($n = 17$). The main effects of childhood maltreatment experience were significantly reduced GMV in the left median cingulate/paracingulate gyri, and the breakdown results mainly included bilateral median cingulate/paracingulate gyri and the left SMA. These results were quite overlapped with the pooled voxel-based meta-analysis findings. The detailed results were presented in online Supplementary Table S1 and Fig. S1 in our Supplementary Material. Meta-analysis of VBM studies in adult participants with childhood maltreatment revealed GMV reductions in the left SMA and left parahippocampal gyrus compared with unexposed comparison subjects (online Supplementary Table S2 in the online Supplementary Material). This was basically consistent with the pooled meta-analyses results. However, we failed to conduct the subgroup meta-analyses for the VBM studies in youths exposed to childhood maltreatment, or studies applying SBM approaches in either youths or adults, due to the inadequate datasets.

Meta-regression analysis

With a stringent threshold of $p < 0.0005$, the meta-regression analyses found that altered CTh in the right median cingulate/paracingulate gyri had a negative correlation with the average age. Besides, GMV in the left SMA was also inversely associated with the average age (Table 4). No other CTh or GMV changes were found to be related with clinical characteristics. The meta-regression of VBM studies in adult subgroup also identified coincident SMA volume alterations negatively correlated with the average age (online Supplementary Table S3 in the Supplementary Material).

Discussion

This present CBMA identified that individuals with childhood maltreatment experience demonstrated significantly CTh decreases in the right median cingulate/paracingulate gyri, the right anterior cingulate/paracingulate gyri, and the left middle frontal gyrus. Meanwhile, significant GMV reductions mainly lied in the left SMA, as well as some adjacent brain areas such as bilateral median cingulate/paracingulate gyri. No greater regions were found for either CTh or GMV. The jackknife sensitivity and heterogeneity evaluations revealed that these outcomes were highly reliable. In addition, several neural morphology changes were associated with the average age of the maltreated individuals. Adults with childhood maltreatment exhibited

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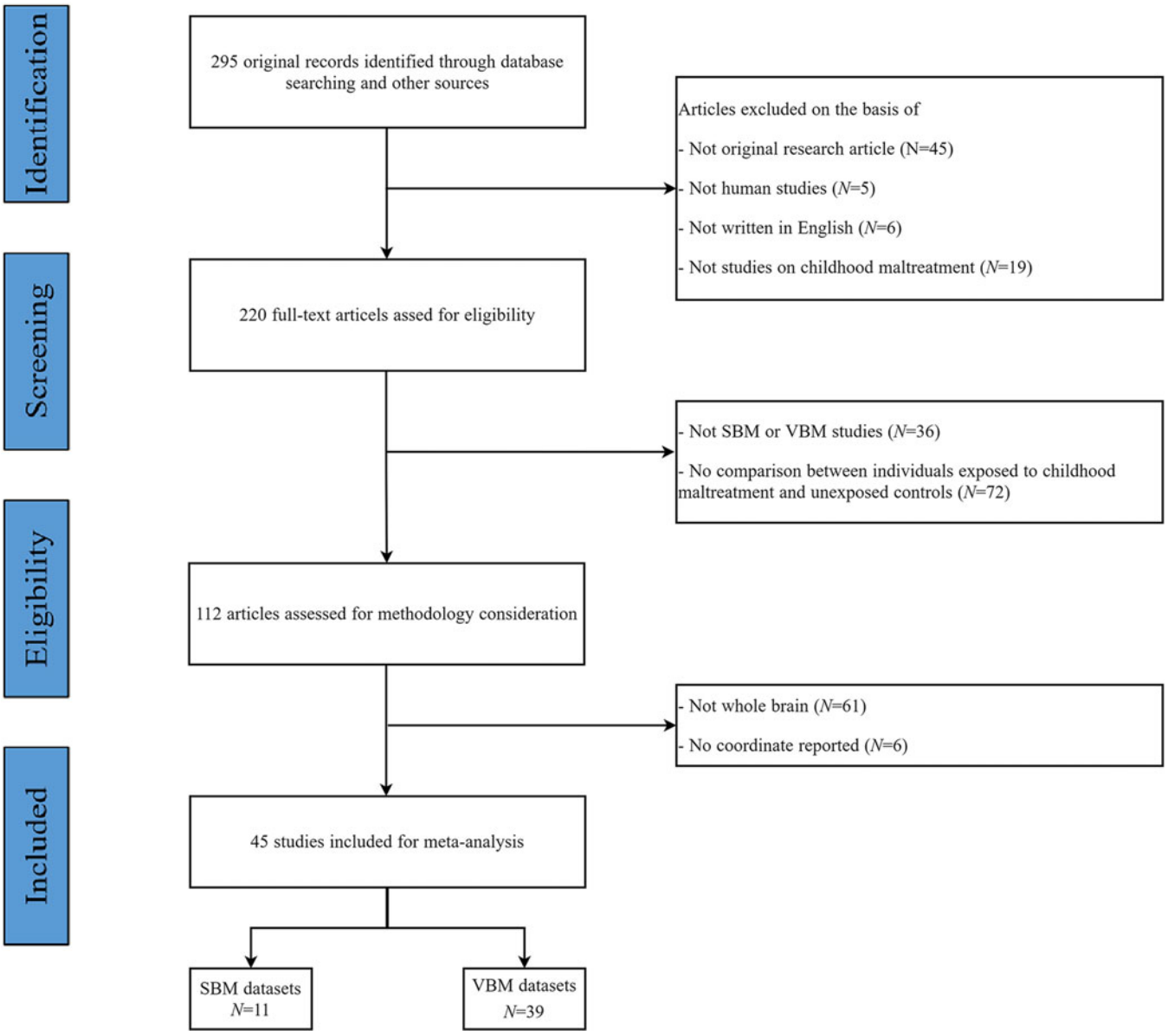

Fig. 1. Flow diagram for the identification and exclusion of studies.

decreased GMV in the left SMA and the left parahippocampal gyrus. It is noteworthy that the brain regions of thinned CTh and reduced GMV were quite overlapped. Our current meta-analysis provided a more comprehensive perspective of the altered GM microarchitectures in childhood maltreatment, including both CTh and GMV findings, and enhanced our understandings of the impact of childhood maltreatment on neurodevelopment.

The predominant manifestations of the microstructural brain abnormalities were decreased CTh and GMV in our results, reflecting unidirectional disruptions of the GM. Atrophy of GM might be related with the main progressive histopathological disorders, including defective neuronal overgrowth or relocation, neurogenesis inhibition, dendritic branching reduction cell density, and microcolumn alterations in the cerebral cortex (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Hakamata et al., 2022), which would interfere with the normal neurodevelopmental process. Especially, the median cingulate/paracingulate gyri revealed overlapped abnormalities in both CTh and GMV findings in our meta-analysis. This brain area belongs to the limbic system, and is critical for integrating emotional processes, and the formation and regulation of pain sensation (Huang, Zhang, Li, Shang, & Yang, 2022). Altered GMV in the median cingulate/paracingulate gyri has been reported in a range of VBM studies in individuals with early-life adversities (Harmelen et al., 2010; Lu et al., 2013; Maier et al., 2020; Opel et al., 2016), indicating a susceptible neural plasticity of this region. Moreover, the median cingulate/paracingulate gyri is also believed to be related with high risks of MDD (Opel et al., 2016), as well as cognitive decline in mild cognitive impairment patients (Ma et al., 2022), which might account for the phenomenon that individuals with an exposure to early-life trauma are more likely to suffer from affective disorders. A former SBM research reported CTh in the median cingulate was inversely

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Table 1. Demographic and clinical characteristics of the studies included in the meta-analysis

		Exposed to childhood maltreatment							Non-maltreated comparison subjects				
Study	Maltreatment types	*N*	Mean age (Years)	% Female	Mean onset age (Years)	Mean trauma duration (Years)	Mean IQ	Comorbid disorders (%)	*N*	Mean age (Years)	% Female	Mean IQ	Comorbid disorders (%)
CTh studies													
Kelly et al. (2013)	Physical abuse Emotional abuse Neglect Sexual abuse	22	12.3	36.4	NA	NA	102.6	Higher conduct problems (NA) Higher hyperactivity scores (NA)	21	12.8	52.4	107.5	NA
Corbo et al. (2014)	Physical abuse Sexual abuse Family violence Partner violence	43	35.6	18.6	NA	NA	NA	Traumatic brain injury (9.3) Higher current PTSD severity (NA) Higher pre-deployment PTSD severity (NA)	65	33.4	9.2	NA	NA
Jaworska et al. (2014)	Physical abuse Physical neglect Emotional neglect Sexual abuse	12	40.0	66.7	NA	NA	NA	MDD (100%)	19	36.4	52.6	NA	MDD (100%)
Kelly et al. (2016)	Neglect Physical abuse Emotional abuse Sexual abuse	62	12.2	46.8	NA	NA	104.8	Higher conduct problems (NA) Higher peer problems (NA) Higher hyperactivity scores (NA)	60	12.7	58.3	108.9	NA
Lim et al. (2018)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	22	17.6	31.8	4.0	8.27	89.5	PTSD (59.1) MDD (27.3) Anxiety disorders (22.7) Social phobia (4.5) ADHD (4.5) ODD/CD/Other disruptive behaviors (22.7)	19	16.8	52.6	93.5	PTSD (63.2) MDD (31.6) Anxiety disorders (26.3) Social phobia (5.3) ADHD (5.3) ODD/CD/Other disruptive behaviors (21.1)
Bounoua et al. (2020)	Physical abuse Sexual abuse Witnessing violence Non-assaultive trauma	50	NA	NA	NA	NA	NA	Concussion (25.4) MDD (41.3) Alcohol use disorder (34.1)	88	NA	NA	NA	NA
Rinne-Albers et al. (2020)	Sexual abuse	21	16.4	85.7	NA	NA	99.3	PTSD (100)	28	15.2	85.7	107.0	None
Ross et al. (2021)	Interpersonal violence Physical assault Physical abuse Sexual assault	172	25.8	100	8.9	NA	NA	PTSD (55.7) Anxiety disorders (44.3) MDD (21.7) Substance use disorder (9.1)	81	19.2	100	NA	None

Cascino et al. (2022)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	26	30.1	100	NA	NA	NA	Eating disorders (100)	24	27.9	100	NA	Eating disorders (100)
Gao et al. (2022)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	108	15.0	0	NA	NA	103.3	Conduct disorder (57.4) Higher emotion symptoms (NA) Higher hyperactivity (NA) Higher peer problems (NA) Lower prosocial behaviors (NA)	74	15.1	0	107.9	CD (45.9)
Lim and Khor (2022)	Physical abuse Physical neglect Emotional abuse Emotional neglect	34	19.9	64.7	NA	NA	104.3	Higher emotion symptoms (NA)	36	20.1	61.1	102.0	None
VBM studies													
Carrion et al. (2009)	Witnessing Violence Physical abuse Physical neglect Emotional abuse Sexual abuse Separation and loss	24	11.0	41.7	NA	NA	90.0	PTSD (100) Depression (16.7) Social phobia (12.5) ADHD (12.5) Separation anxiety disorder (8.0) Generalized anxiety disorder (8.0) Simple phobia (8.0)	24	11.0	41.7	105.0	None
Tomoda et al. (2009a)	Sexual abuse	23	20.2	100	NA	4.1	NA	None	14	19.0	100	NA	None
Tomoda et al. (2009b)	Harsh corporal punishment	23	21.7	34.8	3.9	8.5	118.6	NA	22	21.7	72.7	123.2	None
Thomaes et al. (2010)	Physical abuse Sexual abuse	33	35.3	100	NA	NA	NA	Anxiety disorder (69.7) MDD (63.6) Eating disorders (9.1) Other mood disorders (9.1) Alcohol dependence (3.0)	30	35.2	100	NA	None
Harmelen et al. (2010)	Physical abuse Emotional abuse Emotional neglect Sexual abuse	84	38.7	65.5	NA	NA	NA	Anxiety disorders (25.0) MDD (23.8) Comorbid MDD and anxiety disorder (35.7)	97	36.6	67.0	NA	Anxiety disorder (22.7) MDD (22.7) Comorbid MDD and anxiety disorder (13.4)
Tomoda et al. (2011)	Parental verbal abuse	21	21.2	57.1	NA	NA	119.9	Mood disorders (48.0) Anxiety disorders (24.0)	19	21.1	63.2	122.8	None
Benedetti et al. (2012)	Adverse childhood experiences	20	34.2	35	NA	NA	NA	OCD (100)	20	36.8	35	NA	OCD (100)

(*Continued*)

Table 1. (*Continued.*)

		Exposed to childhood maltreatment							Non-maltreated comparison subjects				
Study	Maltreatment types	*N*	Mean age (Years)	% Female	Mean onset age (Years)	Mean trauma duration (Years)	Mean IQ	Comorbid disorders (%)	*N*	Mean age (Years)	% Female	Mean IQ	Comorbid disorders (%)
Carballedo et al. (2012)a	Physical abuse Physical neglect Emotional abuse Sexual abuse	10	NA	NA	NA	NA	NA	First-degree relatives of patients with MDD	10	NA	NA	NA	None
Carballedo et al. (2012)b	Physical abuse Physical neglect Emotional abuse Sexual abuse	10	NA	NA	NA	NA	NA	None	10	NA	NA	NA	None
Tomoda et al. (2012)	Witnessed domestic violence	22	21.8	72.7	NA	9.8	120.2	MDD (40.9) Anxiety disorders (31.8) PTSD (18.2) Eating disorders (9.1) Personality disorder (4.5)	30	21.6	73.3	123.6	None
Brito et al. (2013)	Physical abuse Emotional abuse Neglect Sexual abuse	11	12.0	38.9	2.9	6.3	103.7	NA	10	12.6	50	109.2	NA
Labudda et al. (2013)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	20	NA	100	NA	NA	NA	Borderline personality disorder (100)	19	NA	100	NA	None
Liao et al. (2013)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	26	16.8	50	NA	NA	NA	Generalized anxiety disorder (53.8)	25	16.8	48	NA	Generalized anxiety disorder (48.0)
Lu et al. (2013)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	24	21.5	62.5	NA	NA	NA	None	24	21.5	62.5	NA	None
Sheffield et al. (2013)	Sexual abuse	24	41.7	66.7	NA	NA	94.7	Psychotic disorder (100)	23	36.3	52.2	95.8	Psychotic disorder (100)
Chaney et al. (2014)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	30	41.7	43.3	NA	NA	NA	MDD (66.7)	53	36.3	67.9	NA	MDD (32.1)

Dam et al. (2014)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	69	36.3	42.2	NA	NA	NA	PTSD (40.6) Depression (23.2) Anxiety disorders (21.7)	108	35.5	32.4	NA	Depression (4.6) PTSD (1.9) Anxiety disorders (1.9)
Walsh et al. (2014)	Physical abuse Emotional abuse	27	18.4	63.0	NA	NA	107.0	Anxiety disorders (25.9) Non-suicidal self injury (22.2) MDD (18.5) OCD (3.7) ODD (3.7) ADHD (3.7) Eating disorder (3.7) CD (3.7)	31	18.4	48.4	106.0	Anxiety disorders (9.7) MDD (9.7) Non-suicidal self injury (3.2) ADHD (3.2) Alcohol abuse (3.2)
Kelly et al. (2015)	Neglect Emotional abuse Physical abuse Sexual abuse	62	12.2	46.8	NA	NA	104.8	NA	60	12.7	58.3	108.9	NA
Duarte et al. (2016)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	20	40.4	70.0	NA	NA	NA	Bipolar disorder type 1 (100)	20	37.4	55.0	NA	None
Everaerd et al. (2016) a	Verbal or physical aggression Sexual abuse or violence	127	22.4	54.3	NA	NA	NA	None	129	22.1	55.8	NA	None
Everaerd et al. (2016) b	Serious illness or injury to a close relative Death of close relative Long-term separation from (one of) parents Severe financial problems	126	21.7	58.7	NA	NA	NA	None	129	22.1	55.8	NA	None
Grabe et al. (2016)	Physical abuse Emotional abuse Sexual abuse	319	NA	NA	NA	NA	NA	MDD (NA)	1507	NA	NA	NA	MDD (NA)
Kuhn et al. (2016)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	32	25.3	62.5	NA	NA	NA	Higher emotion symptoms (NA)	97	24.8	57.7	NA	NA
Mielke et al. (2016)	Physical abuse Sexual abuse	25	38.8	100	NA	NA	NA	MDD (50) PTSD (10) Anorexia nervosa (5) Bulimia nervosa (5) Hypomanic episode (5) Panic disorder (5)	28	39.1	100	IQ	None

(*Continued*)

Table 1. (*Continued.*)

		Exposed to childhood maltreatment							Non-maltreated comparison subjects				
Study	Maltreatment types	*N*	Mean age (Years)	% Female	Mean onset age (Years)	Mean trauma duration (Years)	Mean IQ	Comorbid disorders (%)	*N*	Mean age (Years)	% Female	Mean IQ	Comorbid disorders (%)
Opel et al. (2016)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	20	38.7	50	NA	NA	NA	None	20	36.3	50	NA	None
Rinne-Albers et al. (2017)	Sexual abuse	21	16.4	85.7	NA	NA	99.3	PTSD (100)	25	15.3	88	106.8	None
Yang et al. (2017)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	57	32.0	73.7	NA	NA	NA	MDD (71.9) Anxiety disorders (NA)	111	29.9	72.1	NA	MDD (38.7) Anxiety disorders (NA)
Lu et al. (2018)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	96	33.1	54.2	NA	NA	NA	MDD (50)	66	34.8	53.0	NA	MDD (42.4)
Mielke et al. (2018)	Physical abuse Sexual abuse	33	38.9	100	4.9	NA	NA	None	25	39.2	100	NA	None
Daniels et al. (2019)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	26	41.5	100	NA	NA	NA	PTSD (92.3) MDD (92.3) Anxiety disorders (69.2) Somatoform disorder (30.8) Personality disorders (7.7)	25	39.7	100	NA	None
Lu et al. (2019)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	40	22.7	50	NA	NA	NA	MDD (40)	38	22.2	60.5	NA	MDD (36.8)
Opel et al. (2019)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	108	38.0	59.3	NA	NA	109.7	MDD (100)	53	36.0	49.1	111.8	MDD (100)

Maier et al. (2020)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	29	28.4	82.8	NA	NA	NA	MDD (62.1) Anxiety disorders (44.8) PTSD (20.7) Alcohol abuse/ dependency (17.2) Personality disorders (17.2) OCD (10.3) Eating disorders (10.3) Substance abuse/ dependency (3.4)	33	25.7	72.7	NA	MDD (9.1) Anxiety disorders (3.0) Eating disorders (3.0)
Rinne-Albers et al. (2020)	Sexual abuse	21	16.4	85.7	NA	NA	99.3	PTSD (100)	28	15.2	85.7	107.0	None
Wang et al. (2021)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	130	NA	NA	NA	NA	NA	MDD (100)	83	NA	NA	NA	MDD (100)
Fan et al. (2022)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	43	21.3	44.2	NA	NA	NA	None	68	22.6	52.9	NA	None
Gao et al. (2022)	Physical abuse Physical neglect Emotional abuse Emotional neglect Sexual abuse	108	15.0	0			103.3	CD (42.6)	74	15.1	0	107.9	CD (54.1)
Lim and Khor (2022)	Physical abuse Physical neglect Emotional abuse Emotional neglect	34	19.9	64.7	NA	NA	104.3	Higher emotion symptoms (NA)	36	20.1	61.1	102.0	None

ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; CTh, cortical thickness; MDD, major depression disorder; NA, not available; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; PTSD, post-traumatic stress disorder; VBM, voxel-based morphometry.

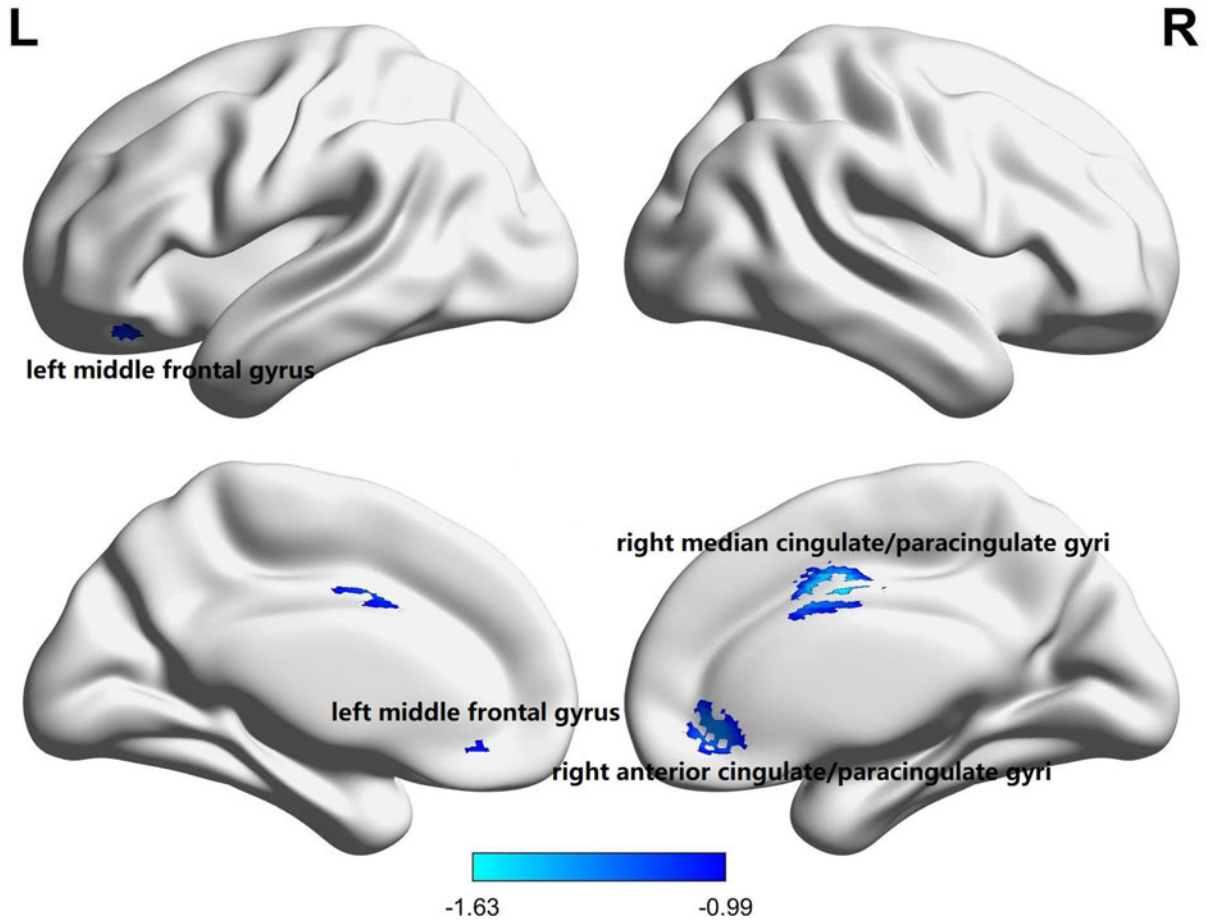

Fig. 2. Regional cortical thickness alterations in in individuals exposed to childhood maltreatment compared with unexposed comparison subjects. Significant clusters are exhibited using BrainNet Viewer.

related to early-life trauma in both adolescents and adults, such that individuals with severer trauma demonstrated lower CTh in this region (Ross et al., 2021). Taken together, the median cingulate/paracingulate gyri morphology changes might be one of the most prominent structural neuroimaging features of childhood maltreatment.

Disrupted anterior cingulate structure is one of the most consistent findings in healthy maltreated cohorts as well as child abuse-related psychiatric disorders (Lim et al., 2014; Paquola et al., 2016; Pollok et al., 2022; Teicher et al., 2016). Thinner CTh and smaller GMV in this region have been detected in individuals exposed to childhood maltreatment (Cascino et al., 2022; Kelly et al., 2013, 2016; Paquola et al., 2016; Rinne-Albers et al., 2017). Previous resting-state fMRI studies further confirmed the crucial effects of early-life trauma on anterior cingulate. Negative correlations between maltreatment severity and resting-state functional connectivity between anterior cingulate functions and other cortical regions have been reported (Birn, Patriat, Phillips, Germain, & Herringa, 2014; Herringa et al., 2013). Also, the anterior cingulate/paracingulate gyri are associated with evaluative mechanisms and reappraisal of emotional stimuli in MDD patients with childhood maltreatment experience revealed by fMRI studies (Nagy et al., 2021). Moreover, the middle frontal gyrus was found to be influenced by childhood maltreatment revealed by our meta-analysis results of SBM studies. CTh and GMV reductions were constantly found in this region by sMRI studies (Cascino et al., 2022; Corbo et al., 2014; Dannlowski et al., 2016; Opel et al., 2016; Tyborowska et al., 2018). The middle frontal gyrus, together with the anterior cingulate, as well as the temporoparietal junction, the superior temporal sulcus and the temporal poles, constitute the anatomical and functional basis of the social cognition (Amodio & Frith, 2006). Previous resting-state fMRI studies reported maltreatment-associated altered connectivity between the amygdala and dorsolateral frontal areas in depressive patients (Goltermann et al., 2022). Considering that the anterior cingulate and frontal gyrus involves in regulating emotions and monitoring cognitive and motor responses during potential conflict situations (Etkin, Egner, & Kalisch, 2011; Teicher et al., 2016), our CTh results highlighted the effects of childhood maltreatment on these regions, and might underlie the potential susceptibility of PTSD and affective symptoms. The frontal CTh is also considered to be one of the most susceptible neuroanatomical structures to early stress revealed by rat models (Spivey et al., 2009). CTh could be served as a feature to examine the effects of childhood trauma on brain structure.

In addition to the aforementioned CTh alterations, the left SMA exhibited decreased GMV in maltreated individuals. The SMA has connections with the limbic system, basal ganglia, cerebellum, thalamus, contralateral SMA, superior parietal lobe, as well as portions of the frontal lobes (Bozkurt et al., 2016). This area has drawn attentions because of a series of clinical deficits

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Table 2. Decreased cortical thickness in individuals exposed to childhood maltreatment compared with unexposed comparison subjects

	Maximum					Cluster		
	MNI coordinates							
Regions	*X*	*Y*	*Z*	SDM Value	*p*	Number of voxels[a]	Breakdown (number of voxels)	Jackknife sensitivity analysis
Right median cingulate / paracingulate gyri, BA 24	2	2	40	−1.627	0.000223100	471	Right median cingulate / paracingulate gyri, BA 24 (171) Left median cingulate / paracingulate gyri, BA 24 (104) Right median cingulate / paracingulate gyri, BA 32 (33) Right median cingulate / paracingulate gyri, BA 23 (30) Left median cingulate / paracingulate gyri (29) Left median cingulate / paracingulate gyri, BA 23 (27) Right median cingulate / paracingulate gyri (27) Right median network, cingulum (14) Left median network, cingulum (14) Left anterior cingulate / paracingulate gyri, BA 24 (9) Right anterior cingulate / paracingulate gyri, BA 24 (5) Right supplementary motor area, BA 24 (4) Left anterior cingulate / paracingulate gyri (3) Right supplementary motor area, BA 32 (1)	10/11
Right anterior cingulate / paracingulate gyri, BA 11	8	38	−6	−1.362	0.001493037	266	Right superior frontal gyrus, medial orbital, BA 11 (68) Right anterior cingulate / paracingulate gyri, BA 11 (60) Right superior frontal gyrus, medial orbital, BA 10 (44) Left superior frontal gyrus, medial orbital, BA 11 (40) Left anterior cingulate / paracingulate gyri, BA 11 (27) Right anterior cingulate / paracingulate gyri, BA 10 (12) Corpus callosum (5) Right median network, cingulum (3) Left superior frontal gyrus, medial orbital, BA 10 (3) Right superior frontal gyrus, medial, BA 10 (2) Left superior frontal gyrus, medial orbital (2)	9/11
Left middle frontal gyrus, orbital part, BA 11	−24	34	−16	−1.160	0.002840221	40	Left middle frontal gyrus, orbital part, BA 11 (26) Left superior frontal gyrus, orbital part, BA 11 (5) Left inferior frontal gyrus, orbital part, BA 11 (5) Left inferior network, uncinate fasciculus (3) Left frontal orbito-polar tract (1)	10/11

BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping.
[a]All voxels with $p < 0.005$.

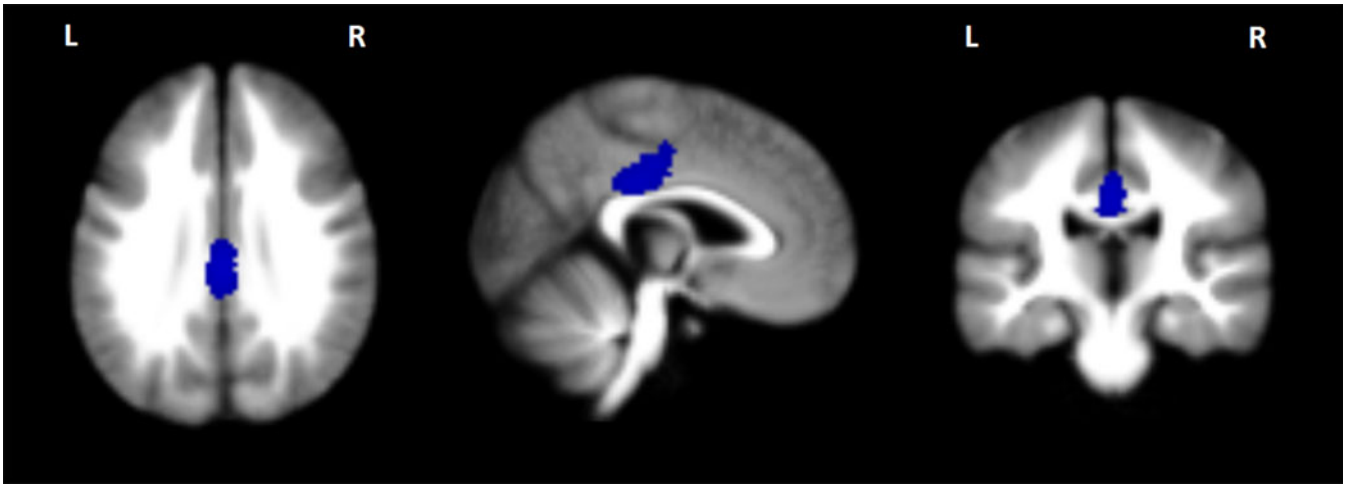

Fig. 3. Regions showing GMV reductions in the left supplementary motor area in axial, sagittal, and coronal views. Significant clusters are overlaid on MRIcron template for Windows for display purposes only.

Table 3. Reduced gray matter volume in participants exposed to childhood maltreatment compared with unexposed comparison subjects

	Maximum							
	MNI coordinates							
Regions	*X*	*Y*	*Z*	SDM Value	*p*	Cluster Number of voxels[a]	Breakdown (number of voxels)	Jackknife sensitivity analysis
Left supplementary motor area, BA 6	−8	−6	64	−1.271	0.000180602	963	Left supplementary motor area, BA 6 (298) Right median cingulate / paracingulate gyri, BA 23 (231) Left median cingulate / paracingulate gyri, BA 23 (170) Corpus callosum (62) Left median network, cingulum (40) Left supplementary motor area (39) Left posterior cingulate gyrus, BA 23 (25) Right median network, cingulum (24) Left median cingulate / paracingulate gyri (19) Right median cingulate / paracingulate gyri (17) Right supplementary motor area, BA 6 (13) Right supplementary motor area (10) Left posterior cingulate gyrus (3) Left precentral gyrus, BA 6 (3) Left cortico-spinal projections (2) Left paracentral lobule, BA 6 (2) Left supplementary motor area, BA 23 (2) Right posterior cingulate gyrus, BA 23 (2) Left superior frontal gyrus, dorsolateral, BA 6 (1)	37/39

BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping.
[a]All voxels with $p < 0.005$.

Table 4. Correlation between brain morphology changes and age in participants exposed to childhood maltreatment revealed by meta-regression analyses

		MNI coordinates					
Factor	Anatomic label	*X*	*Y*	*Z*	SDM Value	*p*	Number of voxels[a]
Age	CTh						
	Right median cingulate / paracingulate gyri, BA 24	6	6	42	−1.228	0.000145853	44
	VBM						
	Left supplementary motor area, BA 6	−8	−6	64	−1.766	0.000129044	63

CTh, cortical thickness; MNI, Montreal Neurological Institute; SDM, seed-based *d* mapping; VBM, voxel-based morphometry.
[a]All voxels with $p < 0.0005$.

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caused by its resection or damage, including abnormal motor integration, recognition of movement and thinking, memory storage, language production, conflict resolution, intention of action (Bozkurt et al., 2016; Coull, Vidal, Nazarian, & Macar, 2004; Kennerley, Sakai, & Rushworth, 2004; Mayka, Corcos, Leurgans, & Vaillancourt, 2006). The SMA also presented emotion and memory-related neural activity changes in people with a history of childhood trauma (Elton, Smitherman, Young, & Kilts, 2015; Lim et al., 2015; Ma et al., 2021; Olsavsky, Stoddard, Erhart, Tribble, & Kim, 2021). The left parahippocampal gyrus revealed GMV reductions solely in the adult sample in our results. This is in accord with the former meta-analysis and an amount of VBM studies (Lim et al., 2014; Pollok et al., 2022). The parahippocampal gyrus plays important roles in scene identification, spatial navigation, and memory encoding as well as recovery (Aminoff, Kveraga, & Bar, 2013). Evidence also indicated that the hippocampus is vulnerable to the neurotoxic effects of excessive glucocorticoid levels, which often related to high levels underlying chronic stress (Lu et al., 2018). Regional GM atrophy in this region might explain early-life stress-related episodic memory and emotion regulation disturbances in adults with childhood maltreatment experience. Notably, the subgroup meta-analysis which contained VBM studies in healthy participants with childhood maltreatment experience together with studies that reported the main effect of childhood maltreatment identified significant GMV decreases in bilateral median cingulate/paracingulate gyri and the left SMA. This further confirmed the reliability and stability of our findings.

Age-related brain morphological changes located in the CTh in right median cingulate/paracingulate gyri, and GMV in the left SMA. With age increasing, the alterations in GM structure will deteriorate further. This is basically consistent with the developmental brain charts across the human lifespan (Bethlehem et al., 2022; Colich, Rosen, Williams, & McLaughlin, 2020). The SMA volume alterations were negatively correlated with the average age in both pooled meta-analysis and in the adult subgroup. Considering the vital roles of the SMA in emotion regulation and executive function (Kennerley et al., 2004; Ma et al., 2021), with the growth of age, older childhood maltreatment sufferers might be more likely to perform emotional and cognitive problems. Interestingly, these regression results might also be consistent with our subgroup analyses findings that the adult subjects with childhood maltreatment exhibited more prominent neural abnormalities than the pooled sample. Early biophysical and molecular processes strongly influence life-long neurodevelopmental trajectories and susceptibility to psychiatric disorders (Bethlehem et al., 2022), while the maltreated brain is more vulnerable and susceptible (Busso et al., 2017). This suggests the importance and urgency of early intervention to prevent accelerated decline of brain structures in individuals exposed to childhood maltreatment. One possible practical implication of these results is that psychologist might recommend sMRI scans on individuals with a history of childhood maltreatment as early as possible, aiming to examine the atrophic degree of the median cingulate/paracingulate gyri and SMA. With timely and effective intervention such as psychological counseling and physical exercise, the progression of these structural deficits might be reversed, or at least be postponed.

There are several limitations to be noted. First, like other CBMA methods, SDM relies on the coordinates of published articles rather than original neuroimaging, which will weaken its accuracy to some extent. Second, our statistical methods cannot eliminate the heterogeneity of data collection parameters and demographic data in the included studies. Third, due to the lack of sample size and original clinical variables, and limited by the algorithm of the SDM software, we were not capable of conducting more subgroup meta-analyses or meta-regression analyses such as special investigations in youths exposed to childhood maltreatment, structural changes of specific major brain systems, the effects of various maltreatment types, or the correlation analyses of CTQ and brain imaging. Fourth, some other important information such as the stress severity/intensity or frequency of the participants, socioeconomic status, child or parental education level were not available in most of the included literatures. This study would be much more valuable if above factors could be explored. Last but not least, only cross-sectional designs were included in this meta-analysis. Longitudinal neurodevelopmental features would surely bring more perspectives to understand the impacts of early-life trauma on brain morphology.

In conclusion, this current research explored the effects of childhood maltreatment on CTh and GMV microstructures by performing a CBMA. The median cingulate/paracingulate gyri exhibited overlapped deficits in both CTh and GMV findings, indicating a robust and characteristic neuroimaging feature of childhood trauma. We also demonstrated regional cortical thinning in the right anterior cingulate/paracingulate gyri and the left middle frontal gyrus, as well as GMV reductions in the left SMA. The effects of childhood maltreatment on the human brain predominantly involved in cognitive functions, socio-affective functioning and stress regulation. The neuroanatomical abnormalities revealed by our current meta-analysis enhanced the understanding of neuropathological changes induced by childhood maltreatment, and might uncover the neurobiology of childhood maltreatment-related mental diseases. Our findings could also bring vital inspirations for building the neuroimaging biomarkers of childhood maltreatment for early interventions in future clinical applications.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723000661

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Conflict of interest. The authors declare no competing interests.

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