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# Greater maltreatment severity is associated with smaller brain volume with implication for intellectual ability in young children☆

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A B S T R A C T

*Background:* Childhood maltreatment profoundly alters trajectories of brain development, promoting markedly increased long-term health risks and impaired intellectual development. However, the immediate impact of maltreatment on brain development in children and the extent to which altered global brain volume contributes to intellectual development in children with maltreatment experience is currently unknown. We here utilized MRI data obtained from children within 6 months after the exposure to maltreatment to assess the association of maltreatment severity with global brain volume changes. We further assessed the association between maltreatment severity and intellectual development and tested for the mediating effect of brain volume on this association.

*Method:* We used structural MRI (3T) in a sample of 49 children aged 3–5 years with maltreatment exposure, i.e. emotional and physical abuse and/or neglect within 6 months, to characterize intracranial and tissue-specific volumes. Maltreatment severity was coded using the Maternal Interview for the Classification of Maltreatment. IQ was tested at study entry and after one year using the Snijders Oomen Nonverbal Test.

*Results:* Higher maltreatment severity was significantly correlated with smaller intracranial volume ($r = -.393$, $p = .008$), which was mainly driven by lower total brain volume ($r = -.393$, $p = .008$), which in turn was primarily due to smaller gray matter volume ($r = -.454$, $p = .002$). Furthermore, smaller gray matter volume was associated with lower IQ at study entry ($r = -.548$, $p < .001$) and predicted IQ one year later ($r = -.493$, $p = .004$.). The observed associations were independent of potential confounding variables, including height, socioeconomic status, age and sex.

*Importance:* We provide evidence that greater maltreatment severity in early childhood is related to smaller brain size at a very young age with significant consequences for intellectual ability, likely setting a path for far-reaching long-term disadvantages. Insights into the molecular and neural processes that underlie the impact of maltreatment on brain structure and function are urgently needed to derive mechanism-driven targets for early intervention.

## 1. Introduction

The human brain is inherently able to dynamically change as a function of experience, and the developing brain is most malleable to the organizing effects of experiences as early childhood is characterized by rapid changes in brain structure and function (Lupien et al., 2009; Gilmore et al., 2018). While neuroplasticity is essential for normal learning and development, it may also enable adversity to profoundly alter neurostructural and neurofunctional development. Both animal and human studies support this hypothesis and report associations between childhood maltreatment and variation in brain structure, function, connectivity and network architecture (reviewed in (Teicher et al., 2016)).

Enduring effects of early adversity on the brain have been proposed

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as one mechanism by which adversity impacts the individual's well-being over the life course. Adversity is one of the most consequential environmental exposures and substantial evidence from epidemiological and clinical studies suggests that exposure to early adversity strongly increases the risk not only for major psychiatric disorders, but also for somatic disorders and poorer cognitive and intellectual development (Felitti et al., 1998; Heim and Binder, 2012; Norman et al., 2012; Cowell et al., 2015; Crozier and Barth, 2005). Early in life, during periods when the brain is particularly malleable, adversity may impact brain development through experience-dependent plasticity and thereby leave the individual at lifelong risk to develop a broad spectrum of diseases and adverse developmental outcomes (Lupien et al., 2009; Heim and Binder, 2012).

Most consistently, alterations in specific regions that are implicated in the regulation of emotion and stress responses, including amygdala, hippocampus and prefrontal cortex, have been associated with early adversity across studies. In a recent study, Mackes et al. (2020) have demonstrated smaller global early adversity-related brain volumes above and beyond adversity-related region-specific variation in brain volumes in adults. They showed that adults, who had been exposed to severe deprivation in early childhood due to institutionalization in Romania, exhibited substantially smaller brain volumes, with relevant consequences for the individual's cognitive status. More specifically, brain size mediated the link between institutionalization and lower intelligence quotient (IQ). This is consistent with studies indicating that total brain volume is associated with intellectual ability, with individuals who score higher on tests of intelligence tend to have larger brains (Haier et al., 2004; McDaniel, 2005; Pietschnig et al., 2015). Thus, adversity may fundamentally disrupt brain development to the extent that it leads to smaller overall brain size and thereby undermines intellectual capabilities and presumably academic achievement. Indeed, impaired intellectual ability is a well-documented sequela related to various forms of early adversity and is suggested to convey not only long-term economic, but also health-related outcomes of the individual (De Bellis et al., 2009; Pechtel and Pizzagalli, 2011).

However, Mackes et al. (2020) employed a cross-sectional study in adults which makes it difficult to disentangle the effects of early adversity on brain development versus effects of later environmental exposures or potential adversity-related psychopathology. Given the specific malleability of the brain in early childhood, it is crucial to advance our understanding of the direct impact of adversity on the developing brain and to study maltreatment-associated brain alterations in children in the immediate aftermath of adversity exposure. Only by gaining further insight into these early effects, and by understanding the involved mechanisms of immediate neural changes, will it be possible to develop more efficient treatment strategies to intervene early and to counteract, reverse or compensate neural sequelae of early adversity.

In the present study, we enrolled children with maltreatment exposure within 6 months before study entry to test whether maltreatment severity is associated with global measures of early brain development, as indicated by intracranial volume (ICV), total brain volume (TBV) and tissue-specific volume, including gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volume. To test whether greater maltreatment severity is associated with tissue-specific development over and beyond being associated with overall brain size, we conducted analyses characterizing the association between maltreatment severity and GM, WM and CSF volume adjusting for ICV. In terms of cognitive-developmental relevance, we tested whether variation in brain volume is related to intellectual ability over time, as assessed by IQ measured at study entry and 12 months later. We hypothesized that smaller global brain volumes are already evident in young children exposed to maltreatment in a dose-response manner (i.e., higher maltreatment severity is associated with smaller brain volumes) and predict IQ at study entry and one year later.

## 2. Materials and methods

### 2.1. Study sample and design

This report is part of a larger research study entitled "Immediate Biological Embedding of Maltreatment in Children: The Berlin Longitudinal Children Study (BerlinLCS)" that was funded by the Federal Ministry of Education and Research (01KR1301). The present report presents data on neurodevelopmental and cognitive markers obtained in this study.

The study was approved by the ethics committees of the Charité – Universitätsmedizin Berlin. All procedures are in accordance with the Ethical Principles for Medical Research as established by the Medical Association Declaration of Helsinki (2013). Written informed consent was obtained from caretakers of all children after procedures were fully explained. Children gave assent by painting or signing a form that was appropriate for the children's age range.

The present sample includes 86 children exposed to maltreatment (physical and emotional abuse and neglect) within six months before study entry. Maltreated children were recruited from a broad range of local child welfare and protection services, including government offices for child welfare, family assistants and counselors, and agencies of the child welfare sector. Sixty-one percent of the sample of children with maltreatment experience was recruited through these offices and can be considered as corroborated cases. To increase the sample size, we further recruited children with maltreatment exposure from pediatric clinics and the community through advertisements and letters sent to families with children aged 3–5 years mainly identified through public census records (39%). For inclusion into the maltreatment group, children had to have experienced maltreatment in the form of physical or emotional abuse or neglect within 6 months, according to the Maltreatment Classification System (Cicchetti, 1993) [for cutoff scores, see below]. General exclusion criteria included parents under the age of 18 years, mental disability or neurodevelopmental disorders, chronic medical illness as well as serious medical disease. Of the 86 children with maltreatment exposure and their families, 67 families gave their consent to participate in the neuroimaging session. In 16 children the complete MRI sequence was not obtained due to discomfort or movement of the children during the MRI study visit. The complete MRI sequence was obtained in 51 scans. MRI scans from 2 children were excluded because they did not pass quality control (see below), resulting in a final sample size of N = 49 (see Table 1 for sample characteristics). Children that were not included in the analyses did not differ from children included in the analyses with respect to age, sex, socioeconomic status or height ($p$'s $> 0.05$). Children included in the final sample had higher scores of maltreatment severity ($t(84) = 2.54$, $p = .04$).

The study involved a prospective design with a structural MRI scan of the children at baseline (T0; n = 49) and two IQ assessments, with the first assessment at study entry (T0; n = 49) and a follow-up assessment scheduled at 12 months (T2, n = 37).

### 2.2. Measures

#### 2.2.1. Maltreatment features

Trained clinicians conducted the Maternal Maltreatment Classification Interview MMCI, (Cicchetti et al., 2003) with caregivers to corroborate and further classify maltreatment incidents. The interview covers six maltreatment subtypes, including sexual abuse, physical abuse, emotional maltreatment, as well as neglect subtypes failure to provide, lack of supervision, and moral, legal, and educational maltreatment. In the current sample, the latter subtype overlapped with lack of supervision due to excessive video gaming or keeping the child busy, which we, therefore, assigned to the physical neglect subtype. Based on the MMCI, maltreatment exposure and features were coded using the Maltreatment Classification System (MCS) (Cicchetti, 1993). Coders rated each incidence in terms of subtype and severity on a

**Table 1**

| Characteristic | Complete Sample |
|---|---|
| | *N* = 49 |
| Age, Months | 54.40 ± 10.42 |
| Sex | |
| Female | 22 (44.9) |
| Male | 27 (55.1) |
| SES[a] | 9.45 ± 4.66 |
| Race/Ethnicity[b] | |
| White (European or Middle East) | 46 (93.9) |
| Black (African or American) | 3 (6.1) |
| Head Circumference | 50.40 ± 1.53 |
| Height | 107.43 ± 7.29 |
| **Maltreatment Categories** | |
| Emotional Abuse | 48 (98.0) |
| Physical Abuse | 22 (44.9) |
| Physical Neglect (Failure to Provide) | 21 (42.9) |
| Physical Neglect (Lack of Supervision) | 17 (34.7) |
| Moral Legal Educational Maltreatment | 2 (4.1) |
| Sexual Abuse | 5 (10.2) |
| Maltreatment Severity[c] (Sum Score) | 8.41 ± 4.97 |
| IQ[d] | 90.67 ± 15.66 |
| **Brain Volume**[e] | |
| Intracranial Volume | 1291.72 ± 115.52 |
| Total Brain Volume | 1147.49 ± 107.12 |
| Cerebrospinal Fluid | 144.23 ± 14.37 |
| Total Gray Matter Volume | 755.37 ± 72.26 |
| Total White Matter Volume | 392.13 ± 42.35 |

Values are mean ± SD or *n* (%).

[a] Socioeconomic Status was defined as a combination of education and occupational qualification, occupational status, and net income.

[b] Ethnicity derived from self report.

[c] Maltreatment Severity was operationalized as a sum score of severity ratings of all maltreatment events.

[d] Assessed with SON-R.

[e] Values in $cm^3$.

5-point scale ranging from mild (1) to severe or life-threatening (5). To yield an overall severity score, we computed a sum score of all severity ratings of each reported incidence of maltreatment.

Inclusion in the study was based on defined severity cut-off scores provided in the MCS manual (physical neglect ≥2 and/or physical abuse ≥1 and/or emotional neglect/abuse ≥2 within 6 months before study entry). We did not specifically recruit for sexual abuse, as sexual abuse usually leads to removal of the child from the home, which constitutes a significant intervention. All families received feedback regarding the child's health and developmental status and recommendations for follow-up where necessary.

#### 2.2.2. Intellectual ability

Children underwent standardized testing for cognitive development at T0 and T2. All tests were conducted by trained clinicians. To assess nonverbal intellectual development, we administered the Snijders Oomen Nonverbal Test for the age range of 2½ to 7 years (Tellegen et al., 1998). This well-validated test provides standardized intelligence quotient (IQ) scores.

#### 2.2.3. Image acquisition and analysis

Children underwent a training session in a mock-scanner that was specifically designed to provide a playful environment for children. Using the mock scanner, children were accustomed to the scanning procedure and were trained not to move. Structural MRI was performed in non-sedated children using a 3-T Siemens Tim Trio MRI scanner. A 1-mm3 isotropic T1 anatomical scan was acquired in the sagittal plane. An inversion-recovery spoiled gradient recalled acquisition sequence with the following parameters was applied: repetition time, 11 ms; echo time, 3.3 ms; inversion time, 100 ms; turbo field echo factor, 192; 150 slices; sensitivity encoding for fast MRI acceleration; and flip angle, 18°.

Intracranial volume, GM and WM volume, as well as cerebrospinal fluid (CSF) volume were obtained by segmentation of T1-weighted images. Automated image segmentation was performed using the Computational Anatomy Toolbox (CAT12; Christian Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany), an extension of the Statistical Parametric Mapping software (SPM12; Welcome Trust Centre for Neuroimaging, University College London, United Kingdom). We used an age-appropriate tissue probability map (TPM) and DARTEL template for tissue segmentation/voxel-based processing (Sanchez et al., 2012). Customized TPM and DARTEL template based on age and sex of the underlying sample were created using the SPM-based CerebroMatic Toolbox Experimental Pediatric Neuroimaging Group, Children's Hospital and Department of Neuroradiology, University of Tübingen, Tübingen, Germany; (Wilke, 2018).

Image quality measures based on tissue segmentation were conducted using the CAT12 toolbox (Dahnke et al.). Weighted average image quality ratings (IQR) were calculated based on measurements of noise and spatial resolution. IQRs of two scans were lower than 2 standard deviations from the mean IQRs and therefore considered as outliers, which were therefore not included in the final sample (see above).

#### 2.2.4. Covariates and potential confounders

Socioeconomic status (SES) is a well-established predictor of both intellectual and brain development in children. SES was estimated based on a modification of the Winkler and Stolzenberg Index (Lange et al., 2007). This multidimensional index score represents the sum of three metric components: Education and occupational qualification, occupational status, and net income. The score reflects low (score 3–8), middle (9–14) or high (15–21) SES of the participating family. The dimensional sum score was entered in our analyses.

All analyses were adjusted for height because it is significantly correlated with brain volume in children (Taki et al., 2012). Height was measured as part of a physician-administered medical examination at study entry.

Sex and age at study entry were included as additional covariates in all analyses.

Correlation coefficients between covariates and maltreatment severity are depicted in Table 2. Covariates were not significantly correlated with maltreatment severity.

### 2.3. Statistical analyses

Partial correlations were used to estimate the association between maltreatment severity and ICV. In a next step we tested the relationship between maltreatment severity and CSF and TBV respectively, as well as between maltreatment severity and GM volume and WM volume, which comprise TBV. To characterize the association between maltreatment severity and relative size in specific brain tissues, analyses were additionally adjusted for ICV. Next, we tested the association between IQ and those global brain outcomes predominantly associated with maltreatment severity applying partial correlation analyses.

To investigate whether maltreatment severity-related variation in global or tissue-specific brain volume mediates the association between maltreatment severity and IQ at both timepoints, we conducted mediation models including those brain outcomes associated with

**Table 2**
Correlations testing the associations between maltreatment severity and covariates.

| | Socioeconomic Status | height | age |
|---|---|---|---|
| **Maltreatment Severity**[a] | −0.104 | −0.030 | 0.182 |

N = 49.

*p < .5; **p < .01.

[a] Malreatment Severity was operationalized as a sum score of severity ratings of all maltreatment events.

maltreatment severity and IQ as potential mediators using the SPSS PROCESS macro (Hayes, 2012).

## 3. Results

### 3.1. Global brain and tissue-specific volumes

Higher maltreatment severity was associated with smaller ICV (partial correlation; $r = -.393$, $p = .008$; see Table 3 Fig. 1). An increase of maltreatment severity by one standard deviation (SD) relates to a 3.61% decrease in intracranial volume, when the effects of age, sex, socioeconomic status (SES) and height are held constant. Interrogating the association between maltreatment severity and volumes of specific brain tissues revealed an association between higher maltreatment severity and smaller total brain volume ($r = -0.393$, $p = .008$; see Table 3) but not CSF volume ($r = -.228$, $p = .133$; see Table 3) after adjusting for age, sex, SES, and height. Following up on total brain volume showed that the principal contributor to the observed association between maltreatment severity and lower total brain volume was GM volume ($r = -.454$, $p = .002$; see Table 3 Fig. 1), while WM volume was not significantly associated with maltreatment severity ($r = -.210$, $p = .166$; see Table 2). Specifically, an increase in maltreatment severity by one SD was associated with a reduction of 4,56% in gray matter volume after adjusting for age, sex and SES. When testing the association between maltreatment severity and relative tissue volumes, by including ICV as an additional covariate, there was a tendency for smaller relative GM volume ($r = -.276$, $p = .067$) and larger relative WM volumes ($r = -.273$, $p = .07$), but not CSF volume ($r = -.019$, $p = .903$).

## 4. Maltreatment and IQ

Higher maltreatment severity was associated with lower IQ at study entry ($r = -.376$, $p = .013$) and with lower IQ after one year ($n = 37$; $r = -.661$, $p < .001$), adjusted for sex, age, and SES. IQ was highly stable between the timepoints ($r = 0.82$, $p < .001$).

### 4.1. Brain volumes and IQ

Smaller ICV and GM volume as the principal contributor to the association between maltreatment severity and lower ICV were associated with lower IQ at study entry (ICV: $r = 0.492$, $p < .001$; GMV: $r = 0.522$ $p < .001$; see Table 3 Fig. 1). Follow-up analyses in a subgroup of children (n = 37) further revealed that smaller ICV and GM volume also predict lower IQ one year post MRI scan, indicating potential long-term maltreatment severity-related effects of brain development on intellectual abilities (ICV: $r = 0.506$, $p = .010$; GMV: $r = 0.548$, $p < .001$; see Table 3).

We next investigated whether maltreatment severity-related

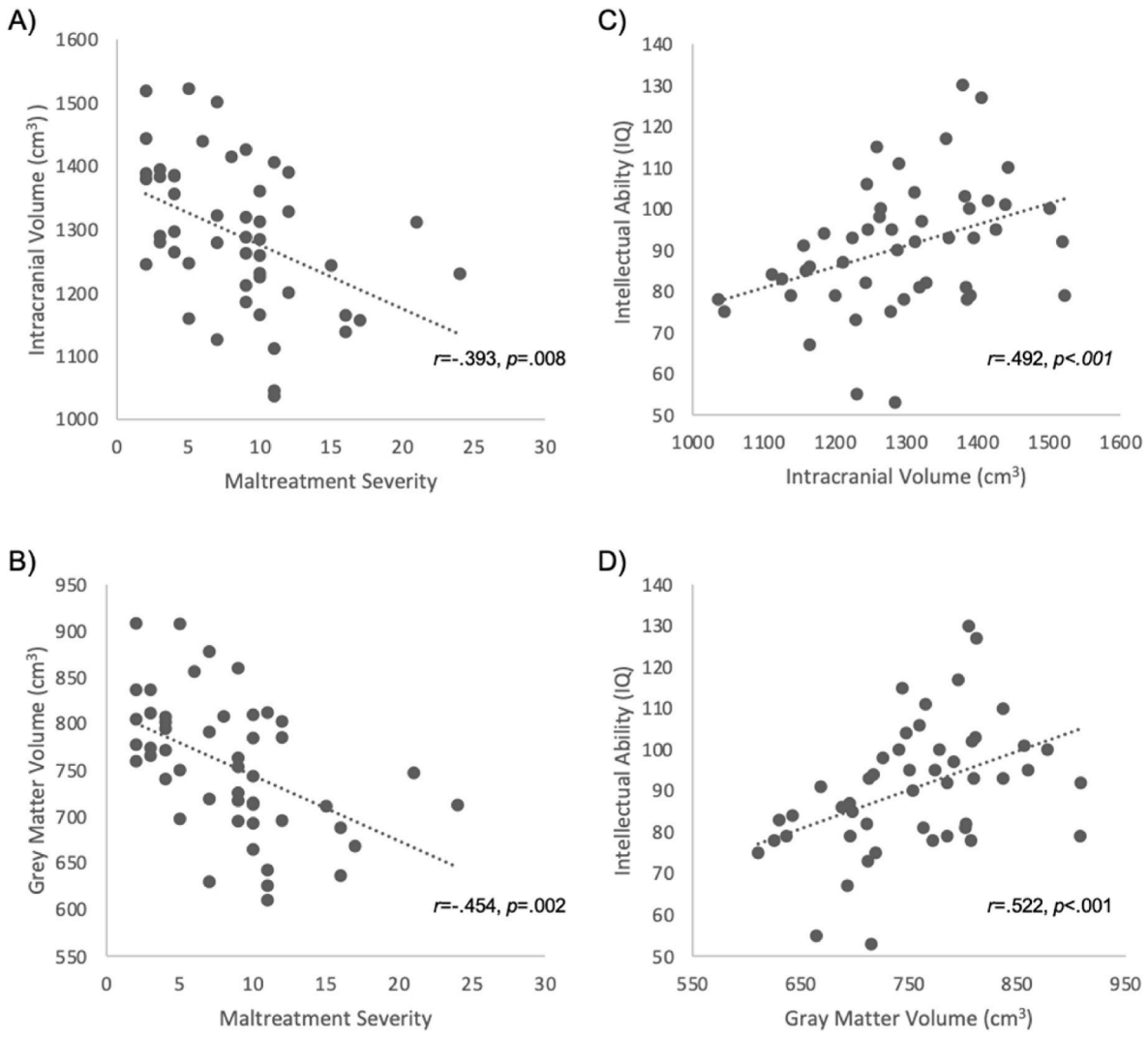


**Fig. 1.** Scatterplots displaying the associations between maltreatment severity and A) intracranial volume, B) gray matter volume, and between IQ and C) intracranial volume and D) gray matter volume. Maltreatment severity was operationalized as a sum score of severity ratings of all maltreatment events.

**Table 3**
Partial Correlations Testing the Associations Between a) Maltreatment Severity and b) IQ with Global and Tissue Specific Brain Volumes.

| | Intracranial Volume | Total Brain Volume | Cerebrospinal Fluid | Total Gray Matter Volume | Total White Matter Volume |
|---|---|---|---|---|---|
| **Maltreatment Severity**[a] | −0.393* | −0.393* | −0.228 | −0.454** | −0.210 |
| **IQ T0** | 0.492*** | 0.474** | 0.418** | 0.522*** | 0.299* |
| **IQ T2**[b] | 0.506** | 0.492** | 0.431* | 0.548*** | 0.297 |

N = 49; All analyses were controlled for age, sex, socioeconomic status, height.
*p < .5; **p < .01; ***p < .001.
[a] Malreatment Severity was operationalized as a sum score of severity ratings of all maltreatment events.
[b] Subsample: n = 37.

variation in ICV and GM volume mediated the relationship between maltreatment severity and IQ at study entry. Mediation models including ICV and GM volume as mediators revealed significant indirect effects of maltreatment severity on IQ through ICV ($b$ = -0.506, 95% BCa CI [-1.093,-0.132]) and GM ($b$ = -0.635, 95% BCa CI [-1.322,-0.204]).

## 5. Discussion

We examined the association of maltreatment severity with global brain structure and intellectual ability in children aged 3–5 years who had been exposed to maltreatment within 6 months. Our findings provide evidence that maltreatment severity is associated with smaller brain volumes, observable in children at such young age. Specifically, maltreatment severity was associated with smaller intracranial volume, which was primarily due to a smaller gray matter volume. These changes in neural structure, in turn, were associated with pronounced and stable effects on intellectual ability. The indication that maltreatment severity is associated with changes in brain structure in early childhood with implication for intellectual ability, is of utmost relevance not only for clinical practice, but also for educational, political, and societal stakeholders. If replicated, our results underscore an urgent and unmet need for early targeted interventions to mitigate the negative neurodevelopmental consequences of maltreatment early on, while the brain is malleable, in order to enable successful development and provide children with maltreatment experience the opportunity to thrive over the life course.

Of note, we demonstrated that gray matter volume is the principal contributor to the observed association between maltreatment severity and total brain volume. Our results showed a reduction of approximately 4.6% of global GM volume corresponding to an increase of 1 SD in maltreatment severity. Changes in GM volume of similar magnitude have been reported in children with developmental disorders (Carmona et al., 2005), as well as in newborns of mothers who had experienced childhood maltreatment (Moog et al., 2018). The observation that maltreatment specifically targets GM development may support the promise that adversity exerts the most profound effects particularly throughout the period of most rapid gray matter changes. GM predominantly due to synaptic and dendritic growth exhibits a particularly pronounced increase within the first six years and may therefore be especially sensitive to the programming effects of the early environment (Gogtay and Thompson, 2010; Phan et al., 2018; Giedd et al., 2015).

Our findings are in line with recent work by Mackes et al. (2020) providing relevant evidence that the modulatory effect of adversity appears not to be limited to specific brain regions shown in the majority of previous studies, but more generally targets the whole brain. They demonstrated in an adult sample that the exposure to severe deprivation in early childhood is associated with profound alterations in total brain size, which endure until adulthood. We suggest that adversity-related smaller brain size does not become apparent as late as in early adulthood, but rather is already detectable in early childhood. Thus, adverse experiences may prevent the individual brain from developing at its full potential and early on set the paths towards social disadvantages.

A number of different pathways and mechanisms can be discussed to explain the effect of maltreatment exposure on global and tissue specific brain size, with stress pathways being most frequently invoked in previous reports. Most existing work postulates that neurotoxic effects of stress hormones and immune mediators are a primary mechanism through which adversity shapes neural development (Lupien et al., 2009). More specifically, it has been suggested that childhood maltreatment impacts regulatory systems, including stress hormone and immune systems, resulting in the increased release of glucocorticoids and inflammatory cytokines, which may in turn signal back into the brain and lead to structural changes (Heim and Binder, 2012). In this context, brain-derived neurotrophic factor (BDNF) represents an additional relevant biological candidate explaining maltreated-related brain alterations, as abnormal BDNF activity is a leading hypothesis by which early adversity may persistently modify brain plasticity. BDNF has an important role in neuronal survival, differentiation and growths throughout the brain (Bernd, 2008). A common polymorphism (Val66-Met) associated with decreased BDNF secretion has repeatedly been associated with both local and global effects on brain volume (Toro et al., 2009) and gene by environment interactions for alterations in brain morphology have been reported in such that maltreatment more profoundly affects brain development in val-carriers (van Velzen et al., 2016). Of note, it has been demonstrated that glucocorticoids downregulate BDNF expression (Chen et al., 2017; Suri and Vaidya, 2013). With regard to our results, it could be suggested that in maltreated children, a neuroprotective effect of BDNF was absent, in part driven by maltreatment-related dysregulation of stress-hormone systems.

Another possible explanation relates to the concept of developmental plasticity and the underlying basic principle of increased synaptic pruning in the absence of age-relevant environmental inputs. Neglect, representing one form of maltreatment in the present cohort, inherently involves a lack of development-appropriate environmental cues, so it likely constitutes an obvious form of early deprivation. Over the past decades, it has clearly been demonstrated in animal models that deprivation results in widespread decreases in dendritic arborization, spines, neuronal depth, glia cells, and ultimately overall brain volume (Globus et al., 1973; Diamond et al., 1972; Bennett et al., 1974).

On a molecular level, the processes underlying the embedding of childhood maltreatment on a neural level are likely driven by epigenetic modifications. Glucocorticoid-induced epigenetic changes have been shown in stress-related genes (Klengel and Binder, 2015; Matosin et al., 2018; Martins et al., 2022; Womersley et al., 2022), with subsequent dysregulation of stress response systems, which are likely to ultimately lead to further brain changes. In addition, maltreatment-related epigenetic signatures have been demonstrated in genes, enriched for biological processes directly related to neurodevelopment, including neuron projection, neurogenesis, axonal guidance (Cecil et al., 2016; Dunn et al., 2019; Labonte et al., 2012; Yang et al., 2013; Ferrer et al., 2019). Notably, a recent study demonstrated that very early childhood, namely before the age of three, appears to be a sensitive period when exposure to adversity predicts differential DNA methylation patterns in genes that are involved in the regulation of developmental growth, axon development, and neuron apoptotic processes (Dunn et al., 2019). In line with the present findings, this further emphasizes the notion of an early critical window for the fundamental biological embedding of maltreatment and the programming of subsequent trajectories of global brain

development. Future studies combining epigenetic and imaging approaches are critical to further elucidate the functional significance of DNA methylation changes in direct association with brain development and to assess whether and by what means these processes may be reversible.

In line with previous cross-sectional studies in children and adults, our present findings reveal profound implication of childhood maltreatment on the individual's intellectual achievement (for review see (Pechtel and Pizzagalli, 2011; Veltman and Browne, 2001)) and suggest that one path through which early life adversity may influence intellectual impairments is by contributing to smaller global brain size and specifically smaller GM volume. We report that IQ is significantly associated with overall brain volume in general which is predominantly driven by lower GM volume. These findings are consistent with current data indicating that brain size relates to intellectual ability, with individuals who have higher IQ tend to have larger brain size (Haier et al., 2004; McDaniel, 2005; Pietschnig et al., 2015). Importantly, a recent report from our group in a larger sample has revealed stable negative effects of maltreatment on IQ over a period of 2 years (Winter et al., 2022). The stable manifestation of intellectual deficits in early childhood is of high political relevance, as these deficits may not only impact emotional and social competence (Enlow et al., 2013), but also likely predict school performance and subsequent academic and socioeconomic outcome. Therefore, early targeted interventions are urgently needed to enable each child to develop at its full potential.

Maltreatment was associated with ICV, which is a reliable surrogate of head size (Hshieh et al., 2016). One mechanism could involve that children with maltreatment exposure exhibit a general nonspecific delay of growth that accounts for the effects on head size and hence limits brain size. In consistency with the latter option, previous studies suggest that adversity is associated with decreased childhood height (Denholm et al., 2013), which may in part be explained by stress-suppressed growth-hormone release (Deltondo et al., 2008). However, we claim that our findings cannot exclusively be explained by a general growth effect for several reasons: First, the effect of smaller ICV in more severely maltreated children was not explained by variation in height because the association between maltreatment severity and ICV remained significant after adjusting for body height. Thus, we exclude the possibility of a general nonspecific delay of growth as an alternative explanation for smaller head size and therefore smaller brain volume. Second, in early childhood cranial skull bones evenly enlarge as the brain grows meaning that brain size determines head size. Head size is therefore highly correlated with brain volume, especially up to the age of 6 years, by when final head size is largely determined (Bartholomeusz et al., 2002). Thus, one might argue that in the present age group smaller head size may reflect smaller expansion of the developing brain and may be interpreted as an indicator of impaired global brain development. In other words, it could be suggested that early adverse circumstances including childhood maltreatment dramatically keep the brain from developing at its full potential, implying far-reaching disadvantages that may affect the individual across life.

A key strength of the present study involves the inclusion of very young children in short aftermath of exposure and enrolled in the study within 6 months. A further strength is the thorough assessment of maltreatment administered by trained clinicians. Nevertheless, the study has several limitations, which should be noted. The point that merits most consideration is the absence of a comparison group of children without exposure to maltreatment, due to the requirement of an indication for conducting an MRI in children. Thus, all findings should be interpreted cautiously. Our results can only be interpreted as an indication for a relationship between maltreatment severity and brain volume. Since the study design does not allow for group comparisons and because we do not have repeated measures of brain volumes before and after exposure to maltreatment, we cannot interpret our results as conclusive evidence of a reduction in brain volume related to early maltreatment exposure. However, given that we observed a dose-dependent effect of maltreatment severity, we might expect even larger effects in group comparison analyses comparing children with and without maltreatment experience. Another limitation relates to the relatively small sample size due to the exploratory character of the present study. The small sample size precluded the possibility of addressing more nuanced research questions which would be statistically underpowered to investigate, e.g. specific effects of maltreatment types, age of onset, specific regions of interest analyses, aspects of early environment other than maltreatment. Future studies with larger sample sizes and a comparison group, longitudinal designs, and consequently greater statistical power to include additional varibles, would enable a more comprehensive investigation regarding those aforementioned aspects and allow for mapping more detailed trajectories of risk versus resilience over the course of development. Furthermore, we were unable to specifically test the sensitive period hypothesis (Teicher et al., 2016), because, firstly, the children were all exposed to the traumatic environment around the same age and, secondly, the study design included a single timepoint shortly after maltreatment exposure, meaning that we could neither compare the impact of exposure during different developmental windows nor draw conclusions about how the effects evolve over the course of development. Moreover, we did not control for heritability factors as we did not assess parental IQ in this study. Also, one might argue that abusive family environment may be related to parental intelligence, which can introduce interpretative biases. However, in early childhood the effect of heritability on intelligence is smaller than in adulthood, namely about 30% in early childhood and then increases to 80% (Deary et al., 2010). A further limitation is the limited prevalence of maltreatment at the more severe end of the spectrum. However, we here demonstrate that even low-to-moderate forms of maltreatment are fundamentally associated with brain development. It is likely that even larger effects may be expected when including children with more severe maltreatment exposure. Accordingly, a recent study demonstrated effects of mild forms of maltreatment on DNAm in very early childhood, whereas effects of maltreatment later in development were only detected for more severe forms of adversity (Dunn et al., 2019). Our findings underscore the urgent need for early targeted interventions to mitigate the detrimental effects of maltreatment. There are various approaches for intervention strategies for which successful results have already been demonstrated. For example, the focus could be on enhancing coping skills or executive functioning (Takacs and Kassai, 2019) or on caregiving interventions, which also have been shown to buffer detrimental effects on IQ (Black et al., 2023). Interventions could forther focus on promoting an intellectually stimulating and enriching environment. Future studies should incorporate targeted interventions to examine their effect on IQ and the presumed underlying parameters of neural development.

In conclusion, our findings contribute to the existing literature on maltreatment related alterations in brain development and provide unprecendented evidence that the severity of maltreatment is remarkably linked to brain size altready in very young children at the age of 3–5 years, with significant consequences on intellectual achievement. This further emphasizes the importance of the development of early prevention and intervention strategies targeting the critical early-life period in order to mitigate the wide-ranging adverse consequences of childhood maltreatement and to enable all children to achieve not only their full health but also overall life opportunities, including academic achievement, employment and income potential.

## CRediT authorship contribution statement

**Judith Joseph:** Investigation, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Claudia Buss:** Conceptualization, Methodology, Formal analysis, Funding acquisition, Investigation, Supervision, Writing – review & editing. **Andrea Knop:** Investigation, Methodology, Formal analysis. **Karin de Punder:** Investigation. **Sibylle M. Winter:** Conceptualization,

Funding acquisition, Investigation, Supervision, Writing – review & editing. **Birgit Spors:** Investigation, Supervision. **Elisabeth Binder:** Conceptualization, Funding acquisition, Writing – review & editing. **John-Dylan Haynes:** Conceptualization, Methodology, Funding acquisition, Supervision. **Christine Heim:** Conceptualization, Methodology, Funding acquisition, Project administration, Investigation, Resources, Supervision, Writing – review & editing.

## Declaration of competing interest

None of the authors declare competing interests.

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