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List of Abbreviations

Abbreviation	Meaning
ANCOVA	Analysis of covariance
BMI	Body mass index
CA	Childhood abuse
CTQ	Childhood trauma questionnaire
FDR	False discovery rate
ICV	Estimated intracranial volume
M	Mean
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
N	Sample size
PHQ-9	Patient health questionnaire 9
SD	Standard deviation
SHIP	Study of health in Pomerania
T	Teslas

1 Introduction

In psychotherapeutic treatment, the patient's biography plays a significant role. Early experiences in childhood and youth were found to be important factors concerning the development of a mental disorder (Dube et al., 2003). Thus, there are especially sensitive periods in which the brain is highly influenced by experiences (Danese et al., 2011). The experience of maltreatment in the period of childhood and youth is a major stressor that has tremendous consequences on the developing brain, the hormone, and immunological systems (Danese et al., 2011).

The world health organisation defines *childhood maltreatment* as

> "The abuse and neglect that occurs to children under 18 years of age. It includes all types of physical and/or emotional ill-treatment, sexual abuse, neglect, negligence and commercial or other exploitation, which results in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power." (WHO, 2019)

Thus, childhood maltreatment can be distinguished into neglect and abuse which can be further categorised into emotional and physical neglect or abuse, with the additional distinction of sexual abuse. Neglect is defined as the failure to meet the essential basic need of a child (English et al., 2005). A child has experienced neglect on the physical level if the caretaker could not provide for safety, shelter, and nourishment, or on the emotional level if it was not taken care of their psychological needs such as love and affection (Hart & Rubia, 2012). Physical abuse is intentional, non-accidental harm, which is deflected on a child by hitting, kicking, burning, stabbing, poisoning, or shaking. It also includes producing symptoms of an illness by intention (Sedlak et al., 2010). Emotional abuse includes insulting, rejecting, or terrorizing a child for being who they are (Sedlak et al., 2010). Sexual abuse is defined as a sexual act with an adult or another child (Sedlak et al., 2010). This thesis focussed on the latter three types of childhood abuse, naming emotional, physical, or sexual abuse.

Childhood abuse is associated with cerebral alterations, mental, and even somatic disorders (Maniglio, 2010; Teicher & Samson, 2016; Wegman & Stetler, 2009). Exposure to one or more maltreatment acts in childhood is related to an attributional risk of depression by 54% (Dube

et al., 2003). It is crucial to understand how childhood abuse increases the risk for mental diseases to implement focused prevention programs and treatment (Teicher et al., 2016). As mentioned, childhood abuse is a fundamental risk factor for the development of major depressive disorder (MDD), therefore it is challenging to disentangle the contribution of both factors, childhood abuse and MDD, to the brain (Lim et al., 2018).

Prior research shows a connection between childhood abuse and brain alterations (Lim et al., 2018; Teicher et al., 2014; Tomoda et al., 2009). However, there is still missing knowledge if and how these alterations are linked to mental diseases.

1.1. Childhood abuse and cerebral alterations

Childhood abuse is associated with changes in the brain structure, connectivity, function, and network architecture (Teicher et al., 2016). Overall, it is related to smaller hippocampal volume, and a reduction in the anterior cingulate, the orbitofrontal, and the dorsolateral prefrontal cortex (Teicher et al., 2012). Maltreated individuals with psychopathology have a more pronounced response of the hypothalamic-pituitary-adrenal axis and the autonomic system to stressors (Teicher et al., 2021). In addition, they have higher inflammation scores showing an increase in the clinically relevant C-reactive protein levels (Danese et al., 2007).

A comprehensible postulation is that cerebral alterations due to childhood abuse go hand in hand with psychopathology. In contrast, Teicher et al. stated in *Nature Reviews Neuroscience* that certain alterations in maltreated subjects are not linked to psychopathology but rather help them compensate (Teicher et al., 2016). They hypothesise an *ecophenotype* proposing that subjects with the same diagnosis (e.g., MDD) may differ profoundly in their brain structures whether they experienced childhood maltreatment. If studies investigate how mental disorders influence the brain without including the effects of childhood abuse, results could be confounded. The same applies vice versa; investigating the effects of childhood abuse on the brain without including mental disorders.

Some studies could show alterations in cerebral regions which were directly affected by the type of maltreatment. Thus, parental verbal abuse was linked to a reduction in the auditory cortex (Tomoda et al., 2012), and sexual abuse was associated with a reduced extended genital representation in the sensorimotor cortex (Heim et al., 2013). These specific modifications

can be interpreted as an adaptive process of the brain to the stressful sensory stimuli of childhood maltreatment (Teicher et al., 2016). Hence, the experience of abuse during childhood may lead to a reduction in synapses to protect the child from a hostile environment (Lim et al., 2018).

1.2. The cortex and cortical thickness

This thesis focuses on analysing the cerebral cortex which is the youngest and the most organised structure of the mammalian brain. This part of the brain defines a person, having distinct functions such as memory, executive organisation, intelligence, and processing sensory input (Câmara, 2015). The neocortex incorporated two major types of neurons: the pyramidal cells and the non-pyramidal cells. The first are projection neurons as part of the efferent cortex system, whereas the latter are intracortical interneurons as their axons regularly do not leave the cerebral cortex.

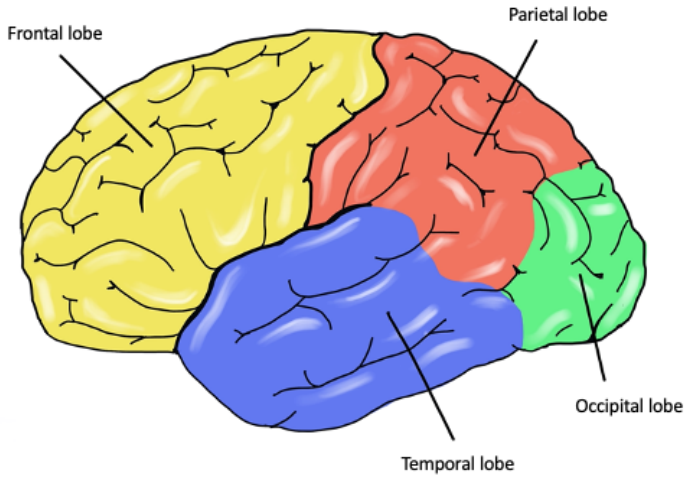

Figure 1 Visualisation of the cerebral cortex with the four lobes

The cortex is divided into four different lobes: the frontal lobe, the temporal lobe, parietal, and occipital lobe. The frontal lobe marks the largest area of the cortex occupying 41% of the cortex (Câmara, 2015). Each lobe has specific tasks; thus, the frontal lobe is associated with executive behavior, emotion regulation, and decision making (Barrash et al., 2018). The parietal lobe processes somatosensory information and complex functions such as language, sensorimotor planning, and spatial recognition (Klingner & Witte, 2018). The temporal lobe is involved in memory, facial perception, and processing sounds (Herlin et al., 2021). Processing

and interpreting visual stimuli, the occipital lobe is the smallest lobe in the cortex (Nelson, 2018).

The cerebral cortex is distinguished into the neocortex (or isocortex) and the allocortex. The neocortex constitutes 90% of the cortex containing around 10 billion neurons. As displayed in Figure 2, it is organised in 6 layers (I-VI) and reaches a thickness of 2.3 to 2.8 mm. Each layer has a distinct architecture that is unique for a certain brain area. The *molecular layer* (layer I) contains foremost axons from underlying neurons. The *external granular layer* (II) includes mostly small pyramidal cells. The *internal granular layer* (III) holds larger pyramidal cells most of which are association and commissural fibre. The *ganglionic layer* (IV) is formed by small solid-packed pyramid cells. It contains cortical afferents from the thalamus; hence this layer is most pronounced in the sensory area. The *inner pyramid layer* (V) entails primary large pyramid cells for efferences and is most distinct in the motoric area. The *multiform cell layer* (VI) blends into the white matter containing various cells, its axons are orientated to the thalamic nuclei. Using these distinct characteristics of each layer, the *Brodmann areas* subdivide the cortex into 52 regions. In contrast, the allocortex contains three to four layers and is the phylogenetic older area of the brain (Creutzfeldt, 1995).

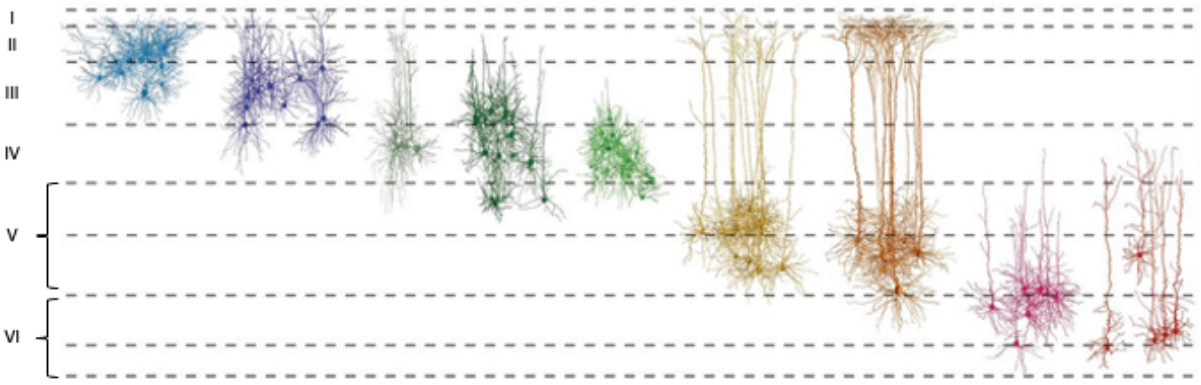

Figure 2 Visualisation of the cell types in the layers (I-VI) of the neocortex. Figure modified from Oberlaender et al. (2012)

Studies show that the cortical thickness is associated with age (Zhou et al., 2013), cognitive training (Jiang et al., 2016), cortical asymmetry (Zhou et al., 2013), and cellular architecture (La Fougère et al., 2011; Wagstyl et al., 2015). Further, cortical thickness is dependent on the number of neurons, glia provision, and the neuronal structure (La Fougère et al., 2011; Pelvig

et al., 2008). Also, the cortex increases in thickness the higher the structural hierarchical level in which a stimulus is processed (Wagstyl et al., 2015).

1.3. Current state of research and aim of this thesis

Present literature supports the hypothesis, that childhood abuse is manifested in cortical alterations (Frodl et al., 2017; Lim et al., 2014; Nemeroff, 2016; Teicher et al., 2003). Still, the question arises if these alterations are linked and connected to mental disorders. Previous studies found inconsistent results concerning whole-brain thickness (Lim et al., 2018; Schmaal et al., 2017; Tomoda et al., 2012; Tozzi et al., 2020).

Further, recent research is confronted with several limitations. First, there is often a small sample size, which can lead to ambiguous or accidental results. Second, results can be confounded by variables such as the level of education, alcohol consumption, and smoking behaviour as these parameters are frequently associated with childhood abuse, MDD, and cortical thickness (Anderson et al., 2007; Sheikh, 2017). Another limitation is the use of the unspecific term “childhood maltreatment” (Hart & Rubia, 2012). Present research rather suggests investigating distinct forms of maltreatment as each type of maltreatment has specific consequences on the cortex. Therefore, childhood abuse and neglect should be analysed separately.

To meet these limitations, this thesis analyses the effects of childhood abuse on the whole-brain thickness in interaction with the current state of depressive symptoms:

1. Is there an association between childhood abuse, depressive symptoms, and the whole-brain cortical thickness?
2. Is there an interaction effect between childhood abuse and depressive symptoms on the whole-brain cortical thickness?
3. Are there specific regions, which are especially sensitive to an interaction effect of childhood abuse and depressive symptoms?
4. Can the results be replicated in a sensitives analysis of a matched sub-sample?

With a sample of 1,551 participants from the population-based *Study of Health in Pomerania* (SHIP), this study regressed whole-brain cortical thickness and the cortical thickness of 34

cortical regions on the interaction effect of childhood abuse (yes/no) and depressive symptoms (none/mild/moderate to severe).

Further, it includes relevant confounders such as sex, age, age², sex-age-interaction, estimated intracranial volume (ICV), educational level, alcohol consumption, smoking behaviour, waist-to-height ratio, and body mass index (BMI). We extended the analysis by a sensitive analysis: Participants with childhood abuse (*n* = 120) were matched 1:1 with non-abused participants (*n* = 120) by sex (male, female), depressive symptoms (using the categories: no, mild, or moderate to severe symptoms), and age.

2 Methods

A detailed description of the used materials and methods are reported in Voss et al. (2022).

2.1. Concept of SHIP

This thesis used data from the Study of Health in Pomerania (SHIP) which is connected to the *Community Medicine* in Greifswald, Germany. The background of this large research project is a collection of the comprehensive differences in morbidity and life expectancy between east and west Germany. A main goal of SHIP is collecting and analysing data of various health-related risk factors in a longitudinal study design. Further, the study aimed to investigate the complex coherence between various risk factors to health, actual illnesses, and subclinical symptoms (Völzke, 2012).

SHIP-TREND-0 was collected from 2008 and 2012 in a basis survey assessing 4,420 participants between the age of 20 and 79. Another follow-up was assessed from 2016 until 2019 (SHIP-TREND-1). The data were grouped into four different regions (Stralsund, former county Nordvorpommern, Greifswald, and the former county Ostvorpommern). Variables of stratification were sex, age, and city/county of residence. The data incorporates laboratory data (i.e. blood and urine status), medical extermination, ultrasound, dental and dermatological examination, whole-body resonance imaging, ophthalmological examinations, sleeping monitory, body plethysmography and cardiopulmonary exercise testing (Volzke et al., 2011).

2.2. Measures

2.2.1. Interview

Sociodemographic information was assessed via a computer-assisted interview. The following variables were assessed: age, sex (male, female), education level (< 10 years (low), = 10 years (medium), and > 10 years of school), smoking behaviour (never, ex-, and current smokers), intake of antidepressants (yes/no), and alcohol consumption (intake of gram ethanol per day over the past 30 days). Further, subjects underwent a physical examination to measure the waist circumference, weight, and height.

2.2.2. Questionnaire Assessment

Depressive symptoms and the history of childhood abuse were assessed via questionnaires. The Childhood Trauma Questionnaire (CTQ) assesses the exposures of maltreatment with 28 items in five subscales: emotional, sexual, and physical abuse, as well as emotional and physical neglect (Bernstein et al., 2003). Each item is rated on a 5-point Likert scale reaching from "not experienced" to "very often experienced". Participants were assorted to the "abused group" if they reached the defined cut-off score for moderate abuse in at least one of the three subscales (sexual abuse ≥ 8; emotional abuse ≥ 13; physical abuse ≥ 10). Participants were assorted to the "non-abuse" group if they did neither reach the defined cut-off score for the abuse nor the neglect subscales. As the study design aimed to analyse participants free of moderate to severe childhood maltreatment with participants with childhood abuse, participants who exclusively reported emotional and/or physical neglect (emotional neglect ≥ 15; physical neglect ≥ 10) were excluded.

The Patient Health Questionnaire 9 (PHQ-9) assesses depressive symptoms with nine items (Kroenke et al., 2001). The items are based on the criteria for a MDD and are scored from having "no symptoms" to "symptoms every day". Participants were assorted into three groups by their sum score if they had no depressive (≤ 4), mild depressive (5 - 9), or moderate to severe depressive symptoms (≥ 10).

2.2.3. Magnetic resonance imaging and parcellation of the cerebral cortex

MRI of the head was measured with a Siemens Magnetom Avanto scanner which gained T1-weighted images with the following parameters: field strength = 1.5 T, orientation = axial plane, repetition time = 1900 ms, echo time = 3.37 ms, flip angle = 15°, slice thickness = 1 mm, and a resolution of 1 mm x 1 mm. Scans were excluded due to poor quality, structural abnormalities, the image segmentation pipeline failed, or if they were categorised as outliers.

The cortical reconstruction and volumetric segmentation were performed via FreeSurfer (version 5.3) which is an application suite to download for free (http://surfer.nmr.mgh.harvard.edu). Each region is allocated to the spherical atlas (Fischl et al., 1999). Cortical thickness was averaged across both hemispheres.

2.3. Statistical analysis

Descriptive methods were used to analyse the characteristics of the sample. To investigate the influence of childhood abuse, depressive symptoms, and the interaction between childhood abuse and depressive symptoms on whole-brain thickness, we implemented an analysis of variance with covariates (ANCOVA). The ANOCA included the whole-brain thickness as the dependent variable and the confounding variables as independent variables. Further, the model included the variables of interest: childhood abuse, depressive symptoms, and the interaction term of childhood abuse and depressive symptoms. In addition, the same analysis was conducted with depressive symptoms as a continuous variable in a linear regression by using the sum score of the PHQ-9. As confounding variables, we included sex, age, age², sex-age-interaction, estimated intracranial volume (ICV), educational level, alcohol consumption, smoking behavior, waist-to-height ratio, and body mass index (BMI). To estimate for variance homogeneity, Levene's test of equality was used. The ANCOVA was tested with a significance level of $p < 0.05$.

In addition, we computed 9 pairwise comparisons across the factor of childhood abuse (yes/no) and depressive symptoms (no, mild, moderate to severe) by using the estimated marginal means. These comparisons were adjusted by the above-named confounding variables. The false discovery rate method was used to adjust for multiple testing with a significance level of p value < 0.05 (Hochberg & Benjamini, 1990).

Further, we investigated how the interaction of depressive symptoms and childhood abuse influenced the 34 segmented cortical regions. Therefore, we implemented 34 single linear regression analyses with the respective cortical region as the dependent variable, and the interaction term (depressive symptoms*childhood abuse) as independent variables. These analyses were also adjusted by the above-named confounding variables and the false discovery rate was used to adjust for multiple testing with a significance level of p value < 0.05.

The descriptive statistics exposed variances in sex proportions and severity of depressive symptoms (Table 1) between the abuse and non-abuse group. Thus, an additional sensitivity analysis was implemented in which 120 participants with childhood abuse were matched 1:1 with non-abused participants concerning sex and depression level. Moreover, participants

were matched concerning age to rule out possible age-education-interactions. With this sub-sample, we used the same statistical analysis as described above with the whole sample.

All statistical analyses were performed with R version 3.6.2 (RStudio Team, 2015).

3 Results

3.1. Descriptive statistics

The whole sample resulted in 1,551 participants, of which 122 participants reported an experience of childhood abuse (Table 1). In the whole sample, the mean age was 50 years and 54% of the participants were female. 397 participants (25.6%) reported mild, and 90 participants (5.8%) reported moderate to severe depressive symptoms. 11% of the female subject reported childhood abuse, thus women were significantly more often affected by childhood abuse than men (4.6%; χ^2= 18.77, $p < 0.001$).

Table 1 Characteristics of the study sample

	All subjects (*N* = 1551)	Abuse (*n* = 122)	No Abuse (*n* = 1429)	*p* value [a]
Sex (female), *n* (%)	834 (54%)	89 (73%)	745 (52%)	< 0.001
Age (years), *M* ± *SD* (Age range: 21-82)	50 ± 14	50 ± 13	50 ± 14	0.908
BMI, *M* ± *SD*	27 ± 4.4	28 ± 4.9	27 ± 4.4	0.591
Educational level				0.294
<10 years, *n* (%)	167 (11%)	17 (14%)	150 (10%)	
=10 years, *n* (%)	870 (56%)	71 (58%)	799 (56%)	
>10 years, *n* (%)	514 (33%)	34 (28%)	480 (34%)	
Alcohol (g/day), *M* ± *SD*	8 ± 11	6 ± 8.7	8 ± 11	0.036
Smoking				0.264
Never smoker, *n* (%)	620 (40%)	41 (34%)	579 (41%)	
Ex-smoker, *n* (%)	559 (36%)	46 (38%)	513 (36%)	
Current smoker, N (%)	372 (24%)	35 (29%)	337 (24%)	
ICV (dm^3), *M* ± *SD*	1.587 ± 0.16	1.555 ± 0.17	1.590 ± 0.16	0.019
Depressive symptoms				< 0.001
No, *n* (%)	1064 (69%)	55 (45%)	1009 (71%)	
Mild, *n* (%)	397 (26%)	44 (36%)	353 (25%)	
Moderate to severe, *n* (%)	90 (6%)	23 (19%)	67 (5%)	
PHQ-9 (summary), *M* ± *SD*	3.7 ± 3.5	6.6 ± 5.4	3.5 ± 3.1	< 0.001
Neglect (yes), *n* (%)	72 (5%)	72 (59%)	0 (0%)	< 0.001
CTQ (summary), *M* ± *SD*	32 ± 9.1	54 ± 17	30 ± 4.1	< 0.001
Abuse severity (summary) *M* ± *SD*	17 ± 4.8	30 ± 9.4	16 ± 1.6	< 0.001
Abuse categories				
Emotional abuse (yes), *n* (%)	61 (4%)	61 (50%)	-	-
Physical abuse (yes), n (%)	62 (4%)	62 (52%)	-	-
Sexual abuse (yes), *n* (%)	52 (3%)	52 (43%)	-	-

Note: PHQ-9 = Patient Health Questionnaire 9; CTQ = Childhood Trauma Questionnaire; BMI = Body mass index; ICV = Intracranial volume; *a* = According to one-way ANOVA for continuous or χ^2-tests for categorical variables to check for possible differences in the groups.

The abuse group consisted of 73% female subjects, this proportion differed significantly from the non-abuse group with 52% female subjects ($\chi^2 = 18.77$, $p < 0.001$). Also, the number of subjects reporting depressive symptoms was significantly higher in the abuse than in the non-abuse group ($\chi^2 = 55.21$, $p < 0.001$). Thus, in the abuse group, 36% of the subjects reported mild and 19% moderate to severe depressive symptoms. Across these two groups, we could find no significant differences across confounding variables such as age, BMI, educational level, and smoking behaviour. However, in the group of no abuse, significantly more alcohol was consumed ($F(2, 1548) = 4.41$, $p = 0.036$), and the intracranial volume was larger ($F(2, 1548) = 5.47$, $p = 0.019$).

3.2. Effects on whole-brain cortical thickness

Levene's test was not significant indicating no violation of variance homogeneity. Concerning the influence of childhood abuse as an independent variable, results indicated no significant effects on whole-brain cortical thickness ($F(1, 1534) = 1.64$; $p = 0.201$). Further, no significant effects for depressive symptoms as independent variable on whole-brain cortical thickness were found ($F(1, 1534) = 0.08$; $p = 0.925$). However, the two-way interaction of childhood abuse and current depressive symptoms as an independent variable yielded a significant influence on whole-brain cortical thickness ($F(2, 1534) = 5.28$, $p = 0.007$).

Table 2 Results of the ANCOVA with whole-brain cortical thickness as dependent variable. Significant *p* values are highlighted

Variable	*F* value	*p* value
Age	**521.07**	**0.000**
Sex	**31.49**	**0.000**
Educational level	**8.84**	**0.000**
Smoking	**6.72**	**0.001**
Alcohol	**5.38**	**0.020**
Waist to height ratio	0.03	0.867
BMI	0.06	0.813
ICV	1.99	0.159
Interaction of age and sex	1.65	0.200
Depressive symptoms	0.08	0.925
Childhood abuse (yes/no)	1.64	0.201
Interaction of childhood abuse and depressive symptoms	**5.28**	**0.005**

Further, there was a statistically significant two-way interaction with the continuous variable of current depressive symptoms and childhood abuse on whole-brain cortical thickness (*t*-value (2, 1534) = -2.97, p = 0.003). This result supported the outcome of the categorical depression variable.

As seen in Table 2, additional significant predictors to the whole brain thickness were age, sex, educational level, smoking behaviour, and alcohol consumption. Their significant influence stresses the inclusion as confounding variables in the investigation models. On the other hand, we found no significant effect of the waist size nor the BMI on whole-brain cortical thickness.

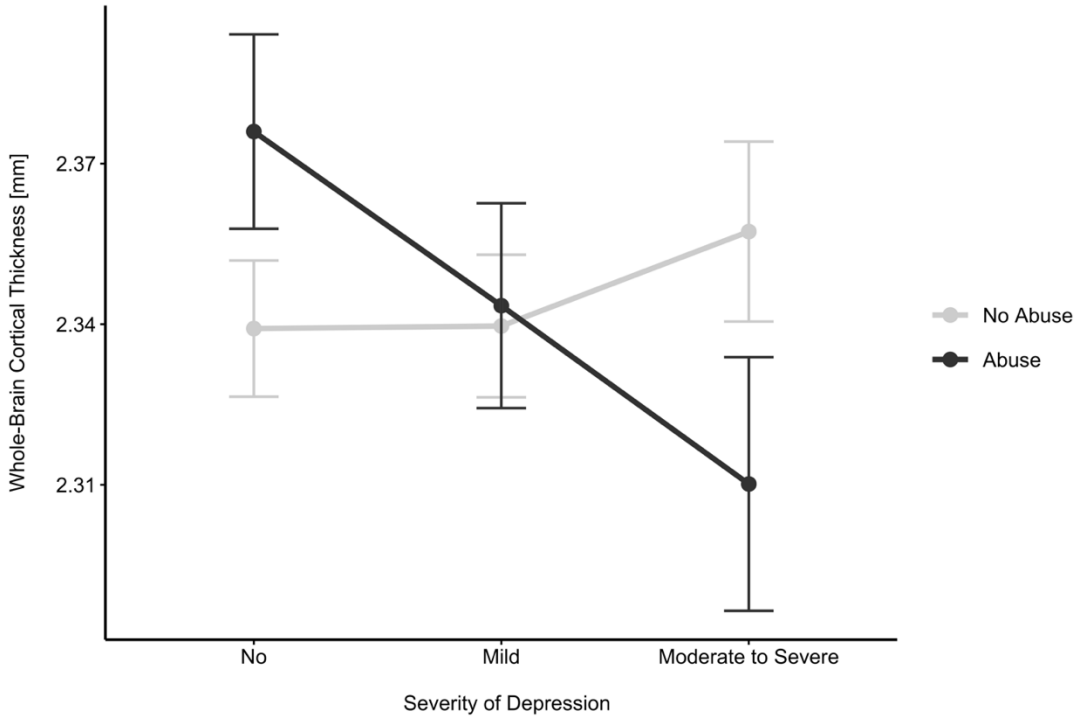

Figure 3 Lineplot showing pairwise comparisons between groups using the estimated marginal means and standard errors of whole-brain cortical thickness across all levels of childhood abuse and depression (Voss et al. 2022)

Pairwise comparisons using the estimated marginal means revealed different interaction effects between the abuse and non-abuse group across the level of depressive symptoms (Figure 3). In the abuse group, the whole-brain thickness was significantly thinner in participants with moderate to severe depressive symptoms than in participants who reported no depressive symptoms (*t*-value = 2.78, p_{FDR} = 0.025). Nevertheless, the statistical analysis revealed no significant distinction between participants with no or mild depressive symptoms

(*t*-value = 1.68, p_{FDR} = 0.209), nor between those with mild or moderately to severe depressive symptoms (*t*-value = 1.36, p_{FDR} = 0.224). Further, we found a significant difference in non-depressed participants with and without a history of abuse (*t*-value = -2.79, p_{FDR} = 0.025). Thus, non-depressed subjects with a history of abuse were associated with thicker whole-brain thickness than non-depressed subjects without a history of abuse.

3.3. Regional differences of the interaction effect

To further analyse the interaction effect concerning regional differences, we analysed 34 cortices from the Desikan-Killiany atlas. The interaction of childhood abuse and current depressive symptoms was a significant predictor in the thickness of 12 regions. These regions are shown in Figure 4 and include the inferior frontalis gyrus (pars opercularis, pars orbitalis, and pars triangularis), supramarginal gyrus, inferior temporal gyrus, lateral occipital gyrus, lateral orbitofrontal cortex, pericalcarine cortex, precuneus, superior parietal lobule, superior temporal gyrus, and temporal pole.

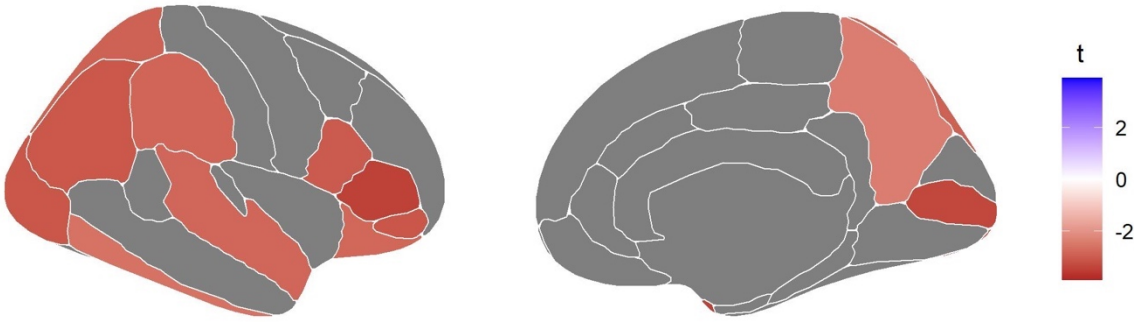

Figure 4 Associations between cortical thickness in 34 cortical regions and the interaction of depression and childhood abuse. Colours represent exclusively significant *t*-values from linear regressions with the brain regions as the dependent variable and adjusted for sex, age, age-sex-interaction, age², ICV, education, alcohol consumption, smoking, BMI, and waist-to-height ratio (Voss et al. 2022)

3.4. Sensitive analysis

In a sensitive analysis, participants with childhood abuse (*n* = 120) were matched 1:1 with non-abused participants (*n* = 120) by sex (male, female), depressive symptoms (using the categories: non, mild, or moderate to severe), and age. In this sub-sample, the two abuse-groups did no longer diverge in the distribution of sexes, ICV, and the depression level, confirming the matching process (Table 3).

Table 3 Characteristics of the matched sample. Nearest neighbour matching (concerning age, sex, and depressive level) was accomplished with the package *MatchIt* in R.

	All subjects (*N* = 240)	Abuse (*n* = 120)	No Abuse (*n* = 120)	*p* value [a]
Sex (female), *n* (%)	68 (28%)	33 (28%)	35 (29%)	0.886
Age (years), *M* ± *SD*	50 ± 13	50 ± 13	50 ± 13	0.707
BMI, *M* ± *SD*	28 ± 4.8	28 ± 4.9	28 ± 4.8	0.441
Educational level				0.595
<10 years, *n* (%)	29 (12%)	17 (14%)	12 (10%)	
=10 years, *n* (%)	143 (60%)	69 (57%)	74 (62%)	
>10 years, *n* (%)	68 (28%)	34 (28%)	34 (28%)	
Alcohol (g/day), *M* ± *SD*	5.9 ± 8.6	6.1 ± 8.8	5.7 ± 8.5	0.718
Smoking				0.423
Never smoker, *n* (%)	82 (34%)	41 (34%)	41 (34%)	
Ex-smoker, *n* (%)	98 (41%)	45 (38%)	53 (44%)	
Current smoker, *n* (%)	60 (25%)	34 (28%)	26 (22%)	
ICV (dm^3), *M* ± *SD*	1.559 ± 0.16	1.558 ± 0.17	1.560 ± 0.15	0.905
Depressive symptoms				0.960
No, *n* (%)	108 (45%)	55 (46%)	53 (44%)	
Mild, *n* (%)	90 (38%)	44 (37%)	46 (38%)	
Moderate to severe, *n* (%)	42 (18%)	21 (18%)	21 (18%)	
PHQ-9 (summary), *M* ± *SD*	5.8 ± 4.6	6.4 ± 5.2	5.2 ± 4.0	0.045
Neglect (yes), *n* (%)	72 (30%)	72 (60%)	0 (0%)	< 0.001
CTQ (summary), *M* ± *SD*	42 ± 17	55 ± 17	30 ± 4.1	< 0.001
Abuse severity (summary), *M* ± *SD*	23 ± 9.7	30 ± 9.5	16 ± 2.0	< 0.001

Note: PHQ-9 = Patient Health Questionnaire 9; CTQ = Childhood Trauma Questionnaire; BMI = Body mass index; ICV = Intracranial volume; *a* = According to one-way ANOVA for continuous or χ^2-tests for categorical variables to check for possible differences in the groups.

In the matched sample, the two-way interaction between childhood abuse and depressive symptoms was significant ($F(2, 223) = 4.40$, $p_{FDR} = 0.013$), therefore supporting the main findings. Post-hoc pairwise comparisons revealed statistically significant differences in the abuse group between participants with no and participants with moderate to severe depressive symptoms (*t*-value = 3.34; $p_{FDR} = 0.009$).

Concerning regional influences, significant interaction effects for childhood abuse and depressive symptoms were observed in the inferior frontalis gyrus (including the pars opercularis (*t*-value = -2.86; p_{FDR} = 0.043) and the pars triangularis (*t*-value = -3.52; p_{FDR} = 0.018)), the inferior parietal gyrus (*t*-value = -2.89; p_{FDR} = 0.043), supramarginal gyrus (*t*-value = -2.75; p_{FDR} = 0.044), and temporal pole (*t*-value = -2.83; p_{FDR} = 0.043). These results stress the impact of the interaction effect on these regions, despite the smaller sample size.

4 Discussion

The present thesis analyses structural brain alterations in a sample of participants exposed to early life stress with and without clinical psychopathology investigating a large sample with 1,551 participants within the SHIP study. The results highlight the influence of early life stress on the development of the cortex. Further, this thesis marks the interconnection of vulnerability factors (childhood abuse) and current stress factors (depressive symptoms).

The results indicate an interaction effect of childhood abuse and depressive symptoms on the whole brain thickness. In participants with childhood abuse, reduced whole-brain cortical thickness is associated with more severe depressive symptoms. Contrary, participants with a history of childhood abuse and without depressive symptoms are associated with increased whole-brain thickness. This outcome highlights the inclusion of the state of psychopathology when analysing the influence of childhood abuse on the cortex. Similarly, the effects of childhood abuse appear to be a notable moderator when analysing the impact of depression on cortical thickness. These results propose a standard in study designs, assessing childhood maltreatment as a confounding risk factor. This is essential in treatment study designs with patient samples as they have a high proportion of childhood maltreatment (Teicher & Samson, 2016). The assessment of childhood maltreatment is manageable with the CTQ. The CTQ is a reliable and practical questionnaire and is also available in a short version with five items (Child Trauma Screener; Grabe et al., 2012).

Further, this thesis analyses regional interaction effects of childhood abuse and depressive symptoms. Concludingly, the results indicate that regions with a higher impact of the interaction variable (depression and childhood abuse) are involved in various fields such as sensory processing (visual and auditive), self-conception, and memory. Thus, the inferior frontal gyrus is significantly associated with the interaction term. In the dominant hemisphere, the pars opercularis and triangularis are part of the Broca's area which is relevant in producing speech (Moini & Piran, 2020). Additionally, the results show significant associations with the inferior parietal lobule and the superior temporal gyrus which are both a vital part of the Wernicke's area; a brain structure that processes the comprehension of spoken language (Moini & Piran, 2020). Previous studies reported a thinning in the precuneus in participants with a history of sexual abuse and further in subjects with recent life stress (Bartlett et al., 2019; Heim et al.,

2013). Amongst others, the precuneus is involved in the notion of the self and memory (Kjaer et al., 2002). Moreover, the results display an association with structures that process visual stimuli such as the lateral occipital and the pericalcarine cortex which were reported in prior studies in relation to childhood abuse (Lim et al., 2020).

This study finds thicker cortical thickness in participants who experienced abuse but did not report depressive symptoms. Similar effects were previously reported in patients with schizophrenia and their healthy siblings, whereas both experienced childhood maltreatment. Reductions in cortical thickness were found in the patient group and an increase of cortical thickness in the healthy sibling group (Habets et al., 2011). The increase in cortical thickness could be interpreted as resilience on a morphological level. Teicher et al. (2016) distinguished a few structural characteristics of the brain that could indicate resilience including an enlarged visual cortex (Tomoda et al., 2012), an outsized amygdala on the left hemisphere, or an increased hippocampal volume on the right hemisphere (Morey et al., 2016). The results of this thesis underline that resilient individuals with childhood abuse are associated with increased thickness in the visual cortex, such as the lateral occipital gyri.

Recapitulating, childhood abuse is a severe intrusion in the early development of the brain, hence, cerebral structures can be prone to future stressful influences (Oldehinkel et al., 2014; Shonkoff et al., 2009; Teicher et al., 2016). The results of this thesis suggest that childhood abuse is a relevant biological disposition interacting with the current state of psychopathology.

4.1. Practical implications

Whole-brain cortical thickness is associated with the interaction of childhood abuse and depressive symptoms. Thus, maltreated individuals with psychopathology could be distinguished as a particular *ecophenotype* (Teicher et al., 2016). The current treatment and diagnostic system only insufficiently integrate this knowledge.

Concerning the treatment, various studies found a less favourable outcome in depressive patients with a history of maltreatment (Nanni et al., 2012). Maltreated individuals have a significantly poorer outcome for pharmacological and combined treatment (psychotherapy and pharmacological) compared to individuals without childhood maltreatment (Nanni et al.,

2012). Further, a recent study suggests that the severity of childhood maltreatment might undermine an antidepressant treatment (Nikkheslat et al., 2020). Thus, Nikkheslat et al. advise a personalised treatment for depressed patients with childhood maltreatment. Individuals might need specialised treatment including approaches to reduce oxidative stress and inflammation such as low endurance sports which are, for example, integrated into the therapy of stress-induced hyperalgesia (Egle et al., 2016).

The assessment of childhood maltreatment might also be a relevant factor to guide different treatment approaches in psychiatry (Heim et al., 2010). In patients with chronic depression and childhood maltreatment, psychotherapy (cognitive behavioral analysis system of psychotherapy) was more efficient than antidepressant monotherapy (nefazodone) (Nemeroff et al., 2003). Also, in a sample of patients with childhood abuse, the combined treatment of psychotherapy and pharmacotherapy was only slightly more efficient than psychotherapy alone. Therefore, Nemeroff et al. (2003) hypothesise that psychotherapy has a higher treatment recommendation in patients with chronic depression and a history of childhood maltreatment.

The incorporation of childhood maltreatment into the psychiatric diagnostic system is of great importance. First, we need to advance from a nosology that focuses on descriptive categories, to a diagnostic system that integrates the aetiology of a mental disorder (Teicher et al., 2021). This will help us as clinicians to improve our treatment results. Until then, in German psychiatric institutions the ICD-10 (International statistical classification of diseases, 10th revision) does allow to include the Z-diagnosis "Z62 *Andere Kontaktanlässe mit Bezug auf die Erziehung"* which refers to the emotional and physical neglect as well as emotional abuse; and "Z61 *Kontaktanlässe mit Bezug auf Kindheitserlebnisse*" which refers to physical and sexual abuse (Deutschen Institut für medizinische Dokumentation und Information, 1994). Using these additional diagnoses will stress the importance of early experiences in childhood within the genesis of a mental disorder.

In summary, it can be stated that it seems urgent to ascertain experiences of childhood maltreatment at the beginning of psychiatric and psychotherapeutic treatment. Recently, a study analysed 3,680 medical files of adult inpatients of a psychiatric hospital in Germany and found that only 6% of the entries refer to experiences of abuse and neglect (Neumann et al., 2021). Those rare documentations show that there is a need for more awareness of childhood abuse and neglect in psychiatric and psychotherapeutic institutions. Especially as this study, in line

with prior research, found distinct higher prevalence of childhood maltreatment in individuals with depressive symptoms or mental disorders (Álvarez et al., 2011; Negele et al., 2015). In this sample, 26% of participants with moderate to severe depressive symptoms reported childhood abuse. Furthermore, Teicher et al. (2021) suggest that the assessment of the maltreatment history could be fundamental for every medical history as childhood maltreatment is a risk factor for several somatic disorders (Wegman & Stetler, 2009).

Besides an individualised treatment approach, this issue must get more alertness in political-societal prevention. Parents need to be educated on the early needs of a child and the impact of childhood abuse. Further, the state needs to focus on early prevention programs, especially for vulnerable family systems. Moreover, early childhood development directly influences economic, health and social outcomes (Heckman, 2008). Especially the first years of life lay the foundation for skills and abilities which need to be fostered. The *Heckman Equation* postulates that by investing in early childhood, society gets the greatest return on investment (Heckman, 2008). The earlier this investment is established, the greater the outcome. Heckman states that the best investment is from birth to 5 years (Heckman, 2008).

4.2. Strengths and limitations

The analysis of this thesis has several strengths, such as the large sample size, the careful study design, the inclusion of several covariates and the integration of participants with and without psychopathology. Despite that, there are several limitations, which are described in in detail the publication (Voss et al., 2022). First, one limitation is the assessment of depressive symptoms with a questionnaire. Thus, we cannot rule out the effects of other psychiatric diagnoses. Second, the severity of childhood maltreatment is not equal across the three groups of depression severity. Therefore, childhood maltreatment severity could be a moderating factor influencing cortical thickness. Third, the study design does not allow a causal interpretation between the alteration of cortical thickness, childhood maltreatment, and depressive symptoms. Thus, longitudinal study designs are necessary to analyse the causal association. Finally, the generalisability of these results is narrowed because of the inaccurate definitions of childhood abuse in the research field. By analysing childhood abuse, this study could miss specific effects of emotional, physical, or sexual abuse as well as neglect on the cortex.

5 Summary

The experience of abuse in the period of childhood and youth is a key stressor that has consequences on the developing brain and is associated with the genesis of mental disorders. Childhood abuse and depression often cooccur together and have both been associated with cortical thickness resulting in a difficulty to detangle the influence of each factor. In prior studies, childhood abuse and depression were inconsistently related to whole-brain cortical thickness. Thus, this thesis aims to investigate the link between childhood abuse, depressive symptoms, and alterations of the cortex.

Therefore, this study analyses 1,551 individuals of the general population. A significant interaction effect of childhood abuse and depressive symptoms is observed for whole-brain cortical thickness. Yet, the results indicate no influence of childhood abuse or depression alone. A thinner cortex was associated with more severe depressive symptoms in the abused, but not in the non-abused group. In non-depressed participants, an increased whole-brain cortex was found in the abused, compared to the non-abused group. Similar interaction effects were observed in 12 out of 34 cortical regions.

The results suggest, in line with prior findings, that depressed individuals with a history of childhood abuse are a specific *ecophenotype* which is also reflected in specific brain alterations. Cortical regions that are distinct associated with the interaction of depressive symptoms and childhood abuse are involved in various fields such as sensory processing, self-conception, and memory. Greater cortical thickness in subjects with childhood abuse and without depressive symptoms might act compensatory and thus reflect resilience against depressive symptoms.

Practical implications concern the treatment and diagnostic system as well as the importance of early prevention programs. An individualised treatment is necessary as various studies found a less favourable outcome in depressive patients with a history of maltreatment. Therefore, it seems urgent to assess experiences of childhood abuse at the beginning of psychiatric and psychotherapeutic treatment. In addition, early prevention programs are in need to support vulnerable family systems and thereby strengthening the economic, health and social system.

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ORIGINAL PAPER

Interaction of childhood abuse and depressive symptoms on cortical thickness: a general population study

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Abstract

Childhood abuse was inconsistently related to whole-brain cortical thickness in former studies. However, both childhood abuse and cortical thickness have been associated with depressive symptoms. We hypothesised that childhood abuse moderates the association between depressive symptoms and cortical thickness. In 1551 individuals of the general population, associations between whole-brain cortical thickness and the interaction of childhood abuse (emotional, physical, and sexual) and depressive symptoms were analysed using an ANCOVA. Linear regression analyses were used to estimate the same effect on the cortical thickness of 34 separate regions (Desikan-Killiany-atlas). A significant interaction effect of childhood abuse and depressive symptoms was observed for whole-brain cortical thickness ($F(2, 1534) = 5.28$, $p = 0.007$). A thinner cortex was associated with depressive symptoms in abused (t value = 2.78, $p = 0.025$) but not in non-abused participants (t value = − 1.50, $p = 0.224$). Focussing on non-depressed participants, a thicker whole-brain cortex was found in abused compared to non-abused participants (t value = − 2.79, $p = 0.025$). Similar interaction effects were observed in 12 out of 34 cortical regions. Our results suggest that childhood abuse is associated with reduced cortical thickness in subjects with depressive symptoms. In abused subjects without depressive symptoms, larger cortical thickness might act compensatory and thus reflect resilience against depressive symptoms.

Keywords Cortical thickness · Childhood abuse · Depressive symptoms · Resilience

Introduction

The *American Professional Society on the Abuse of Children* (APSAC) defines childhood abuse as "words or overt actions that cause harm, potential harm, or threat of harm to a child" [1] and differentiates between emotional, physical, and sexual abuse. In Germany, the prevalence of emotional abuse was estimated at 6.5%, physical abuse at 6.7%, and 7.6% at sexual abuse [2].

Childhood abuse initiates physiological and psychological stress-response systems [3], contributing to long-term changes in epigenetic processes, gene regulation, and brain development [4, 5]. Thus, childhood abuse is associated with higher lifetime risks of somatic illnesses such as metabolic syndrome, cardiovascular and respiratory disorders [6]. Additionally, childhood abuse is associated with the development of mental diseases such as major depressive disorder (MDD) [7, 8] and posttraumatic stress disorder [8]. Therefore, the genesis of mental diseases is, besides genetic factors, influenced by environmental aspects such as childhood abuse, probably through epigenetic mechanisms [9]. Hence, structural alterations may precede the onset of the mental disease [9]. In contrast, Teicher et al. [5] stated in their review in *Nature Reviews Neuroscience* that certain alterations in maltreated subjects are *not*

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linked to psychopathology and that maltreated subjects could also differ in brain changes which help them compensate [5]. Thus, understanding how childhood abuse increases the risk of physical and mental diseases and, thus, enabling the implementation of focused prevention programs to reduce pathological consequences is of high demand [5]. The exact mechanisms behind these associations are still elusive.

Several studies suggest that different patterns of brain alterations are associated with different types of maltreatment. Thus, parental verbal abuse was linked to a reduction in the auditory cortex [10] and sexual abuse was associated with a reduced extended genital representation in the sensomotoric cortex [11]. On the other hand, social deprivation was associated with reductions in regions of the association cortex processing social stimuli [12]. To address these findings, we focussed only on the consequences of childhood abuse on the cortex.

More recently, Tozzi et al. [13] analysed interaction effects of severity and type of childhood maltreatment (abuse or neglect) and MDD on cortical thickness in 3,872 participants within the ENIGMA consortium [13]. They found associations of childhood maltreatment severity with reductions of thinner cortices in the banks of the superior temporal sulcus and supramarginal gyrus [13]. However, they did neither find an interaction effect between childhood maltreatment and MDD, nor a main effect of MDD on cortical thickness. Within the ENIGMA consortium, Schmaal et al. [14] analysed the cortical thickness in 1,902 MDD patients and 7658 controls. They found thinner cortices in MDD patients in the temporal and frontal lobes, including the orbitofrontal cortex [14]. Further, Lim et al. [15] analysed a youth sample (excluding sexual abuse) and found lower cortical thickness in abused participants with psychiatric comorbidities in comparison to healthy non-abused participants. Given that childhood abuse is a crucial risk factor for the development of MDD, it is challenging to disentangle the contribution of both conditions to the cortical thickness [15]. Former findings show divergent results on how depression and childhood abuse affect the cortex. Investigating if and how the interaction of depression and childhood abuse might explain some of these differential outcomes, is a relevant concern.

Although the ENIGMA studies investigating the childhood-maltreatment-MDD-interaction on cortical regions analysed large sample sizes [13], there are limitations essential to consider: covariates such as level of education, alcohol consumption, smoking behaviour, and obesity were missing. However, as these parameters are frequently associated with childhood abuse, MDD, and cortical thickness, they could act as confounders [16, 17]. Further, the inclusion of many different samples increased the heterogeneity of the overall sample which might have lowered the effect sizes [18].

To address these limitations, we used a sample of 1,551 participants from the population-based Study of Health in Pomerania (SHIP) to analyse the interaction of childhood abuse and depressive symptoms on cortical thickness. We focused on current depressive symptoms, which were associated with childhood maltreatment in former studies [19, 20]. More precisely, this study regressed whole-brain cortical thickness in addition to the cortical thickness of 34 single cortical regions on the interaction effect between childhood abuse (yes/no) and depressive symptoms (none/mild/moderate to severe). Previous research revealed differential results on how depression and childhood abuse affect the cortex. We hypothesise that the interaction of childhood abuse and depressive symptoms is associated with the cortical thickness and might explain some of the diverse results.

Methods

Sample

SHIP is a population-based cohort study [21]. Local registries randomly drew the study sample of West Pomerania between 2008 and 2011 (SHIP-Trend-0: $N=4420$). For more details see Völzke et al. [21]. SHIP-Trend-0 participants free of exclusion criteria (e.g. cardiac pacemakers, pregnancy) were invited for a whole-body magnetic resonance imaging (MRI) [22]. MRI of the head was available for 2,154 participants of SHIP-Trend-0 [23]. MRI scans of sufficient quality were available for 1,986 participants (see subdivision *Magnetic Resonance Imaging* for the detailed selection process). This study design excluded participants from the following analyses if the information on depressive symptoms ($n=60$) or childhood abuse ($n=138$) was missing or due to incomplete covariate data ($n=22$; see subdivision *Statistical Analyses*). Finally, as we aimed to compare participants without any history of abuse or neglect with abused participants, we excluded participants if they reported an experience of neglect, but not abuse ($n=215$). Thus, our final sample comprised 1,551 participants.

The institutional review board of the University Greifswald approved SHIP. Examinations and assessments have been conducted by the declaration of Helsinki, including written informed consent.

Measures

Interview

Sociodemographic data including age, sex, education level, smoking behaviour, intake of antidepressants (yes/no) and alcohol consumption was collected via a computer-assisted face-to-face interview. According to the German

school system, educational level was divided into < 10 years (low), = 10 years (medium), and > 10 years of school education (high). SHIP-Trend-0 categorised smoking behaviour into never, ex-, and current smokers. Alcohol consumption was defined as the mean intake of gram ethanol per day over the past 30 days according to Baumeister et al. [24]. Afterwards, participants underwent a physical examination including the measurement of the waist circumference, weight, and height. The examiner measured the waist circumference with the participant standing on both feet to the nearest 0.1 cm. Weight was measured in light clothes to the nearest 0.1 kg. Height was measured to the nearest 1 cm. Participants were asked to report the medication used during the past 7 days and to bring their package containers. Medication was categorised according to the ATC-Index [25]. Antidepressants were defined as ATC codes N06A.

Childhood abuse

To enquire about the exposure to childhood abuse, this study used the German version of the Childhood-Trauma-Questionnaire (CTQ) [26, 27]. The CTQ is a 28-item questionnaire assessing maltreatment in childhood and youth [27, 28]. The CTQ measures different exposures of maltreatment in five subscales: emotional, sexual, and physical abuse, emotional and physical neglect. Participants rated each item on a 5-point Likert scale, from "not experienced" to "very often experienced". The CTQ is an established instrument with decent reported validity (depression: $r = 0.36$, anxiety: $r = 0.40$, health: $r = -0.23$) and reliability (emotional abuse: Cronbach's $\alpha = 0.87$, physical abuse: $\alpha = 0.80$, sexual abuse: $\alpha = 0.89$) with a Cronbach's α of 0.94 for the whole questionnaire. For an overview of the German version see Klinitzke et al. [29]. Note again that, as we aimed to compare participants free of moderate to severe childhood maltreatment with abused participants, we excluded participants who exclusively reported emotional and/or physical neglect (emotional neglect ≥ 15; physical neglect ≥ 10) from the study (see section *Sample*). This exclusion criterion, however, did not take effect if participants reported co-experience of abuse and neglect. A dichotomized variable of childhood abuse was generated including sexual, physical, and emotional abuse. This study categorised participants to the abused group if they reached the defined cut-off score for moderate abuse in at least one of the three subscales (sexual abuse ≥ 8; emotional abuse ≥ 13; physical abuse ≥ 10) [27]. Participants were categorised to the non-abused group when they did neither score on the abuse nor the neglect subscales.

Depressive symptoms

To enquire depressive symptoms, this study used the Patient-Health-Questionnaire-9 (PHQ-9) [30]. The PHQ-9 assesses the existence of depressive symptoms with nine items, based on the nine criteria for MDD of the Diagnostic and Statistical Manual of Mental Disorders 4th Revision (DSM-IV). A 4-point Likert scale assesses the symptoms from having "no symptoms" to "symptoms every day". The PHQ-9 has a suitable internal consistency with a Cronbach's α of 0.88 [31]. Based on the summary score of the PHQ-9, this study design assorted participants into three groups according to the criteria of Kroenke et al. (2002): no depressive (≤ 4), mild depressive (5–9), and moderate to severe depressive symptoms (≥ 10).

Magnetic resonance imaging (MRI)

MRI of the head was available for 2154 participants of SHIP-Trend-0 [23]. A Siemens Magnetom Avanto scanner acquired T1-weighted images with following parameters: field strength = 1.5 T, orientation = axial plane, repetition time = 1900 ms, echo time = 3.37 ms, flip angle = 15°, slice thickness = 1 mm, and resolution 1 mm × 1 mm. Three scans were eliminated due to poor quality (strong frontal darkening). In addition, 100 scans were excluded due to structural abnormalities (e.g., tumours, cysts) and cerebral stroke. The image segmentation pipeline failed to process four scans. We excluded further 61 participants which were categorised as outliers in various cortical thickness regions (see below), resulting in an imaging sample of 1986 participants.

Parcellation of the cerebral cortex

The FreeSurfer image analysis suite (version 5.3) performed the cortical reconstruction and volumetric segmentation. This application suite is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu).

Briefly, this process included the removal of non-brain tissue using a hybrid watershed/surface deformation procedure [32], automated Talairach transformation, intensity normalization [33], tessellation of the grey/white matter boundary, and automated topology correction [34, 35]. Further, surface deformation follows intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [36–38].

Individual cortical models were registered to a spherical atlas [39] and parcelled into 68 units with respect to gyral and sulcal structure [40, 41]. Average thickness of each region was computed. Statistical quality control was performed by excluding cases with thickness values higher/lower than four standard deviations from the whole sample mean after adjustment for age, sex, body height, and the interaction of age with sex. 61 participants were excluded based on this criterion.

Cortical thicknesses were averaged across both hemispheres resulting in 34 brain region parameters. Besides, whole-brain cortical thickness was defined as the average of the thicknesses of the left and right hemisphere. The estimated intracranial volume (ICV) was generated by FreeSurfer.

Statistical analysis

All analyses were adjusted for sex, age, age^2, sex-age-interaction, estimated intracranial volume (ICV), educational level, alcohol consumption, smoking behaviour, waist-to-height ratio, and body mass index (BMI).

To analyse the main and interaction effects of childhood abuse (yes/no) and depressive symptoms (none/mild/moderate to severe) on whole-brain cortical thickness, we implemented three models for an analysis of variance with covariates (ANCOVA) with whole-brain cortical thickness as the dependent variable. Two models were implemented with the confounding variables and either childhood abuse or depressive symptoms as independent variable. The third model included the interaction term childhood abuse*depression. The same analysis model was conducted with depressive symptoms as a continuous variable in a linear regression by using the sum score of the PHQ-9 (see SI). In an additional model, we included the intake of antidepressants (yes/no) as a covariate in addition to the other covariates mentioned above (see SI). Levene's Test of Equality estimated the variance homogeneity. The overall test on whole-brain cortical thickness tested with a significance level of $p < 0.05$. Afterwards, 9 post-hoc tests were calculated for the interaction groups using the estimated marginal means. Therefore, we computed pairwise comparisons between the abuse groups at each level of depression and vice versa. These tests were adjusted by sex, age, age^2, sex-age-interaction (sex × age), BMI, waist-to-height ratio, alcohol consumption, educational level, smoking, and ICV. Educational level and smoking were dummy coded and, thus, represented by two dummy variables, respectively. We used the false discovery rate (FDR) method of Benjamini and Hochberg [42] to adjust the p values for multiple testing for the 9 post-hoc pairwise comparisons.

To investigate which brain regions are affected by the interaction of childhood abuse and depressive symptoms, the cortical thickness of 34 segmented cortical regions was examined in separate linear regression analyses. We implemented the childhood abuse*depression interaction term as the independent variable and each cortical region separately as the dependent variable. These tests were adjusted by sex, age, age^2, sex-age-interaction, BMI, waist-to-height ratio, alcohol consumption, educational level (dummy coded), smoking (dummy coded), and ICV. To correct for multiple testing, FDR correction was used for 34 linear regression analyses.

Descriptive statistics revealed differences in sex proportions and depression level (Table 1) between the abuse and non-abuse group. Thus, abused participants ($n = 120$) were matched 1:1 with non-abused participants ($n = 120$) by sex (male, female), depressive symptoms (using the categories: non, mild, or moderate to severe), and age. We matched for age to adjust for possible age-education-interactions. Nearest neighbour matching was accomplished with the package *MatchIt*. Descriptive statistics of the matched sample are presented in Table SI2. We recalculated all analyses with the matched sample as sensitivity analyses.

A p value of < 0.05 was considered statistically significant. All statistical analysis were performed using R version 3.6.2 [43].

Results

Demographics

Descriptive statistics are summarised in Table 1. Overall, 1,429 participants reported no exposure to any childhood maltreatment, 122 (8.5%) experienced at least one type of childhood abuse. In the whole sample, 11.0% of the female population reported childhood abuse, thus women were significantly more often affected by childhood abuse than men (4.6%; $\chi^2 = 18.77$, $p < 0.001$). Further, 1,064 participants (68.6%) reported no current depressive symptoms, whereas 397 participants (25.6%) reported mild, and 90 participants (5.8%) reported moderate to severe symptom severity. The participants of the group allocation (abuse: yes/no) did not vary regarding age, waist circumference, smoking, BMI, and educational level. However, there were substantial variations across the two groups in the distribution of sexes ($\chi^2 = 18.77$, $p < 0.001$), ICV ($F(2, 1548) = 5.47$, $p = 0.019$), alcohol consumption ($F(2, 1548) = 4.41$, $p = 0.036$), and in the frequency of the depressive categories ($\chi^2 = 55.21$, $p < 0.001$). Descriptive characteristics of the study sample ordered by the severity of depressive symptoms are displayed in Table SI1.

Thus, to consider these differences in the analyses more clearly, a subsample matched for sex, depression level, and age was extracted. Table SI2 summarizes the descriptive statistics for the matched sample in the supplementary information. In the matched sample, the two abuse-groups did no longer vary in the distribution of sexes, ICV, and the depression level (non, mild, moderate to severe) validating the matching process.

Table 1 Characteristics of the study sample

	All subjects ($N=1551$)	Abuse ($n=122$)	No abuse ($n=1429$)	p value[a]
Sex (female), *n* (%)	834 (54%)	89 (73%)	745 (52%)	< 0.001
Age (years), M ± SD (age range: 21–82)	50 ± 14	50 ± 13	50 ± 14	0.908
BMI, M ± SD	27 ± 4.4	28 ± 4.9	27 ± 4.4	0.591
Educational level				0.294
< 10 years, *n* (%)	167 (11%)	17 (14%)	150 (10%)	
= 10 years, *n* (%)	870 (56%)	71 (58%)	799 (56%)	
> 10 years, *n* (%)	514 (33%)	34 (28%)	480 (34%)	
Alcohol (g/day), M ± SD	8 ± 11	6 ± 8.7	8 ± 11	0.036
Smoking				0.264
Never smoker, *n* (%)	620 (40%)	41 (34%)	579 (41%)	
Ex-smoker, *n* (%)	559 (36%)	46 (38%)	513 (36%)	
Current smoker, *N* (%)	372 (24%)	35 (29%)	337 (24%)	
ICV (dm^3), *M ± SD*	1.587 ± 0.16	1.555 ± 0.17	1.590 ± 0.16	0.019
Depressive symptoms				< 0.001
No, *n* (%)	1064 (69%)	55 (45%)	1009 (71%)	
Mild, *n* (%)	397 (26%)	44 (36%)	353 (25%)	
Moderate to severe, *n* (%)	90 (6%)	23 (19%)	67 (5%)	
PHQ-9 (summary), M ± SD	3.7 ± 3.5	6.6 ± 5.4	3.5 ± 3.1	< 0.001
Neglect (yes), *n* (%)	72 (5%)	72 (59%)	0 (0%)	< 0.001
CTQ (summary), M ± SD	32 ± 9.1	54 ± 17	30 ± 4.1	< 0.001
Abuse severity (summary) M ± SD	17 ± 4.8	30 ± 9.4	16 ± 1.6	< 0.001
Abuse Categories				
Emotional Abuse (yes), *n* (%)	61 (4%)	61 (50%)	–	–
Physical Abuse (yes), n (%)	62 (4%)	62 (52%)	–	–
Sexual Abuse (yes), *n* (%)	52 (3%)	52 (43%)	–	–

PHQ-9 Patient-Health-Questionnaire-9; *CTQ* Childhood-Traumatisation-Questionnaire; *BMI* Body Mass Index; *ICV* Intracranial volume

[a]According to one-way ANOVA for continuous or χ^2 tests for categorical variables to check for possible group differences

Effects of childhood abuse and depressive symptoms on whole-brain cortical thickness

The Levene's-Test was non-significant for the ANCOVA analysis indicating no violation of variance homogeneity. Analysing the influence of childhood abuse on whole-brain cortical thickness, we found no significant effects ($F(1, 1534) = 1.64$; $p = 0.201$). Further, no significant effects were observed for depressive symptoms ($F(1, 1534) = 0.08$; $p = 0.925$). However, there was a statistically significant two-way interaction between childhood abuse and current depressive symptoms on whole-brain cortical thickness ($F(2, 1534) = 5.28$, $p = 0.007$). In addition, there was also a statistically significant two-way interaction between childhood abuse and the continuous variable for depressive symptoms on whole-brain cortical thickness ($F(2, 1534) = -2.97$, $p = 0.003$).

To investigate this interaction effect in more detail, post-hoc pairwise comparisons were calculated using the estimated marginal means (see Fig. 1 and Table SI3). We adjusted all nine post-hoc comparisons with the false discovery rate method of Benjamini and Hochberg.

Pairwise comparisons were computed between the abuse groups (yes/no) at each level of depression (non, mild, and moderate to severe) and vice versa. In abused participants, we found a statistically significant difference between non-depressed participants and participants with moderate to severe depressive symptoms (t value = 2.78, $p_{FDR} = 0.025$). However, there was no significant difference between non-depressed and mildly depressed participants (t value = 1.68, $p_{FDR} = 0.209$), nor between mildly depressed and moderately to severe depressed participants (t value = 1.36, $p_{FDR} = 0.224$). In contrast, in non-abused participants, no significant differences reached the level of significance across the factor of depression.

In non-depressed participants, we found significant differences between abused and non-abused participants (t-value = − 2.79, $p_{FDR} = 0.025$). In contrast, childhood abuse had no significant effect in mildly depressed (t value = − 0.25, $p_{FDR} = 0.904$), nor moderate to severely depressed participants (t value = 2.052, $p_{FDR} = 0.121$).

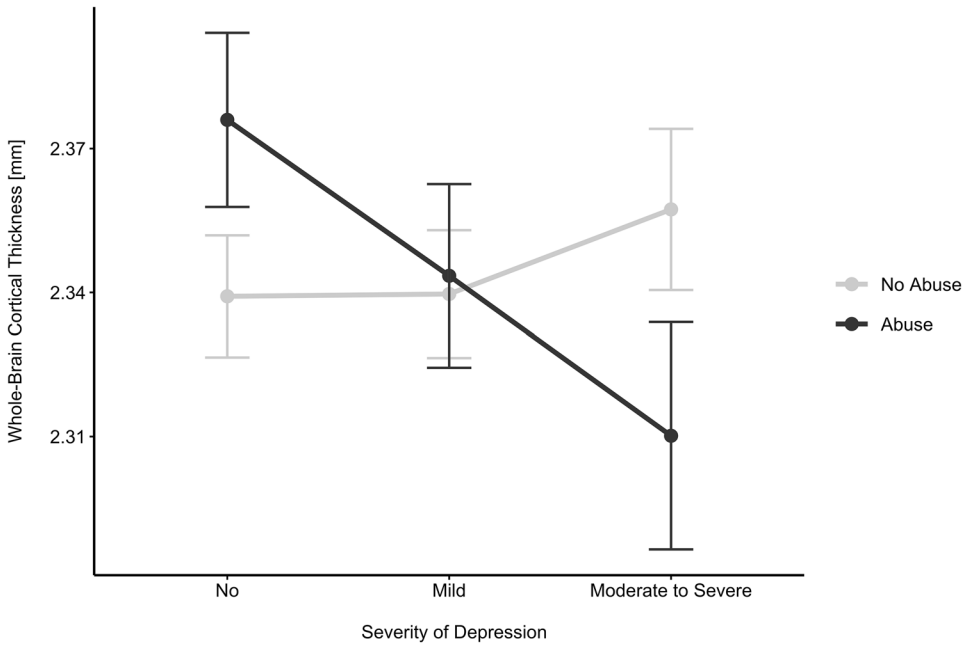

Fig. 1 Line plot showing pairwise comparisons between groups using the estimated marginal means and standard errors of whole-brain cortical thickness across all levels of childhood abuse and depression. In the abused-group (black line), participants with moderate to severe depressive symptoms had significantly thinner whole-brain cortices than non-depressed subjects ($p = 0.025$). In the non-depressed (left), whole-brain cortical thickness was larger in abused compared to non-abused participants ($p = 0.025$). See Table SI3 for further information

Using the matched sample ($N = 240$), we recalculated all results. The two-way interaction between childhood abuse and depressive symptoms remained significant ($F(2, 223) = 4.40$, $p_{FDR} = 0.013$). Post-hoc pairwise comparisons revealed statistically significant differences in the abuse group between non-depressed participants and participants with moderate to severe depressive symptoms (t value $= 3.34$; $p_{FDR} = 0.009$) (Fig. SI1).

Effects of childhood abuse and depressive symptoms on regional cortical thickness

To investigate region-specific effects, we tested the interaction of childhood abuse and depressive symptoms on the cortical thicknesses of 34 cortical regions, separately. Table 2 and Fig. 2 present the results**.**

After the FDR-correction for 34 cortical regions, the interaction effect was significantly associated with cortical thickness in 12 cortical regions within the inferior frontalis gyrus (pars opercularis, pars orbitalis, pars triangularis), supramarginal gyrus, inferior temporal gyrus, lateral occipital gyrus, lateral orbitofrontal cortex, pericalcarine cortex, precuneus, superior parietal lobule, superior temporal gyrus, and temporal pole ($p < 0.05$ after FDR correction). These cortical regions replicated the interaction effect as seen in the analysis of the whole-brain thickness; cortical thickness is most reduced in the depressed participants with a history of abuse.

Using the matched sample, significant interaction effects were observed in the inferior frontalis gyrus (including the pars opercularis, and the pars triangularis), the inferior parietal gyrus, supramarginal gyrus, and temporal pole, highlighting these regions despite the smaller sample size (see Table SI4).

Discussion

To deepen the understanding of the interplay between childhood abuse and depressive symptoms, this study investigated the interaction of both risk factors on cortical thickness in a large population-based sample. This study adds essential results to the research domain examining the effects of childhood abuse on mental health by focusing exclusively on childhood abuse interacting with depressive symptoms, extending the commonly used covariate list, and analysing both healthy and depressed, in addition to abused and non-abused participants.

Table 2 Associations of the interaction of childhood abuse (CA) and depressive symptoms (categorial variable) (Depr) with regional cortical thickness

Cortical Structure	Interaction Depr X CA	FDR *p* value
Banks of the superior temporal sulcus	− 2.12	0.064
Caudal anterior cingulate	− 0.25	0.818
Caudal middle frontal	− 1.26	0.261
Cuneus	− 1.66	0.137
Entorhinal	0.23	0.818
Frontal pole	− 1.33	0.242
Fusiform	− 1.75	0.118
Inferior parietal	− 3.07	0.010*
Inferior temporal	− 2.60	0.028*
Insula	− 1.92	0.089
Isthmus cingulate	− 1.21	0.274
Lateral occipital	− 3.11	0.010*
Lateral orbitofrontal	− 2.80	0.016*
Lingual	− 2.22	0.062
Medial orbitofrontal	− 2.17	0.062
Middle temporal	− 2.19	0.062
Paracentral	− 1.04	0.352
Parahippocampal	− 2.08	0.068
Pars opercularis	− 3.04	0.010*
Pars orbitalis	− 3.10	0.010*
Pars triangularis	− 3.46	0.010*
Pericalcarine	− 3.37	0.010*
Postcentral	− 2.15	0.062
Posterior cingulate	− 1.01	0.355
Precentral	− 1.35	0.242
Precuneus	− 2.39	0.045*
Rostral anterior cingulate	− 0.76	0.485
Rostral middle frontal	− 2.05	0.070
Superior frontal	− 0.75	0.485
Superior parietal	− 2.90	0.015*
Superior temporal	− 2.81	0.016*
Supramarginal	− 2.85	0.015*
Temporal pole	− 3.46	0.010*
Transverse temporal	− 1.90	0.090

Linear regression analyses were adjusted for sex, age, age-sex-interaction, age^2, estimated intracranial volume, education, alcohol consumption, smoking, BMI, and waist-to-height ratio. FDR-*p*-values are displayed. Significant FDR-*p*-values are highlighted

The interaction of childhood abuse and depressive symptoms on whole-brain cortical thickness

In the present study, only in abused participants, lower whole-brain cortical thickness was associated with more severe depressive symptoms.

Based on our results, studies analysing the effects of childhood abuse on cortical thickness should not neglect the impact of depressive symptoms. Against our assumption, abused participants without depressive symptoms showed an increased whole-brain cortical thickness in contrast to non-depressed and non-abused participants in our sample. This finding is in congruence with a recent study reporting increased cortical thickness in non-depressed (compared to depressed), abused participants in the orbitofrontal cortex [44]. Here, we found a significant interaction in the lateral orbitofrontal gyri. Interestingly, Habets et al. [45] found a similar effect in patients with schizophrenia and their healthy siblings, whereas both experienced childhood maltreatment. They found a reduction in cortical thickness in the patient group and an increase of cortical thickness in the healthy sibling group. These studies show, consistent to our data, that comparing healthy participants without a history of childhood abuse with both abused and depressed participants does display only a small reflection of the whole interaction context.

On the other hand, the variable of childhood abuse appears to be a relevant moderator when analysing the effects of depressive symptoms on cortical thickness. Thus, studies analysing the association between depression and cortical thickness might be more likely to find significant results if they do not control for childhood abuse or have a high proportion of abused participants, which might be especially true for patient samples [5]. Our results suggest that depressive symptoms alone, do not significantly influence the whole-brain cortical thickness, as correspondingly reported [13]. Another explanation suggests that the effect sizes are too small to detect the influence. Analysing the effects of depression on cortical thickness, critical parameters in neurological alterations are the age of onset and the severity of depression (either recurrent or severity of symptoms) [14]. We could emphasize that moderate to severe depressive symptoms are a relevant factor concerning neurological alteration by being significantly associated with thinner cortices (compared to no symptoms) combined with a history of abuse. Future research could combine these factors to deepen the understanding of the influence of depressive symptoms on cortical thickness.

The influence of childhood abuse and depressive symptoms on cortical regions

Our results demonstrated a widespread effect of the interaction of childhood abuse and depressive symptoms on cortical thickness. Cortical regions with the highest interaction effects are involved in emotional processing, social cognition, and sensory processing. Cortical thickness of the inferior parietal lobe and the inferior parietal lobe was significantly associated with the childhood

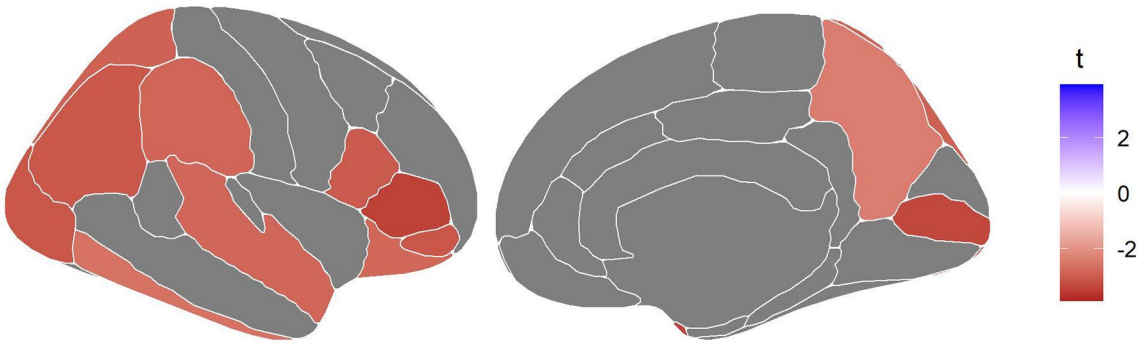

Fig. 2 Associations between cortical thickness in 34 cortical regions and the interaction of depressive symptoms and childhood abuse. Colours represent exclusively significant t-values from linear regressions with the brain regions as the dependent variable and adjusted for sex, age, age-sex-interaction, age^2, ICV, education, alcohol consumption, smoking, BMI, and waist-to-height ratio

abuse-depression-interaction effect in our study. The inferior parietal lobe, divided into the supramarginal gyrus and the angular gyrus, is crucial for overcoming emotional egocentricity avoiding biased social judgments [46]. The inferior parietal lobe was described to handle visuospatial information, be involved in perspective-taking and emotional processing through distancing [47, 48]. Moreover, we found associations with the inferior frontal gyrus, involved in response inhibition and attention control as part of the executive control [49, 50] and previously reported to be thinner in abused participants [51, 52]. Similarly, the cortical thickness of the temporal pole was associated with childhood maltreatment, and physical abuse in particular, before [53, 54]. It is essential in processing social cognition, naming the theory of mind [55]. Furthermore, we found reduced cortical thickness in visual cortex structures, such as the pericalcarine and the later occipital cortex. Earlier studies found reduced grey matter volume, cortical volume, and cortical thickness in the visual cortex in participants with a history of abuse [10, 56–58]. However, associations between these regional reductions and depressive symptoms were not explicitly reported before (e.g., by Schmaal et al. [14]). Thus, we conclude that these reductions show explicitly relevant interaction effects of childhood abuse and depressive symptoms.

Consequences of childhood abuse on cortical thickness

Every cortical region processes certain qualities of a sensory stimulus [59]. Studies analysing the cellular architecture of the cortex demonstrate that the cortical thickness is contingent on the number of neurons, glia provision, and the neuronal structure [60, 61]. Also, differences in cortical thickness are associated with the structural hierarchical level of processing the stimulus [59]. In the group of participants with no depressive symptoms, the present study found larger cortical thickness in abused compared to non-abused subjects. An explanation for our findings could be the sensitisation theory of Heim et al. (2008) hypothesising that childhood abuse sensitises the pituitary and a counter-adjustment is needed to compensate [62]. In line with this, Teicher et al. [5] argued that maltreated subjects could also differ in brain changes which help them compensate [5]. Previous studies found associations between increased cortical thickness and resilience [73].

Experiencing early life stress, such as childhood abuse, is a severe intrusion in the early development stage [5]. This intrusion can interfere with the neuronal development [63–65]. Consequently, cerebral structures can be prone to future stressful influences [66, 67]. Based on our results, we hypothesise that childhood abuse is a relevant biological disposition that interacts with the current state of psychopathology. Thus, structural brain alterations might follow a different pattern in depressed participants with a history of abuse compared to participants without a history of abuse [5]. Certainly, these results need to be carefully interpreted as other factors such as cognitive training [68], cortical asymmetry [69], and cellular architecture [59, 61] affect the cortical thickness.

Lim et al. [15] argued that the experience of abuse during childhood may lead to a reduction in synapses to protect the child from a hostile environment. These alterations could affect emotional and social processing in depressed patients resulting in a lower treatment outcome. In line with that, meta-analyses revealed that depressed patients with childhood adversity showed reduced benefit from treatment [19, 70]. Future research would be of prime importance to investigate if these abused, and treatment-resistant patients also have remarkably low cortical thickness. Furthermore, the research could focus on how these associations might change with pharmacological or psychotherapeutic therapy and whether these alterations are reversible. We focussed on the consequences of childhood abuse as it is well described

in the literature and has a tremendous effect on the cortex [11, 52, 56]. However, it would be important to analyse the interaction effect of neglect and depressive symptoms interacting.

Limitations

Despite our careful study design, there are several limitations worth noticing. First, we used self-report measures to assess the depressive symptoms and to assess the history of childhood abuse. The PHQ-9 is a validated measurement, but it does not replace a formal psychiatric anamnesis. Also, we focussed only on current depressive symptoms and did not include the influence of lifetime diagnosis of MDD or other psychiatric diagnoses. Therefore, we cannot eliminate other psychiatric diagnoses, which could influence our results. As we did not analyse a psychiatric cohort, we assume that psychiatric symptomatology is low. The CTQ is a self-reported measure that does not assess at which age the abuse or neglect happened. Further, participants with a history of abuse could intentionally not report these traumata due to avoidance or repression.

Second, we focused on abuse-related effects but incorporated participants with the exposure of abuse and neglect. Hence, we cannot differentiate between effects due to childhood abuse or childhood neglect. Childhood abuse and childhood neglect are strongly correlated, and childhood maltreatment is associated with depressive symptoms. However, as we excluded participants exclusively reporting childhood neglect but included participants exclusively reporting childhood abuse, our results are more likely to reflect the effects of childhood abuse. We decided to include subjects with a history of neglect and abuse, as there is a considerable overlap of subjects who experienced both forms of maltreatment [71]. Future studies are needed to differentiate between the effects of abuse and neglect.

Third, the distribution of the abuse and neglect severity is not equally distributed across the depression groups (see Table SI1). As the sample was recruited from the general population and associations between childhood maltreatment and depressive symptoms are well described [19, 20], this is an expected, data immanent issue. Nevertheless, we cannot rule out that this association might impact the results and future studies are needed matching abuse and neglect severity in depressed and non-depressed participants to validate our results.

Fourth, due to the cross-sectional study design, our results do not allow any causal conclusion. Further, although the analysed study sample was large and a large set of potential covariates was included, we did not collect a replication sample. In addition, age-range and sex differences often moderate effects on cortical thickness [72, 73]. We tried to rule out these effects by including both variables as covariates in our statistical models and analysing the results within a sample matched for sex, age, and depression level. We did not adjust for potential comorbidities (such as hypertension or diabetes) as we focus on the general population in which comorbid medical conditions are common. Finally, our study sample is not entirely independent from the ENIGMA consortium, but we included different covariates in our analysis.

Conclusion

This study investigated the interaction of childhood abuse and depressive symptoms on cortical thickness. Based on a large population-based sample, only in the presence of childhood abuse did depressive symptoms influence the whole-brain cortical thickness. This might explain some of the inconsistencies reported in previous studies. The interaction between childhood abuse and depressive symptoms was associated with a widespread reduction in cortical thickness in regions involved in emotional processing, social cognition, and sensory processing. Larger cortical thickness, in abused subjects without depressive symptoms, might act compensatory and thus reflect resilience against depressive symptoms. Our results support the hypothesis that childhood abuse is moderating the associations between cortical thickness and depressive symptoms, particularly in participants with more severe depressive symptoms. Further research could focus on how different treatments can affect brain alterations associated with childhood abuse and depressive symptoms and whether those are reversible.

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Availability of data and materials SHIP data are applicable via fvcm.med.uni-greifswald.de.

Code availability Not applicable.

Declarations

Conflict of interest HJG has received travel grants and speakers' honoraria from Fresenius Medical Care, Neuraxpharm, Servier and Janssen Cilag as well as research funding from Fresenius Medical Care.

Ethical approval 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.

Informed consent All participants provided written informed consent.

Consent to participate The institutional review board of the University Greifswald approved SHIP. Examinations and assessments have been conducted by the declaration of Helsinki, including written informed consent from all participants.

Consent to publish All authors have read and approved the manuscript for publication. The publication of the used data is consented by a data application.

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Supplementary Information

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Interaction of childhood abuse and depressive symptoms on cortical thickness: a general population study

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Effects of childhood abuse and depressive symptoms as continuous variable on whole-brain cortical thickness

There was a statistically significant two-way interaction between the dichotomous childhood abuse and continuous current depressive symptoms on whole-brain cortical thickness ($F(2, 1534) = -2.966$, $p = 0.003$). This result supports the outcome of the categorical depression variable.

Effects of childhood abuse and depressive symptoms whole-brain cortical thickness with

Table S1 Characteristics of the study sample ordered by the severity of depressive symptoms

	All subjects (N = 1551)	Healthy (*n* = 1064)	Mildly Depressed (*n* = 397)	Moderately to Severely Depressed (*n* = 90)	*p*-value [a]
Sex (female), *n* (%)	834 (54%)	515 (48%)	259 (65%)	60 (67%)	< 0.001
Age (years), *M* ± *SD*	50 ± 14	50 ± 14	50 ± 13	49 ± 11	0.783
BMI, *M* ± *SD*	27 ± 4.4	27 ± 4.3	28 ± 4.6	28 ± 4.6	0.065
Educational level					< 0.001
<10 years, *n* (%)	167 (10.8%)	94 (8.8%)	64 (16.1%)	9 (10.0%)	
=10 years, *n* (%)	870 (56.1%)	577 (54.2%)	231 (58.2%)	62 (68.9%)	
>10 years, *n* (%)	514 (33.1%)	393 (36.9%)	102 (25.7%)	19 (21.1%)	
Alcohol (g/day), *M* ± *SD*	8 ± 11	8.3 ± 11	7.3 ± 11	7.8 ± 12	0.199
Smoking					0.263
Never smoker, *n* (%)	620 (40.0%)	440 (41.4%)	151 (38.0%)	29 (32.2%)	
Ex-smoker, *n* (%)	559 (36.0%)	383 (36.0%)	140 (35.3%)	36 (40.0%)	
Current smoker, *n* (%)	372 (24.0%)	241 (22.7%)	106 (26.7%)	25 (27.8%)	
ICV (dm^3), *M* ± *SD*	1.587 ± 0.16	1.600 ± 0.16	1.562 ± 0.15	1.544 ± 0.14	< 0.001
PHQ-9 (summary), *M* ± *SD*	3.7 ± 3.5	1.9 ± 1.4	6.5 ± 1.4	13 ± 3.8	< 0.001
CTQ (summary), *M* ± *SD*	32 ± 9.1	30 ± 7.5	33 ± 9.1	39 ± 17	< 0.001
Abuse severity (summary), *M* ± *SD*	17 ± 4.8	17 ± 3.7	18 ± 5.3	21 ± 9.8	< 0.001
Abuse (yes), *n* (%)	122 (7.9%)	55 (5.2%)	44 (11%)	23 (26%)	< 0.001

Note: PHQ-9 = Patient-Health-Questionnaire-9; CTQ = Child-Traumatisation-Questionnaire; BMI = Body Mass Index; ICV = Intracranial Volume; *a* = According to one-way ANOVA for continuous or χ^2-tests for categorical variables to check for possible differences in the groups.

antidepressants as additional covariate

In an additional model, we included the intake of antidepressants (yes/no) as a covariate. 65 participants were on antidepressant medication. Of them, 24 individuals were assorted to the non-depressed group, 21 to the mild depressed, and 20 to the group of moderate to severely depressed. The two-way interaction between childhood abuse and current depressive symptoms on whole-brain cortical thickness remained significant ($F(2, 1533) = 5.141$, $p = 0.007$).

Table S2 Characteristics of the matched sample

	All subjects (N = 240)	Abuse (n = 120)	No Abuse (n = 120)	p-value [a]
Sex (female), *n* (%)	68 (28%)	33 (28%)	35 (29%)	0.886
Age (years), *M* ± *SD*	50 ± 13	50 ± 13	50 ± 13	0.707
BMI, *M* ± *SD*	28 ± 4.8	28 ± 4.9	28 ± 4.8	0.441
Educational level				0.595
<10 years, *n* (%)	29 (12%)	17 (14%)	12 (10%)	
=10 years, *n* (%)	143 (60%)	69 (57%)	74 (62%)	
>10 years, *n* (%)	68 (28%)	34 (28%)	34 (28%)	
Alcohol (g/day), *M* ± *SD*	5.9 ± 8.6	6.1 ± 8.8	5.7 ± 8.5	0.718
Smoking				0.423
Never smoker, *n* (%)	82 (34%)	41 (34%)	41 (34%)	
Ex-smoker, *n* (%)	98 (41%)	45 (38%)	53 (44%)	
Current smoker, *n* (%)	60 (25%)	34 (28%)	26 (22%)	
ICV (dm^3), *M* ± *SD*	1.559 ± 0.16	1.558 ± 0.17	1.560 ± 0.15	0.905
Depressive Symptoms				0.960
No, *n* (%)	108 (45%)	55 (46%)	53 (44%)	
Mild, *n* (%)	90 (38%)	44 (37%)	46 (38%)	
Moderate to severe, *n* (%)	42 (18%)	21 (18%)	21 (18%)	
PHQ-9 (summary), *M* ± *SD*	5.8 ± 4.6	6.4 ± 5.2	5.2 ± 4.0	0.045
Neglect (yes), *n* (%)	72 (30%)	72 (60%)	0 (0%)	< 0.001
CTQ (summary), *M* ± *SD*	42 ± 17	55 ± 17	30 ± 4.1	< 0.001
Abuse severity (summary), *M* ± *SD*	23 ± 9.7	30 ± 9.5	16 ± 2.0	< 0.001

Note: PHQ-9 = Patient-Health-Questionnaire-9; CTQ = Childhood-Traumatisation-Questionnaire; BMI = Body Mass Index; ICV = Intracranial Volume; *a* = According to one-way ANOVA for continuous or χ^2-tests for categorical variables to check for possible differences in the groups.

Table SI3 Estimated marginal means, standard error, and confidence level (in mm) are displayed for the whole-brain thickness in the whole sample. They were adjusted for sex, age, age*sex-interaction, age^2, estimated intracranial volume, education, alcohol consumption, smoking, BMI, and waist-to-height ratio

Factor depression	Factor abuse	Estimated means for whole-brain thickness	Standard error	Lower confidence level	Higher confidence level
No	No Abuse	2.339	0.013	2.314	2.364
Mild	No Abuse	2.340	0.013	2.314	2.366
Moderate to Severe	No Abuse	2.357	0.017	2.324	2.390
No	Abuse	2.376	0.018	2.340	2.412
Mild	Abuse	2.343	0.019	2.306	2.381
Moderate to Severe	Abuse	2.310	0.024	2.264	2.357

Table SI4 Associations of the interaction of childhood abuse (CA) and depression (Depr) with cortical thickness for the matched sample. Linear regression analyses were adjusted for sex, age, age*sex-interaction, age², estimated intracranial volume, education, alcohol consumption, smoking, BMI, waist size, height, and weight. FDR-*p*-values are displayed. Significant FDR-*p*-values are highlighted

Cortical Structure	Interaction Depr X CA	FDR *p-value*
Banks of the superior temporal sulcus	-1.64	0.182
Caudal anterior cingulate	-0.15	0.909
Caudal middle frontal	-1.51	0.198
Cuneus	-1.42	0.214
Entorhinal	-0.01	0.996
Frontal pole	-1.61	0.182
Fusiform	-1.59	0.182
Inferior parietal	**-2.89**	**0.043**
Inferior temporal	-1.98	0.126
Insula	-2.39	0.060
Isthmus cingulate	-0.65	0.606
Lateral occipital	-2.42	0.060
Lateral orbitofrontal	-2.12	0.099
Lingual	-1.42	0.214
Medial orbitofrontal	-1.61	0.182
Middle temporal	-2.17	0.096
Paracentral	-0.53	0.680
Parahippocampal	-1.09	0.349
Pars opercularis	**-2.86**	**0.043**
Pars orbitalis	-2.41	0.060
Pars triangularis	**-3.52**	**0.018**
Pericalcarine	-2.50	0.060
Postcentral	-1.62	0.182
Posterior cingulate	-1.05	0.357
Precentral	-1.09	0.349
Precuneus	-1.50	0.198
Rostral anterior cingulate	-0.37	0.759
Rostral middle frontal	-1.95	0.126
Superior frontal	-0.41	0.745
Superior parietal	-2.52	0.060
Superior temporal	-1.62	0.182
Supramarginal	**-2.75**	**0.044**
Temporal pole	**-2.83**	**0.043**
Transverse temporal	-1.71	0.182

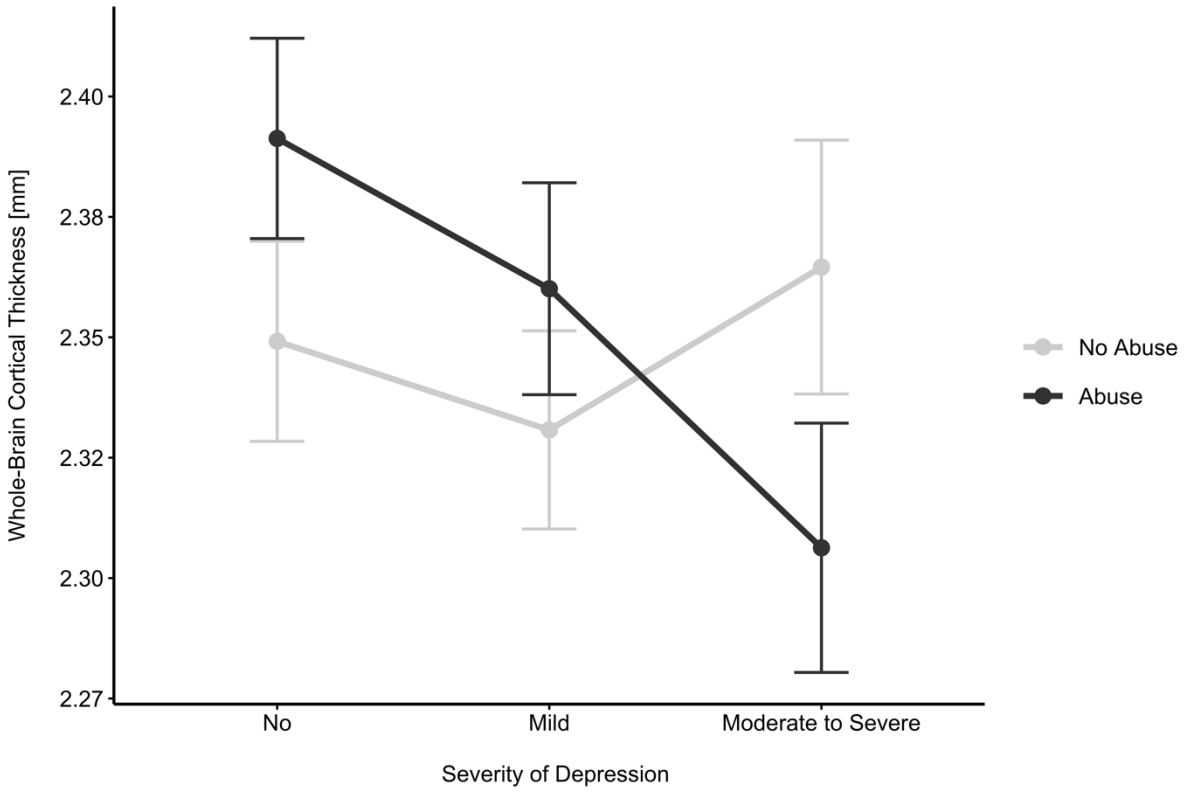

Fig. SI1 Lineplot showing pairwise comparisons in the matched sample between groups using the estimated marginal means and standard errors of whole-brain cortical thickness across all levels of childhood abuse and depression. In the abused-group (black line), participants with moderate to severe depression had trend significantly thinner whole-brain cortices than non-depressed subjects (t-value = 3.34; $p = 0.009$)