Childhood Trauma Associated Changes in Brain Structure, Investigated with 7 Tesla Magnetic Resonance Imaging; a Retrospective Data Analysis

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Abstract

**Background:** Major depressive disorder (MDD) affects about 14% of European population during lifetime. This disorder is often associated with experienced traumata, like emotional, sexual or physical maltreatment during childhood. Childhood maltreatment (CM) is predisposing for developing MDD, whereas emotional abuse and neglect are strong predictors for anxiety and depressive symptoms. Furthermore, changes of brain structure related to CM were found in several regions of the brain like the hippocampus, amygdala and frontal regions but also in temporal, parietal and occipital regions. Yet, findings have been inconsistent depending on study sample and analysis of morphological data. This diploma thesis, to the best of our knowledge, is the first examination of CM related morphological brain changes in patients with MDD and HC using 7Tesla (7T) magnetic resonance imaging (MRI).

**Methods:** Thirteen patients with MDD (mean age ± SD, 32.85 ± 12.01) and 14 healthy controls (HC) (26.14 ± 7.12) were included in this cross-sectional study. Ultra high field 7T MRI was used for structural data acquisition of the brain. For retrospective examination of experienced CM the German version of the short form of the Childhood Trauma Questionnaire (CTQ) by Bernstein and Fink was used. Total scores of CTQ and scores of subscales emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse were correlated with cortical thickness (CT) of each region of interest (ROI).

**Results:** In patients with MDD emotional abuse was positively correlated with left posterior cingulate cortex (PCC) (Pearson R = 0.58; p = 0.038) and negatively correlated with right frontal pole (Pearson R = -0.62; p = 0.023). Emotional neglect was negatively correlated with left pars triangularis (Pearson R = -0.61; p = 0.028) and right frontal pole (Pearson R = -0.68; p = 0.011) in patients. In HC emotional neglect was negatively correlated with right inferior parietal cortex (Pearson R = -0.55; p = 0.044), right lateral occipital cortex (Pearson R = -0.73; p = 0.003) and left lingual gyrus (Pearson R = -0.75; p = 0.002). Results did not remain statistically significant after Bonferroni correction for multiple testing.

**Conclusion:** Our findings show CM related differences of brain structure in regions that are involved in cognitive processes, memory and emotional processing. Yet, our findings did not remain statistically significant after Bonferroni correction for multiple testing, which is probably caused by the small sample size. Further investigations with greater sample size in respect to CM and brain structure using 7T MRI will be needed to confirm our findings.
Zusammenfassung


Ergebnisse: In der Gruppe der Patienten konnte eine positive Korrelation zwischen emotionalem Missbrauch und dem linken posterioren cingulären Cortex (Pearson R = 0.58; p = 0.038) gefunden werden. Emotionaler Missbrauch war bei den Patienten negativ korreliert mit dem rechten frontalen Pol (Pearson R = -0.62; p = 0.023). In der Gruppe der Patienten konnte weiter eine negative Korrelation zwischen emotionaler Vernachlässigung und der linken Pars triangularis (Pearson R = -0.61; p = 0.028) und dem rechten frontalen Pol (Pearson R = -0.68; p = 0.011) festgestellt werden. In der Gruppe der gesunden Kontrollprobanden wurde eine negative Korrelation zwischen emotionaler Vernachlässigung und dem rechten inferioren parietalen Cortex (Pearson R = -0.55; p = 0.044) sowie dem
rechten lateralen occipitalen Cortex und dem lingualen Gyrus gefunden. Nach Korrektur für multiples Testen nach Bonferroni waren keine der Ergebnisse statistisch signifikant.

1. Introduction

1.1 Background

1.1.1 Major Depressive Disorder

During life time, about 14% of the European population suffers from severe mood disorders. Major depressive disorder (MDD) is the most occurring mood disorder, contracting about 7% of the population each year. Yet, 50% of the people suffering from MDD are not treated [1]. The prevalence of MDD in Austrian population in 10 years amounts approximately 15% [2]. These numbers reflect the importance of knowledge about mental illness.

Major depressive disorder is described by the “International Statistical Classification of Diseases and Related Health Problems” (ICD10), an international system for classification of medical conditions, within the category of mood (affective) disorders, mainly characterized by mood changes. Main symptoms of the depressive disorder are depressed mood, decreased impulse and activity, reduced interests and concentration, fatigue, sleep disturbance, diminished appetite, lower self esteem, feelings of guilt, thoughts of being worthless, loss of libido, psychomotoric inhibition and agitation. According to number and severity of symptoms, depressive disorder can be classified to mild, moderate and severe episodes and depending on appearance in single episode or recurrent disorder [3].

Another diagnostic tool to categorize mental illnesses is the “Diagnostic and Statistical Manual of Mental Disorders” (DSM), published by the American Psychiatric Association [4, 5]. Experiencing at least two weeks of depressed mood or loss of interest and a minimum of four additional symptoms of depression is described as a depressive episode. Major Depressive Disorder is diagnosed as one or more depressive episodes have been experienced [4, 5].

According to the 4th Edition of DSM, diagnostic criteria for a depressive episode are at least five of the following symptoms occurring for a minimum of two weeks, whereat depressed mood or the loss of interest is one of the symptoms:

- Depressed mood
- Loss of interest or pleasure
- Decrease or increase of appetite or more than 5% change of body weight
- Insomnia or hypersomnia
- Experiencing nearly every day psychomotoric agitation or retardation
- Fatigue or energy deficit
- Feeling guilt in an excessive or inappropriate extent or feeling worthless
- Reduced efficacy of thinking, concentration or indecisiveness
- Thoughts of own death, suicidal tendency [4]

Additionally, for diagnosing a depressive disorder, the symptoms may not meet criteria for a mixed episode of mood disorders. Furthermore, functioning in important areas is impaired due to the symptoms and symptoms are not caused by substances or a physical medical condition or due to mourning [4].

1.1.2 Risk Factors for Major Depressive Disorder

Numerous studies examined the cause and risk factors of depression. Family and twin research revealed a heritability of approximately 37% in MDD, yet no specific gene was found as a risk factor. It can rather be assumed, that the genetic component of MDD is composed of various genes, each contributing small effect on development of MDD [6]. Center of several studies are, for example, genes encoding for serotonin transporters and receptors, tryptophan synthesis as part of the serotonergic system and genes encoding for brain-derived neurotrophic factor (BDNF) [6].

Beside a genetic component, gender appears to be a second main risk factor. A population based study accomplished in Germany showed a 10.1% prevalence of professional diagnosed MDD hitting DSM criteria of 4th edition in women and with 6.1% a lower prevalence in men [7].

Furthermore, a relationship between stressful life events (SLE) and increased risk for a depressive episode was found in twin studies among both female and male participants [8]. Additionally, studies found that SLE lead to an increased risk for more SLE, which subsequently elevates the probability for a depressive episode [8, 9].

Some evidence was shown that there are differences in respect to life events between men and women, such as quantity, type of experienced stress and vulnerability [10, 11]. For instance, women quoted more SLE than men. This may possibly be explained by the fact that women further reported SLE that happened to related individuals, while men seemed to pay less attention to comparable situations. These interpretations implicate that both, male and female, experience a comparable amount of SLE. However, women are in addition vulnerable to SLE which happened to their near ones [10]. Vulnerability to specific life events also differ between gender since men are more sensitive to stress experienced on their own such as problems at work, robbery or legal issues, while women experience housing problems, loss of close ones or issues with individuals in their social life as more stressful [11]. Hence, there is
a great gender related bias in the perception of SLE which can trigger a diversity of psychiatric disorders.

1.1.3 Childhood Maltreatment and the Impact on Major Depressive Disorder

Childhood maltreatment (CM) is defined by the World Health Organization (WHO) 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. Exposure to intimate partner violence is also sometimes included as a form of child maltreatment” [12].

Since evidence of effects of SLE on MDD was shown [8, 9], numerous studies examined the effects of CM, such as sexual and physical abuse, neglect, interpersonal loss and parental maladjustment on the risk of developing a major depression during lifespan [13-19].

A study of a female cohort examined the occurrence of sexual abuse in childhood and the incidence of psychiatric symptoms. The findings revealed that women which experienced early sexual abuse showed significant higher rates of psychiatric symptoms [13]. Another survey included women with depressive symptoms in the past 12 months and female healthy controls (HC). The group of depressed females reported a higher rate of low parental care in childhood than the control group. Also a lower rate of maternal care was stated by recently depressed females compared to HC [14]. In addition, a study examined a group of female participants who experienced CM compared to females with no history of CM in respect to the occurrence of anxiety and depressive disorder. Female with CM-history scored higher in questionnaires evaluating anxiety, depressive disorder and dissociation [15]. Also the recovery rate of MDD and reported sexual abuse before the age of 16 in female inpatients was investigated, resulting that women with no history of abuse had a 3.7 times higher chance for recovery from MDD in a time span of 12 months than females who reported abuse [16].

A longitudinal cohort study in Sweden investigated the occurrence of different aspects of SLE in childhood such as parental death, separation, criminality, substance abuse or psychiatric disorder and rates of depressive disorder. In line with other epidemiological studies, all investigated SLE in childhood were correlated to a higher risk of developing a depressive disorder [20]. Furthermore, 18.6% of all clinical diagnosed depression was linked with SLE in childhood. Opposed to that only 2.7% of depression was linked to SLE in childhood when only administered antidepressant medication was considered [20].
The WHO analyzed different aspects of CM regarding SLE in childhood and the influence on onset of several psychiatric disorders such as mood and anxiety disorders. In this survey adults from different countries were included. All investigated SLE in childhood correlated with a higher risk for developing a psychiatric disorder, while parental death was the most occurred SLE [17]. Moreover, a survey revealed an earlier onset of symptoms for depressive and anxiety disorder in adults, who reported different SLEs in childhood compared to other adults with a psychiatric disorder but no reported SLEs. [18].

Another investigation showed not only that CM is associated with symptoms of anxiety and depressive disorder but also that emotional abuse and neglect are the strongest predictors for anxiety and depressive symptoms in adults compared to other aspects of CM [19]. These findings are in line with the results of an investigation including nonclinical adults, where it was found, that the mean age of depression onset in individuals experienced CM was significant diminished compared to the participants which had not experienced any adversities in childhood. Emotional abuse was the main contributor in forecasting the earlier appearance of depression. Moreover, it was found that undergoing CM is further associated with comprehensive comorbidities and a higher quantity of depressive episodes, which lead to the assumption that there might be a traumatic subtype of depression [21].

As many individuals who experienced CM or other stressful life events do not develop any psychiatric disorder, even if it is a predisposing factor, resilience seems to play a crucial role [22]. Resilience is described as the ability to adapt effective to acute stress, trauma or chronic forms of adversity during lifetime. Various factors influencing one individual’s resilience were determined such as psychosocial or genetic effects [23]. For instance, perceived social support was linked to decreased chance of the occurrence of depressive symptoms in individuals with experienced CM [24].

An ideal accommodation of patients suffering from MDD might benefit from above mentioned results, based on research which examined that the occurrence of specific childhood events such as physical, sexual and emotional abuse may predict response to psychopharmacological treatment in patients suffering from MDD, which in turn let assume that there are acting biological changes in individuals due to experiencing early specific events [25].

1.1.4 Childhood Trauma Questionnaire

For retrospective examination and as a screening measure of CM the short form of the Childhood Trauma Questionnaire (CTQ-SF, here CTQ) originally generated by Bernstein and
Fink was developed including sexual, physical and emotional abuse and physical and emotional neglect [26]. It was shown that total scores of CTQ were significantly higher in patients suffering from depression compared to HC [21]. The German version of the CTQ was applied to a sample of psychiatric patients, revealing that patients with a diagnosed borderline personality disorder had significant higher scores in all subscales compared to patients with other psychiatric disorders. Furthermore, women reached significant higher scores than men in all subscales except “physical abuse” [27]. The CTQ is widely used as a screening measurement in clinical population [21, 28].

1.1.5 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides a noninvasive detailed insight in human’s anatomy and is used for clinical diagnosis and for research as well [29-31]. Currently the diagnosis of major depression or other psychiatric disorders is based on occurrence, quantity and quality of symptoms and their classification at the DSM or the ICD10 [3, 5]. The request for biological markers is rising to enable or to approach a consistent diagnosis for psychiatric disorders, resulting in neuropsychiatric imaging and the focus on changes and differences in brain structure between patients with MDD and HC in various research [32].

Applications of Magnetic Resonance Imaging

The physics of magnetic resonance was enhanced to an imaging procedure by Paul C. Lauterbur in 1973 [33]. Magnetic resonance imaging enables not only structural data but also functional information of the human brain. While structural magnetic resonance imaging (sMRI) takes advantage of different signal intensity between the various tissues of the brain including gray matter, white matter and cerebrospinal fluid by excited hydrogen protons to produce an image, functional magnetic resonance imaging (fMRI) enables to draw conclusions for neural activity based on blood oxygen level by measuring the different signals of oxygen-carrying or oxygen-depleted hemoglobin. This means that higher blood flow in a brain area and measures of decreased oxygen-depleted hemoglobin are gathered to neuronal activity [30]. Further applications for MRI are diffusion weighted imaging (DWI), diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS). Diffusion weighted imaging detects diffusion of water molecules and therefore provides detailed insight in a tissue’s structure. Diffusion tensor imaging is used for measuring white matter tractography. Metabolism of tissue can be detected using MRS by detecting spatial distribution and molecular compounds of creatine, choline, N-acetyl-acetate, citrate, lactate and lipids [30].
Physics of Magnetic Resonance Imaging

The hardware of MRI is composed of a strong magnet to create a stationary magnetic field, a gradient coil for slice selection and spatial encoding by magnetic field gradients, a radio frequency transmitter, high frequency receiver and a computer for controlling, coordination and image construction. The main magnetic field in MRI is commonly generated by a superconducting magnet. The electrical resistance of the magnetic field is decreased by a cooling system containing liquid helium resulting in independency from power supply, once the magnetic field is built up. The field strength is measured in Tesla (T). Superconducting magnets are capable of producing field strength up to 18T while in clinical use commonly field strengths reaching from 0.1 to 3T occur. For research ultra high field MRI is used with field strengths from 7T and above [34].

Through the combination of a steady magnetic field and radiofrequency pulses (RF-pulses), hydrogen protons in the tissues of a human’s body are stimulated. After excitation, protons align in parallel or antiparallel patterns compared to the magnetic vector of the scanner. When protons are exposed to the magnetic field of the scanner, they start to spin around their own axis. The stronger the magnetic field, the faster they spin. For image acquisition, RF-pulses are applied in the same frequency as the protons spinning, leading them to pick up the energy and reverse from parallel to antiparallel position. This process results in decreasing the longitudinal magnetic field of the scanner and the protons synchronize their spinning and create a new transversal magnetic direction. As the RF-pulse is turned off, the protons start to re-adjust parallel to the stationary magnetic field of the scanner; hence the magnetic strength is ascending, which is termed as T1 relaxation time. Moreover, the synchronization of the proton’s spinning and the resulting transversal magnetic field is decreasing which is termed as T2 relaxation time. Both processes are proceeding simultaneously and independently from each other, yielding the possibility of determining different tissues of the human body. T1-weighted MRI data represents an image of the brain formed of T1-relaxation time measurement. Various tissues of the brain composed of proteins, carbohydrates, fat and salt water can be distinguished from each other due to the different behavior for T1 and T2 relaxation time e.g. stronger intensities of white matter compared to gray matter’s signals in T1-weighted images. This interaction leads to the possibility to differ between various brain tissues [31].
Image Acquisition

To produce a sliced image of the brain, a magnetic gradient is created by gradient coils in the vector of the main magnetic field which enables the selection of a specific plane of the requested area by adding an RF-pulse in a specific frequency. A voxel, a three-dimensional version of a pixel, is measured by adding two further magnetic gradients in the other two vectors [31]. There are various MRI sequences or pulse sequences to generate an image, consisting of particular radiofrequency and gradient-pulses, repeating within a measurement and resulting in a several possibilities of composing an image with particular image qualities. Widely used sequences are spin echo sequences, inversion-recovery sequences and gradient-echo sequences [34].

1.1.6 Neuroimaging in Psychiatric Disorders

The most common structural neuroimaging techniques are gray matter volume (GMV) measures using an a priori region of interest (ROI) approach or whole brain voxel-based morphometry (VBM) approach and cortical thickness (CT) analysis of ROI in MRI. Gray matter volume analysis indicates the volume of the whole ROI, while CT analysis represents the average thickness of a defined neo-cortical brain area [35, 36].

In the past the analysis of the CT was conducted manually by an experienced anatomist and were time-consuming [37]. As the human cortex consists of gyri, the surface is not orthogonal to the point of view in sliced images, which makes a precise measurement of the CT challenging. An automated procedure enables accurate tissue classification and representing gray and white matter and the pial surface. Cortical thickness is now defined as the distance between white matter and pial surface. The average thickness of a human cortex ranges from 1 mm to 4.5 mm [37].

Changes of CT in comparison to HC were found in various psychiatric disorders. For instance, cortical thinning of left caudal middle frontal, left superior frontal and left posterior parietal areas were found in patients with panic disorder and respiratory symptoms [38]. Another example, in paediatric patients with generalized anxiety disorder cortical thickening in the right inferolateral and orbitofrontal cortex (OFC), left inferior and middle temporal cortex and right lateral occipital cortex (LOC) was shown [39].

Also changes of GMV in psychiatric disorders are reported. A meta-analysis of GMV using VBM in patients with anxiety disorder resulted in reduced volumes of the anterior cingulate gyrus, left inferior frontal gyrus (IFG), left middle temporal gyrus and right precentral gyrus.
Increased GMV was found in the right dorsolateral prefrontal cortex (DLPFC) in patients with anxiety and MDD as comorbidity [40].

1.1.7 Depression and Neuroimaging

Several neuroimaging studies investigated changes in brain structure related to MDD using MRI. A variety of studies reported structural changes including volumetric loss of the hippocampus, basal ganglia, OFC, and sub-genual prefrontal cortex (PFC) [32]. The severity of structural changes appeared to be related to length of duration and number of episodes with greater impact on changes in brain structure in more severe courses of MDD [32].

Hippocampus and Amygdala in Major Depressive Disorder

In a neuroimaging study, were young female patients with short illness history and antidepressant medication were compared to HC, smaller volumes of left and right hippocampus were demonstrated, while GMV of the left and right amygdala volumes appeared to be enlarged [41]. Another study examined volumes of hippocampus and amygdala using MRI T1 relaxation time data. Male and female patients fulfilling criteria for MDD and HC were included. In patients with MDD smaller left hippocampal volume in contrast to HC were found. An asymmetry in hippocampus with smaller left hippocampal volume than right hippocampal volume was described for both groups. Volume of amygdala showed equal distributions in both groups, while patients with MDD showed an asymmetry with smaller right amygdala. These findings were not consistent when examining data from T2 weighted MR images [42]. Findings about hippocampal volume are partial inconsistent in literature and differ in respect to sort of measurement. Meta-analysis of studies including patients with MDD and HC examined using MRI showed that lower hippocampal volumes in patients suffering from MDD compared to HC are more likely to be detected when hippocampus was viewed separately from other structures due to statistical power. Furthermore, duration of illness may also affect findings as reduced hippocampal volume was more likely to be found in older patients [43].

Since depressive episodes are characterized by elevated cortisol levels, animal studies let assume that high levels of cortisol eventually lead to a loss of hippocampal cell number and therefore possibly explain changes in hippocampal volume [44, 45].

Cortical Thickness in Major Depressive Disorder

When measuring CT in T1-weighted MRI data in patients with first episode MDD, thinning was detected in right medial OFC, right inferior temporal cortex, right insula and right inferior
parietal regions compared to HC. Moreover, no cortical thickening was measured when patients with MDD were compared to HC. Subcortical volume analysis showed reduced volumes in the left putamen and amygdala as well as in right putamen in patients with MDD [46]. Cortical thickness was also analyzed in adolescent patients with MDD and in adolescent HC. Left and right middle frontal gyrus appeared to be enlarged in patients with MDD. Additionally, thickening in the left caudal anterior cingulate cortex (ACC) was detected. When analyzing data in terms of volume, no differences were shown for these regions comparing patients and HC [47]. Comparing CT in patients with early onset of MDD and late onset of MDD, increase was found in the left and right posterior cingulated cortex (PCC), the right lingual gyrus, fusiform gyrus and the precuneus in patients with early onset of MDD. Left and right parahippocampal gyrus showed cortical thinning for patients with early onset. Moreover, decreased DLPFC volume was shown in patients with early onset MDD compared to HC [48].

Relapse in Major Depressive Disorder and the Impact on Brain Structure
Relapse in MDD is also associated with changes in brain structure. Gray matter volume of patients suffering from MDD with no relapse, MDD patients with experienced relapse and HC were examined. Magnetic resonance imaging was done at baseline and 2 years later. Patients with MDD were then separated in 2 groups depending on whether they experienced relapse or not. Reduction of insular and DLPFC volume was found over time in patients with MDD with experienced relapse. Additional CT analysis revealed an increase of ACC and OFC in patients with no relapse an increase. [49].

White Matter in Major Depressive Disorder
Female and male patients with first episode of MDD were examined in respect to hippocampal volume in reference to GMV and white matter (WM) volume. Gray matter volume of hippocampus in male patients was diminished when compared to male HC. For both genders suffering from first episode of MDD reduced white matter fibers in hippocampus were found as against HC [50]. Moreover, changes in WM structures related to MDD using DWI and DTI in MRI is reported. A study examining a large number of imaging data of subcortical brain structural MRI and white matter with DTI assessment, revealed no differences in subcortical volumes including the hippocampus in patients with MDD compared to HC but reduced WM integrity. However, decreased global WM integrity was found comparing MDD patients to HC [51].
Functional Magnetic Resonance in Major Depressive Disorder

A fMRI study reported that patients with MDD had increased brain activity in cortical and limbic regions [52]. A meta-analysis showed decreased activation for patients with MDD compared to HC in bilateral middle frontal gyri, pregenual anterior and posterior cingulate, insula and left superior temporal gyrus. Deeper brain structures like caudate, thalamus, medial and inferior frontal gyri and cortical structures like right middle frontal and the left superior frontal gyri were linked to increased brain activation [53].

Positron Emission Tomography in Major Depressive Disorder

Studies investigating blood flow and glucose metabolism in patients with MDD via positron emission tomography (PET) revealed a decrease in the PFC, ACC and basal ganglia associated with MDD [54]. Changes in the serotonergic system of patients with mood disorders investigated with PET was reported as receptor binding potential of 5-HT$_{1A}$ was reduced in the raphe nuclei, mesiotemporal cortex, postcentral gyrus and occipital cortex [55]. Receptor binding potential of the 5-HT$_{1A}$ receptor further seems to correlate with GMV [56].

Magnetic Resonance Spectroscopy in Major Depressive Disorder

Furthermore, metabolic changes using MRS was reported in major depression including decreased concentrations of N-acetyl aspartat, g-amino butyric acid (GABA), glutamate and glutamine in different brain regions such as thalamus, caudate, ACC, PFC, basal ganglia, amygdala and hippocampus. For some of these metabolic changes an improvement was found after electroconvulsive therapy [57].

There is evidence that GABA and glutamate levels can be influenced by life stress and subsequently may lead to changes in brain structure [58, 59].

1.1.8 Childhood Maltreatment and Neuroimaging

As CM is a predisposing factor for several psychiatric disorders, neuroimaging studies mainly focused on patients with MDD or post traumatic stress disorder (PTSD) and experienced CM to examine the relation of CM and brain structure. Only a few studies examined CM without considering psychiatric comorbidity. A MRI analysis of women with history of sexual abuse in childhood, with no experienced further types of CM was done and compared to female HC. No specific psychiatric disorder was described for these participants. Grey matter volume of the frontal cortex and volumetric analysis of hippocampus and amygdala revealed decreased volume of hippocampus in women with sexual abuse at age 3 to 5 and 11 to 13. Moreover, decreased corpus callosum was found in women with sexual abuse at age 9 to 10 and
attenuated frontal cortex was discovered when sexual abuse at age 14 to 16 was experienced [60]. A meta-analysis including data from children, adolescent and adults with and without CM-history examined the effects of CM on GMV. Psychiatric comorbidity was no exclusion criteria, thus the specific diagnosis were not described. Decrease in GMV was found in the right orbitofrontal gyrus, superior temporal gyri, amygdala, insula, parahippocampal gyrus, middle temporal gyrus, left IFG and postcentral gyrus relative to CM-history. Increased GMV in the right superior frontal gyrus and left middle occipital gyrus was found in individuals with CM compared to control subjects [61].

Post Traumatic Stress Disorder in Adults and Brain Structure

Findings of hippocampal volume loss in patients suffering from PTSD lead to a study examining whether decreased hippocampal volume is predisposing for developing PTSD or results from experiencing psychological stress. Therefore male twins were examined, whereat one was previously exposed to psychological stress as a Vietnam combat veteran. Some of the exposed twins later suffered from chronic PTSD. Results let indicate that smaller hippocampal volumes may predispose for developing PTSD when exposed to stress. Severity of symptoms in patients with PTSD was associated with decreased volumes of their own and their healthy twin brother’s hippocampus. Additionally, twin pairs who included one PTSD patient had both decreased volumes in hippocampus compared to healthy twin pairs [62].

Childhood Maltreatment Related Post Traumatic Stress Disorder in Adults

Various studies examined the relation of CM and brain development or later life brain changes in patients, diagnosed with PTSD. Magnetic resonance imaging volume analysis of hippocampus in adult patients with CM related PTSD revealed 12% smaller volumes compared to HC. No differences in respect to volume were found in amygdala, caudate and temporal lobe [63]. These findings are conform with a study including women experiencing CM in terms of sexual abuse with diagnosed PTSD and no PTSD comparing to HC. Analysis of MRI of hippocampus revealed 16% smaller hippocampal volume in PTSD patients with CM-history compared to abused women without PTSD. Compared to female HC with no CM-history at all and no PTSD diagnosis, patients with experienced sexual abuse and PTSD had even 19% smaller hippocampal volume [64]. In contrast, no changes in volume of hippocampus were detected in a study including adult women with PTSD related to CM including emotional, physical and sexual maltreatment. Instead, decrease in volume of right amygdala and negative correlations to the subscale of sexual abuse in left and right amygdala were measured [65].
When investigating the relation of CM and brain structure it suggests itself to examine children with PTSD. Volume analysis from 1.5T MRI revealed decreased total brain and cerebral volumes and a decrease in frontal lobe asymmetry in children with diagnosed PTSD compared to HC. Contrary, findings of changes in hippocampal volumes in adults with PTSD were not confirmed in children. However, it was not surveyed which kind of trauma was causal for developing a PTSD [66]. A longitudinal study examined if CM in paediatric PTSD might lead to altered growth of hippocampus. Volume measures of temporal lobes, amygdala and hippocampus did not reveal any changes comparing patients and HC over time. However, comparison of these regions at baseline did not show any differences too. These findings are not in line with previous MRI data analysis in paediatric PTSD and may be due to small sample size [67].

Explicit measures of hippocampal volume and blood level of cortisol were carried out in children 14 years or younger. Inclusion criteria was experienced CM in form of physical, sexual or emotional abuse, physical neglect, witnessing violence, separation and loss. Furthermore, paediatric PTSD was diagnosed and PTSD symptoms were quantified. Right hippocampal volume was negatively correlated to cortisol levels in the morning and severity of PTSD symptoms. Moreover, 12 to 18 months intervals revealed, that PTSD symptoms and stress levels in terms of cortisol baseline measures predicted decreased hippocampal volume of children [68].

Following study investigated MRI data measuring GMV from young patients with CM related PTSD compared to infants or adolescents with experienced CM but not suffering from PTSD and HC with no history of CM. Comparing patients with CM-history and PTSD to non-maltreated HC and maltreated adolescents without PTSD, smaller posterior cerebral and cerebellar GMV were shown. Also GMV of total cerebrum and cerebellum was negatively correlated to symptoms of PTSD [69]. Gray matter volume analysis of 1.5T MRI data in PFC and midline areas of the brain was also done in children with PTSD matched to HC, while type of experienced trauma was not depicted. Results showed that paediatric PTSD is linked to increased GMV in the PFC while GMV in pons and posterior vermis areas appeared to be decreased [70]. Furthermore, GMV analysis of the superior temporal gyrus showed increased GMV in CM related paediatric PTSD patients in contrast to HC [71]. There is evidence about connections between volumes of cerebellum and CM as smaller cerebellar volumes were shown in children with paediatric PTSD compared to HC [72].
Moreover, there is evidence of gender differences in paediatric PTSD related to CM since decrease in cerebral volumes and callosum regions, more precisely in rostrum and isthmus, and an increase in lateral ventricular volumes was found in male patients suffering from CM related PTSD in comparison to maltreated females with PTSD [73].

**Childhood Maltreatment in Patients with Major Depressive Disorder**

A neuroimaging study examined patients with MDD with and without CM-history, quantified using the CTQ, in respect to GMV. Decreased Volume of left and right hippocampus was found in patients and HC with experienced CM compared to patients and HC with no CM-history, examined using VBM from 3T MRI data with hippocampus as a ROI. Moreover, ROI VBM analysis in right dorsomedial PFC and OFC showed increased volumes when CM was experienced in comparison to patients and HC who did not. Comparison of hippocampal volume between patients with and without CM, decreased volume was found in patients with CM-history. Whole brain analysis showed no significant changes in brain structure after Family-Wise Error correction [74].

Female patients with MDD and experienced CM in terms of physical or sexual abuse in childhood were examined in respect to whole brain volumes and volumes of hippocampus and temporal lobe. Women with MDD and no CM-history plus female HC were also included in this trial. When comparing patients with MDD and experienced CM to patients with MDD and no CM-history, 18% decreased volume of hippocampus was found, while 15% reduction of left hippocampus is found compared to HC. Similar volumes of left and right hippocampus were found comparing patients with MDD and HC both with no experienced CM. These findings let assume that the impact of CM on brain structure, especially on hippocampal volume, might be the explanation on inconsistent findings in research in respect to MDD and hippocampal volume [75].

The connection of CM and brain structure was also investigated in patients with first episode of MDD matched with HC. Changes in GMV were analysed with VBM of 3T MRI images. The Childhood Trauma Questionnaire was used to check for CM and quantify CM-history. Using these methods CM was mainly associated with changes in the right DLPFC, left posterior cingulate gyrus (PCG), inferior occipital gyrus (IOG) and cerebellum anterior lobe. At length, when comparing HC with experienced CM to HC without any CM-history, decreased GMV in the left PCG and increased GMV in right DLPFC were shown. Patients suffering from MDD with experienced CM showed decreased GMV in the left IOG and increased GMV in the left cerebellum anterior lobe in contrast to patients with no CM-history.
Furthermore, Correlation of total scores of CTQ and GMV was analysed, resulting in a negative correlation to GMV in the left IOG and a positive correlation with GMV in the right caudate, left dorsomedial PFC and left middle temporal gyrus [76].

*Cortical Thickness Analysis in Respect to Childhood Maltreatment*

Cortical thickness analysis from 3T MRI data was performed in depressed and healthy women with and without in CTQ reported CM-history. Total scores of CTQ were associated with cortical thinning in the ACC, the precuneus and the parahippocampal gyrus. Smaller left hemisphere, more specific the somatosensory cortex representing female genital area, was also linked to the score of the subscale sexual abuse. Decrease of left and right precuneus, the left ACC and PCC and the face region of the somatosensory cortex were linked to the subscale emotional abuse [77]. Sexual and physical abuse in childhood and effects on CT in maltreated and non-maltreated female and male adolescent were also examined using the CTQ for quantifying abuse and imaging data from 3T MRI. Decrease in OFC, right IFG, bilateral parahippocampal gyrus, left temporal pole and bilateral inferior, right middle and right superior temporal gyri were related to CM in form of sexual and physical abuse in childhood [78].

Data of 1.5T MRI was used to analyse CT in maltreated and non-maltreated children. Reduction in ACC, OFC and superior frontal gyrus was found in children with CM-history [79].

*Childhood Maltreatment in Other Psychiatric Disorders and Brain Structure*

An analysis of GMV in patients with bipolar disorder without psychotic symptoms and the relation to total scores of CTQ showed a negative correlation in the right thalamus and the DLPFC. Moreover, there was a negative correlation between GMV in the left and right thalamus and the subscale treating physical neglect. The subscale with the topic of emotional neglect was also negatively correlated with GMV in the right thalamus [80].

*Childhood Maltreatment and Changes of Brains White Matter*

The relation of CM and WM structures in brain were also part of several research. White matter analysis using VBM on WM ROIs in patients with MDD and HC with and without CM-history showed no changes in respect to CM [74]. Magnetic resonance imaging DTI analysis revealed CM associated changes in WM. Young adults with CM-history, explicit parental verbal abuse and no other terms of experienced CM, were matched to non-maltreated controls. Reduced WM fractional anisotropy in cingulum bundle by the posterior tail of the left hippocampus, in the arcuate fasciculus in the left superior gyrus and the left body of the
fornix was shown in participants with CM [81]. Analysis of MRI DTI of corpus callosum in children with CM related PTSD and matched HC revealed reduced fractional anisotropy in medial and posterior corpus [82].

*Childhood Maltreatment and Functional Magnetic Resonance Imaging*

Functional magnetic resonance imaging studies in female patients recruited in a psychosomatic clinic with CM investigated if non-traumatic stimuli of daily life may be processed altered when compared to non-maltreated patients. Olfactory stimuli lead to normal activation in the projection areas in both patients with CM and HC. In patients additional activation especially in neocortical areas, but also the precentral frontal lobe, posterior parietal lobe, inferior and middle frontal structures, occipital lobe and the PCC was detected [83]. Moreover, fMRI studies examined CM without any psychiatric disorder using the CTQ in healthy subjects. Besides the confirmation of previous studies with decrease in GMV in hippocampus, OFC, anterior cingulate gyrus, caudate and insula also responsiveness of amygdala to threat-related facial expressions was associated with higher CTQ-scores [84]. Young adults with CM-history and non-maltreated HC were also examined in respect to changes in response of basal ganglia to the consideration of monetary rewards and losses as well as to the monetary gains and penalties. Childhood maltreatment was related to weaker response to reward in the left globus pallidus in connection with less positively reports to reward [85].

*Childhood Maltreatment and Positron Emission Tomography*

To further examine the association of CM and brain activation, PET imaging to measure brain blood flow was done in women exposed to sexual abuse in childhood with and without PTSD. Increased blood flow during memories of childhood in women with PTSD was found in parts of anterior PFC, in PCC and motor cortex compared to women with no PTSD. Furthermore, decreased blood flow was detected in subcallosal gyrus and ACC of the medial PFC while retrieving memories of sexual abuse in patients with PTSD. Also in visual association cortex, right hippocampus, fusiform inferior temporal gyrus and supramarginal gyrus of women with PTSD decreased blood flow associated with memories of sexual abuse was detected [86]. In a similar group of participants PET analysis showed a failure of activation in left hippocampus during verbal memory encoding task in female PTSD patients with sexual abuse in childhood [64].
Brain derived neurotrophic factor is a protein which is expressed in neurons of different regions of the brain including the hippocampus, seems to act neuroprotective and is involved in neuronal plasticity [87]. Moreover, BDNF plays a key role in processing memory, especially long-term memory [88]. There is evidence that BDNF is involved in the development of MDD. Hippocampal BDNF levels were observed to be decreased in MDD. The Val66Met polymorphism of BDNF coding gene has been of high interest of various studies [6].

As lower BDNF concentrations in consequence of SLE have been reported, the relationship of CM and BDNF has been examined in patients with MDD and/or anxiety disorder and HC. All participants were genetically examined if they were carrier of the Met-allele or heterozygote for the Val-allele. Patients with MDD, CM-history and no anxiety disorder who were Met-allele carrier had lower BDNF serum levels. Also in this group, recent SLE were linked to lower BDNF levels regardless of BDNF genetics [89]. In the following study effects of CM on BDNF and specific regions of the hippocampus were examined. More specific the subfields CA1, CA2/3 and CA4/DG, parts of the cornu ammonis and dentate gyrus were analysed. Carrier of the Met-allele and experienced CM had smaller volumes of CA4/DG and CA2/3 than homozygote carriers of the Val-allele. In turn, larger volumes of these regions were found in Met-allele carriers without any CM-history compared to homozygote Val-allele carriers [90].

The hypothalamic-pituitary-adrenal axis was examined in respect to changes of binding to glucocorticoid and mineralcorticoid receptors and response in adulthood after experienced CM. Therefore patients with current MDD with and without CM-history and HC were included. Cortisol levels were measured in saliva and plasma after intake of placebo, mineralcorticoid agonist and glucocorticoid agonist. Results showed differences in responses to mineralcorticoid and glucocorticoid agonist in patients with MDD with and without CM in contrast to HC. While depressed patients without CM showed lower cortisol awakening responses to mineralcorticoid and glucocorticoid agonist compared to placebo intake, patients with CM-history only had suppression after mineralcorticoid agonist in contrast to placebo intake [91]. Receptor sensitivity of glucocorticoid is influenced by the FK506 binding protein 51 expressing gene. The T allele in rs1360780 single nucleotide polymorphism is described as a risk allele for MDD. Patients with MDD and HC were examined in respect to genetics of the FK506 binding protein 51 gene, brain structure and CM-history. Brain structure and function was analysed using fMRI, sMRI and DTI. Changes in brain function were found in patients
with risk allele in contrast to patients without. The risk allele in patients was linked to reduced activity in the rolandic operculum, heschl gyrus, insula, parahippocampal gyrus, PCC and IFG. In WM changes were witnessed in association with CM and the risk allele expressed in higher mean diffusivity and decrease in fractional anisotropy in insula, rolandic operculum and the IFG [92].

Yet another genetic factor associated with development of depression is the 5HTTLPR polymorphism of the serotonin transporter gene 5-HTT. Genetic status of young patients with and without MDD was examined in respect to CM to find out if the occurrence of CM interacts with 5-HTTLPR in the prediction of MDD. Gender seemed to be a protective factor when examining genetics and CM in respect to development of MDD. Female carrier of the risk allele and CM had an elevated risk for MDD, while males with the same criteria had no increased risk. In turn, females with no risk allele had a lower risk for developing a MDD in interaction with CM. Furthermore, genetic effects were more prominent in predicting MDD than CM [93]. When examining adolescent in respect to CM with currently no MDD, 5HTTLPR genotype and brain structure, no effects of 5HTTLPR genotype on GMV was shown [94].

Polymorphism of the serotonin transporter gene 5-HTT and monoamine oxidase A (MAO-A) gene in interaction with CM in respect to depressive symptoms were examined in adolescents. Low activity of MAO-A and CM was linked to increase of depressive symptoms. Also sexual abuse in terms of CM and a specific genotype, the short/short genotype of 5-HT, was linked to increased depressive symptoms. In turn, higher levels of MAO-A in maltreated children were associated with milder forms of depression. These findings reflect the role of genetics in resilience [95].

1.1.9 Further Factors Related to Changes in Brain Structure

When examining a specific effect on brain structure, several additional factors with brain changing potential should be considered. A compendium of common events which are possibly linked to altered brain structure is described below.

*The impact of Antidepressant Drug Therapy on Brain Structure*

Gray matter volume seems to be correlated to the receptor binding potential of Serotonin 1A on 5-HT_{1A} receptors according to a combined MRI and PET study including healthy participants. Gray matter volume was correlated to the binding of 5-HT_{1A} heteroreceptor in hippocampus, posterior inferior temporal cortex, posterior medial temporal cortex, the medial
occipital cortex and the pericalcarine region. Moreover, GMV of the ACC was positively correlated to 5-HT1α receptor binding in the raphe region. In two regions of cerebellum a negative correlation of GMV and 5-HT1α receptor binding was found [56]. To examine effects of an antidepressant medication with selective serotonin reuptake inhibitors (SSRI) on brain structure, healthy subjects of both genders underwent three MRI measures each after ten days of citalopram, escitalopram and placebo intake. Voxel based morphometry analysis revealed increases in GMV of the PCC and ventral precuneus and decreases in precentral and postcentral gyri secondary to SSRI intake [96].

To eliminate the brain changing potential of antidepressant medication when examining CM related changes in brain structure, in this diploma thesis patients were at least 3 months drug free prior MRI scans.

**Age and the Impact on Brain Structure**

In a MRI study healthy adults from 18 to 85 years were examined in respect to age related changes in brain structure. Voxel based morphometry analysis of the brain revealed decreased cortical and subcortical GMV. More precisely GMV was decreased in amygdala, striatum, prefrontal, temporal and parietal cortical areas, cerebellum, midline structures, cingulate cortex and precuneus [97]. Furthermore, GMV and WM volumes were decreased in subjects older than 50 years compared to younger individuals. Gray matter volume analysis beginning at the youngest subject revealed a with age linear decrease [98]. Linearly decreased GMV was also shown in male and female participants, with more prominent findings in men. Local areas with increasing loss were found bilateral in insula, superior parietal gyri, cingulate sulci and central sulci. In contrast to other studies amygdala showed little effects related to age. Also in hippocampus and entorhinal cortex and global WM little or no effects of age were found [99].

Cortical thickness analysis in respect to age showed cortical thinning in several areas. In relation to aging decrease in primary sensory, primary somatosensory, motor and association cortices was found [100]. Age related increase was reported in ACC, medial OFC and medial subcallosal cortex. Further volume measures were in line with previous studies and showed also a decrease in respect to age [100].

**Gender Differences in Brain Structure**

In a study examining GMV and WM volume in respect to age related changes in brain structure, no differences were observed between male and female participants after controlling for cranium size [98]. These results are in agreement with CT measures of male
and female brains of all ages resulting in thicker Cortex in men, but not after correcting for total intracranial volume. When examining only middle aged individuals of age 41 to 57, men have increased left hemisphere and a trend to increased right hemisphere. As women undergo a hormonal change by menopause, these findings let assume that cortical thinning is associated with the concentration of sex hormones [100].

Gender differences in brain structure of patients with MDD were reported. As mentioned before, in male patients with first episode of MDD smaller volumes of left hippocampus were found compared to male HC. Female patients with first episode of MDD showed larger right hippocampal volume in contrast to female HC. In this study also gender as brain changing main factor was viewed. Larger GMV of hippocampus was found in males compared to females. In WM no specific differences were found between male and female participants [50].

1.2 Hypothesis

1. Patients with MDD score higher in total scores of CTQ and scores of subscales emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse than HC.
2. Total Scores of CTQ and scores of subscales are positively correlated with scores of Hamilton Depression scale (HAM-D) in patients.
3. Total scores of CTQ correlate with CT in patients with MDD and in HC differently.
4. Scores of subscales of CTQ of patients with MDD and HC significantly correlate with CT.

1.3 Study Aim and Relevance

With this diploma thesis, we want to examine the impact of emotional or traumatic events experienced in childhood on morphological brain alterations. Numerous studies examined the association of CM and brain development in childhood and adolescence and brain structure as well as brain function in adulthood. So far, data to CM related changes of brain structure are partial inconsistent, especially when comparing diverse methods for analysing structural data. Structural imaging data to date was collected using 3T and less MRI and numerous questionnaires for examining and quantifying different aspects of CM were carried out. For this diploma thesis structural data from 7T MRI was used to conduct CT analysis and correlations to CTQ-scores for examining trauma associated changes in brain structure. Showing differences in CT between patients and HC with and without experienced CM might
be a next step to identify biological markers for diagnosis and treatment response of psychiatric disorders.
2. Materials and Methods

2.1 Study Design

This diploma thesis was designed as a retrospective data analysis examining data collected within a longitudinal multimodal clinical trial named “Multimodal Assessment of Neurobiological Markers for Psychiatric Disorders (MANBIOPSY)” (Principal Investigator: O. Univ. Prof. Dr. hc. mult. Dr. med. Siegfried Kasper) conducted at the NEUROIMAGING LAB (NIL), at Medical University of Vienna, Department for Psychiatry and Psychotherapy (head: O. Univ. Prof. Dr. hc. mult. Dr. med. Siegfried Kasper) under the supervision of Dr. med. Thomas Vanicek, PhD.

Thirteen patients with a current depressive episode, fulfilling the criteria for a MDD, and 14 HC subjects were included for this diploma thesis. Patients and HC subjects underwent a screening visit including the German version of the Structural Clinical Interview for 4th edition of DSM axis I and II (SCID I and II), performed by an experienced psychiatrist to determine diagnosis and obviate psychiatric disorders in HC subjects [101, 102]. Moreover, the participants endured a physical examination, blood sampling for routine parameters, electrocardiogram, drug screen and pregnancy test in females during screening visit to ensure physical health. Hamilton Depression Scale with 24 items was provided to examine depressive symptoms such as sleep disturbance, loss of interest and joy or lack of concentration [103].

If all inclusion criteria were fulfilled and no exclusion criteria (see section 2.2.2 and 2.2.3) occurred, participants underwent a cranial 7T MRI measurement.

Afterwards, patients and HC were asked to complete the CTQ to examine the occurrence of CM [26, 27].
Figure 1: Study Design

The figure shows an illustration of the study design. Patients and healthy controls (HC) underwent a screening visit, that included physical and psychiatric examination including Hamilton Depression Scale (HAM-D) followed by magnetic resonance imaging (MRI) measurement. Childhood Trauma Questionnaire (CTQ) was subsequently filled out by study participants.
2.2 Subjects

A subset of the MANBIO study including 13 patients with MDD and 14 HCs were considered in this retrospective data analysis. Nine patients with MDD were female and 4 male, while 7 HC were male and 7 female. Mean age of the whole sample was 29.32 years (SD: ± 10.39).

The study participants were recruited within the study named “Multimodal Assessment of Neurobiological Markers for Psychiatric Disorders MAN-BIOPSY” via flyer at public places in Vienna, electronic media and mailing to doctors, psychiatrists and psychologists in Vienna. Patients suffering from MDD were also recruited from the outpatient clinic of the Department of Psychiatry and Psychotherapy (head: O. Univ. Prof. Dr.hc.mult. Dr. med. Siegfried Kasper) at the General Hospital of Vienna (Allgemeines Krankenhaus Wien, AKH). Participants signed written informed consent prior to the inclusion after written and oral elucidation.

2.2.1 Inclusion Criteria for Patients

- Age between 18 and 50 years
- DSM 4\textsuperscript{th} edition diagnosis of MDD (excluding PTSD, specific phobias and bipolar disorder) by SCID I and SCID II
- Drug-free within the last 3 months prior inclusion
- Willingness and competence to sign the informed consent form

2.2.2 Inclusion Criteria for Healthy Controls

- Age between 18 and 50 years
- Drug free
- No history of neurological or psychiatric diseases

2.2.3 Exclusion Criteria for Study Participants

- Psychopharmacological treatment within 3 months prior inclusion
- Pregnancy for female participants
- Major internal or neurological illness
- Previous or present psychiatric disorders (except depression for patients)
- Current substance abuse
- Failure to comply with the study protocol or to follow the instructions
Currently the 5th edition of DSM is used by researchers and clinical doctors to classify psychiatric disorders, while at time of data acquisition the 4th edition of the DSM was prevailing and therefore consulted for inclusion criteria [104].

### 2.3 Childhood Trauma Questionnaire

The CTQ contains 28 items, which are separated in 5 subscales. The subscales consist of the topics emotional abuse, physical abuse, sexual abuse, physical neglect and emotional neglect. Three of those items are belonging to the minialization scale, that encounters a denial or minimalization in reporting CM [26].

Each of the 28 items is answered by a 5 point Likert-scale, resulting in at least 5 points per scale if no CM was experienced and 25 points maximum in case of severe CM. These numbers result in a maximum total score of 125 points and 25 points minimum. For the scale measuring minimalization of CM overall 0 to 3 points can be scored, however they are not added in total scores of CTQ. Scoring 3 points in the minimalization scale is interpreted as a sign, that the CTQ completing individual may underreport or deny experienced CM [26].

The German version of the CTQ presents appropriate factor loadings and a good internal consistency for all subscales, except physical neglect, with a Cronbach’s $\alpha$ of 0.94 for the total CTQ [27]. These findings were reproduced in a representative sample of German population, were also acceptable construct validity was measured [105].

For this diploma thesis the total scores as well as scores of subscales from five subscales of the CTQ were considered. A cut-off value is described for each subscale of the original version of the CTQ (see table 1). No cut off value for total score of CTQ is described [106].

There is no data available of reliability and validity for the cut off value applied for the German version. As correlation analyses with total scores and scores of subscales of CTQ were done, no cut off value was elected for this diploma thesis.
Table 1: Cut-off Value for Subscales of Childhood Trauma Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>PN</th>
<th>EA</th>
<th>EN</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non to low</td>
<td>5-7</td>
<td>5-7</td>
<td>5-8</td>
<td>5-9</td>
<td>5</td>
</tr>
<tr>
<td>Low to moderate</td>
<td>8-9</td>
<td>8-9</td>
<td>9-12</td>
<td>10-14</td>
<td>6-7</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>10-12</td>
<td>10-12</td>
<td>13-15</td>
<td>15-17</td>
<td>8-12</td>
</tr>
<tr>
<td>Severe</td>
<td>13 or higher</td>
<td>13 or higher</td>
<td>16 or higher</td>
<td>17 or higher</td>
<td>13 or higher</td>
</tr>
</tbody>
</table>

This table states cut off values for the subscales physical abuse (PA), physical neglect (PN), emotional abuse (EA), emotional neglect (EN) and sexual abuse (SA) of the original version of the Childhood Trauma questionnaire. None to low CM was experienced when 5 to 7 points were scored for PA and PN, 5 to 8 points for EA, 5 points for SA and 5 to 9 for EN. Low to moderate CM is interpreted when 8 to 9 points were scored for PA and PN, 9 to 12 points for EA, 6 to 7 for SA and 10 to 14 points for EN. Moderate to severe CM can be interpreted when 10 to 12 points were achieved for PA and PN, 13 to 15 points for EA, 8 to 12 points for SA and 15 to 17 points for EN. Severe CM was experienced in case of a score from 13 or higher for subscales PA, PN and SA, 16 or higher for EA and 18 or higher for EN [106].

2.4 Structural Magnetic Resonance Imaging

Ultra high field 7T scanner (SIEMENS Magnetom) was used for high-resolution structural MRI, installed at the MR Center of Excellence at the Medical University of Vienna. In terms of this diploma thesis, an 32-channel head coil and isocubic magnetization-prepared rapid gradient-echo (MPRAGE, T1-weighted) sequence (512 slices, 384 x 312 matrix, voxel size 0.74 x 0.68 x 0.68 mm, TE = 3.07 ms, TR = 4060 ms) was used.

2.4.1 Cortical Thickness Analysis

Freesurfer 5.3 (freesurfer-Linux-centos6_x86_64-stable-pub-v5.3.; http://surfer.nmr.mgh.harvard.edu/, version 5.3) was used for automated segmentation of derived T1-weighted images [107]. Individual MRIs were segmented using the Desikan atlas which divides the human cortex into 68 ROIs. Areas are predefined for 34 ROIs for each hemisphere enabling an automated anatomical classification of measured CT [108]. (see section 2.5.1)

2.5 Statistics

2.5.1 Statistical Analysis

The first step of statistical analysis was to examine if HAM-D and CTQ-scores are normally distributed in the groups of patients suffering from MDD and HC separately. This was analysed using Shapiro-Wilk test due to small sample size.

Furthermore, we analysed differences related to ranks of HAM-D-scores between the two groups via Man-Whitney-U test. Then, Man-Whitney-U test for total scores of CTQ of patients and HC was done to show group differences of scores. Correlation analysis using
Spearman correlation coefficient was provided between HAM-D-scores and CTQ-score for each group.

Bonferroni correction for multiple comparisons was carried out due to multiple testing and significance was considered when p-value was < 0.05 after correction.

Cortical Thickness Analysis
Statistical analysis of sMRI data was performed using IBM SPSS Statistics (v22.0, 2010, SPSS, Inc., an IBM Company, Chicago, United States of America).

By reason of artifacts in 7T MRI structural data, temporal regions were not considered in statistical analysis. The following brain regions of each left and right hemisphere of the Desikan atlas where included: caudal ACC, caudal middle frontal gyrus, cuneus cortex, inferior parietal cortex (IPC), isthmus-cingulate cortex, LOC, lateral orbital frontal cortex, lingual gyrus, medial orbital frontal cortex, paracentral lobule, pars opercularis, pars orbitalis, pars triangularis, pericalcarine cortex, postcentral gyrus, PCC, precentral gyrus, precuneus cortex, rostral ACC, rostral middle frontal gyrus, superior frontal gyrus, superior parietal cortex, supramarginal gyrus, frontal pole and insula [108].

To test for difference between average CT in patients and HC, additional t-test was provided as we assumed approximate normally distributed data after visual inspection for statistical outliers.

Correlation of CT of each ROI and CTQ-scores was calculated using Pearson correlation coefficient.

Data was corrected for multiple testing using Bonferroni correction. P-values less than 0.05 were considered as significant.

2.5.2 Sample Size Justification
For the original study, sample size was performed based on previous longitudinal MRI studies in patients with MDD (EK 103/2011). All available data was included in statistical analysis for this diploma thesis.
3. Ethics and Risk-Benefit Evaluation

The Ethics Committee of the Medical University of Vienna [EK 2110/2016, ethic-kom@meduniwien.ac.at] has approved the retrospective data analysis. Procedures for data acquisition in the original study (EK 103/2011) were performed in accordance to the Deceleration of Helsinki (1964), including recurrent revisions, the Austrian Arzneimittelgesetz and the guidelines for Good Scientific Practice required at the Medical University of Vienna.

This diploma thesis was designed as a retrospective data analysis, therefore no risks or benefits were to expect for the included subjects. For sensitive data from MRI and the CTQ anonymization was provided using numbering and pseudonymization in line of the original study (EK 103/2011). Moreover, there is no connection between used data for analysis and sensitive patient data.
4. Results

In table 2 mean age of study sample is described.

Table 2: Age of Study Sample

<table>
<thead>
<tr>
<th>Mean age</th>
<th>Whole sample</th>
<th>MDD</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>29.32</td>
<td>32.85</td>
<td>26.14</td>
</tr>
<tr>
<td>σ</td>
<td>10.39</td>
<td>12.01</td>
<td>7.12</td>
</tr>
</tbody>
</table>

This table shows mean age of the study sample and σ=SD.

Shapiro-Wilk normality test showed no normal distribution for HAM-D and CTQ-scores of HC. A normal distribution was present for patient’s HAM-D-scores and scores of CTQ subscales emotional abuse and emotional neglect. Due to data distribution, scores were compared using Man-Whitney-U rank test and correlation analysis between HAM-D and CTQ-scores was carried out using Spearman correlations coefficient.

Visual inspection of data distribution of CT in both groups showed no critical outliers, therefore further correlation analysis was performed using Pearson correlations coefficient.

HAM-D-scores from patients with MDD compared to HC differed significantly (mean score ± SD: MDD 22.92 ± 4.39, HC 0.21 ± 0.58, p = < 0.001) (see table 3).

Table 3: Mean Scores of HAM-D

<table>
<thead>
<tr>
<th>HAM-D-Score</th>
<th>MDD</th>
<th>MDD female</th>
<th>MDD male</th>
<th>HC</th>
<th>HC female</th>
<th>HC male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score</td>
<td>22.92</td>
<td>22.33</td>
<td>24.25</td>
<td>0.21</td>
<td>0.14</td>
<td>0.29</td>
</tr>
<tr>
<td>σ</td>
<td>4.39</td>
<td>3.67</td>
<td>6.13</td>
<td>0.58</td>
<td>0.38</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Mean scores and standard deviation (σ) of HAM-D for all patients with depression and for all HC as well as for female and male patients and HC separately are described in this table.

Total scores of CTQ of patients with MDD differed significantly from HC’s totals score of CTQ (mean score ± SD, MDD 45.15 ± 19.03; HC 31.86 ± 7.38; p = < 0.001 after Bonferroni correction). Patients scored significantly higher in the subscale examining emotional neglect (mean score ± SD, MDD 12.15 ± 4.43; HC 7.43 ± 2.44; p = 0.014 after Bonferroni correction). There was no significant difference in scores of other subscales (see table 4).
Table 4: Distribution of CTQ-Scores

<table>
<thead>
<tr>
<th></th>
<th>CTQ EA</th>
<th>CTQ PA</th>
<th>CTQ SA</th>
<th>CTQ EN</th>
<th>CTQ PN</th>
<th>CTQ Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>10.92</td>
<td>7.08</td>
<td>7.23</td>
<td>12.15</td>
<td>7.77</td>
<td>45.15</td>
</tr>
<tr>
<td>σ</td>
<td>5.79</td>
<td>5.54</td>
<td>4.90</td>
<td>4.43</td>
<td>3.32</td>
<td>18.03</td>
</tr>
<tr>
<td>MDD female</td>
<td>10.22</td>
<td>5.78</td>
<td>7.22</td>
<td>10.89</td>
<td>7.67</td>
<td>41.78</td>
</tr>
<tr>
<td>σ</td>
<td>4.74</td>
<td>1.56</td>
<td>5.33</td>
<td>3.72</td>
<td>3.46</td>
<td>9.32</td>
</tr>
<tr>
<td>MDD male</td>
<td>12.5</td>
<td>10</td>
<td>7.25</td>
<td>15</td>
<td>8</td>
<td>52.75</td>
</tr>
<tr>
<td>σ</td>
<td>8.35</td>
<td>10</td>
<td>4.5</td>
<td>5.10</td>
<td>3.46</td>
<td>30.93</td>
</tr>
<tr>
<td>HC</td>
<td>6.79</td>
<td>5.71</td>
<td>5.86</td>
<td>7.43</td>
<td>6.07</td>
<td>31.86</td>
</tr>
<tr>
<td>σ</td>
<td>2.86</td>
<td>2.40</td>
<td>2.32</td>
<td>2.44</td>
<td>2.79</td>
<td>7.38</td>
</tr>
<tr>
<td>HC female</td>
<td>7.29</td>
<td>5.14</td>
<td>6.14</td>
<td>6.29</td>
<td>5</td>
<td>29.86</td>
</tr>
<tr>
<td>σ</td>
<td>3.99</td>
<td>0.38</td>
<td>3.02</td>
<td>0.95</td>
<td>0</td>
<td>5.70</td>
</tr>
<tr>
<td>HC male</td>
<td>6.29</td>
<td>6.29</td>
<td>5.57</td>
<td>8.57</td>
<td>7.14</td>
<td>33.86</td>
</tr>
<tr>
<td>σ</td>
<td>1.11</td>
<td>3.40</td>
<td>1.51</td>
<td>2.10</td>
<td>3.76</td>
<td>15.14</td>
</tr>
</tbody>
</table>

Mean scores and σ (SD) of total scores of Childhood Trauma Questionnaire (CTQ) are described in this table for each female and male healthy controls (HC) and females and males with major depressive disorder (MDD). Mean scores and SD of Subscales for emotional abuse (CTQ EA), physical abuse (CTQ PA), sexual abuse (CTQ SA), emotional neglect (CTQ EN) and physical neglect (CTQ PN) are also described for each group. Stated p-values are corrected for multiple testing.

Spearman correlation analyses of HAM-D-scores and total scores of CTQ for each group were not statistically significant (see figure 2 and 3).
Figure 2: Correlation of HAM-D and CTQ-Scores in Patients with MDD

The figure shows a graphic demonstration of correlation analysis of Hamilton Depression Scale (HAM-D) scores and total scores of Childhood Trauma Questionnaire (CTQ) in patients (Spearman Rho = 0.35, p = 0.473 corrected for multiple testing). On x-axis HAM-D-scores can be read, total scores of CTQ are described on y-axis. Gray boxes represent HAM-D-score and total scores of CTQ for each patient.

Figure 3: Correlation of HAM-D and CTQ-Scores in HC

The figure depicts a correlation of Hamilton Depression Scale (HAM-D) and total scores of Childhood Trauma Questionnaire in healthy controls (HC) (Spearman Rho = -0.42, p = 0.280 corrected for multiple testing). On x-axis HAM-D-scores can be read, total scores of CTQ are described on y-axis. Gray boxes represent HAM-D-score and total scores of CTQ for each HC.
4.1 Cortical Thickness Analysis

Cortical thickness of all measured areas ranged from 1.499 mm to 3.215 mm in patients (mean ± SD, 2.414 mm ± 0.312 mm). Healthy control’s CT amounts a minimum of 1.512 mm and a maximum of 3.499 mm (mean ± SD, 2.432 mm ± 0.318 mm). Minimal CT was found for both groups in left pericalcarine cortex (mean ± SD, MDD 1.785 mm ± 0.113 mm; HC 1.839 mm ± 0.125 mm). Maximal CT was measured in left superior frontal cortex in patients (mean ± SD, 2.864 mm ± 0.161 mm) and in left insula in group of HC (mean ± SD, 2.949 mm ± 0.194 mm).

When applying a t-test, no significant difference was detected in regards of average CT of all measured areas in patients and HC.

Correlation analysis of patient’s CT and each CTQ subscale revealed a negative correlation between emotional abuse and the right frontal pole (Pearson r = -0.62, p = 0.023) and a positive correlation with the right PCC (Pearson r = 0.58, p = 0.038). Subscale emotional neglect of CTQ showed also a negative correlation to CT in right frontal pole (Pearson r = -0.68, p = 0.011). Furthermore, patient’s CTQ subscale emotional neglect was linked negatively to CT of the left pars triangularis (Pearson r = -0.61, p = 0.028; figure 4-7).

Healthy control’s correlation analysis of CT and each CTQ subscale revealed a negative correlation of CTQ subscale emotional neglect and right IPC (Pearson r = -0.55, p = 0.044), right LOC (Pearson r = -0.73, p = 0.003) and left lingual gyrus (Pearson r = -0.75, p = 0.002) (see figure 8-10).

Correlation analysis between CT and total scores of CTQ an scores of subscales in patients and HC did not remain significant after Bonferroni correction for multiple testing.
Figure 4: Right Frontal Pole and Emotional Abuse in Patients with MDD
This figure depicts a correlation analysis of patient’s cortical thickness (CT) in millimetre (mm) in frontal pole of right hemisphere and patient’s score of Childhood Trauma Questionnaire’s subscale emotional abuse (CTQ EA). X-axis represents the scores of CTQ subscale emotional abuse. On y-axis the CT in mm can be read. (Pearson R = -0.62, uncorrected p = 0.023)

Figure 5: Left Posterior Cingulate Cortex and Emotional Abuse in Patients with MDD
The figure illustrates correlation analysis of patient’s cortical thickness (CT) in millimetre (mm) of posterior cingulate cortex (PCC) of left hemisphere and patient’s score of Childhood Trauma Questionnaire’s subscale emotional abuse (CTQ EA). X-axis represents scores of CTQ EA. CT in mm is shown on y-axis. (Pearson R = 0.58, uncorrected p = 0.038)

Figure 6: Right Frontal Pole and Emotional Neglect in Patients with MDD
This figure depicts correlation analysis of patient’s cortical thickness (CT) in millimetre (mm) in frontal pole of right hemisphere and patient’s score of Childhood Trauma Questionnaire’s subscale emotional neglect (CTQ EN). X-axis represents the scores of
CTQ subscale emotional neglect. On y-axis the CT in mm can be read. (Pearson R = -0.62, uncorrected p = 0.011)
Figure 9: Right Lateral Occipital Cortex and Emotional Neglect in HC

The figure illustrates correlation analysis of healthy control’s (HC) cortical thickness (CT) in millimetre (mm) in lateral occipital cortex of right hemisphere and HC’s score of Childhood Trauma Questionnaire’s subscale of emotional neglect (CTQ EN). X-axis shows scores of CTQ EN. CT is represented on y-Axis in mm. (Pearson R = -0.73, uncorrected p = 0.003)

Figure 10: Left Lingual Gyrus and Emotional Neglect in HC

This figure depicts correlation analysis of healthy control’s (HC) cortical thickness (CT) in millimetre (mm) in lateral occipital cortex of right hemisphere and HC’s score of Childhood Trauma Questionnaire’s subscale emotional neglect (CTQ EN). X-axis represents the scores of CTQ EN, while on y-axis CT in mm can be read. (Pearson R = -0.75 uncorrected p = 0.002)
5. Discussion

The aim of this study was to assess a linkage between CM and MDD and that CM is associated with changes in brain structure. Therefore, we hypothesized that there will be a positive correlation between HAM-D-scores and CTQ-scores as well as between CM and morphological brain alterations. Thus, we investigated for a potential correlation of CTQ-scores with CT in patients with MDD and HC.

5.1 Childhood Maltreatment and Depression

Scores of HAM-D differed significantly comparing mean scores of patients and HC, whereas no depressive symptoms were found, as expected, in healthy participants. There is evidence, that CM is linked to the occurrence of, as well as to recovery from MDD, severity and earlier onset of depressive symptoms and to a higher occurrence of comorbidities [15-18, 21]. According to these findings we hypothesized that patients with MDD have higher scores in CTQ than HC and that HAM-D-score is positively correlated with total score of CTQ. In line with our hypothesis, we demonstrated significant higher total scores of CTQ in the group of patients compared to HC. Analysing CTQ subscales, patients scored significantly higher in emotional neglect than HC. Physical, sexual and emotional abuse and physical neglect were not reported more frequently in patients compared to HC. These results are suitable with findings of emotional abuse and neglect to be potent predictors for occurrence of depression [19, 21].

Contradictable to above mentioned findings about the link between CM and severity and number of depressive symptoms we found no statistical significant correlation between scores of HAM-D and total scores of CTQ in patients [15-18, 21]. Correlation analysis of HAM-D and CTQ-scores in group of HC showed no significant results, which is possibly due to low HAM-D-scores (HAM-D range: 0 and 2) as no depressive symptoms were to expect in healthy participants. Moreover, possibility of resilience to CM was not considered in this sample. This might have influenced our results.

Though experiencing CM is linked to psychiatric symptoms in later life, CM was also reported in the sample of HC. Psychological and neurobiological effects, such as social support, or genetic effects are assumed to play a role in developing resilience or strategies to cope with CM and not develop a psychiatric disorder [22, 24].
5.2 Childhood Maltreatment Associated Changes in Brain Structure

Structural data of patients with MDD and HC were analysed using CT measurements. The thinnest cortex was found in left pericalcarine cortex for both groups. Maximum of CT differed between groups, while thickest cortex in patients was found to be located in left superior frontal cortex, HC’s thickest cortex was found in left insula. Mean CT did not differ between groups.

To show CM associated alterations in adult’s brain structure correlation analysis between total scores of CTQ, scores of each subscale and CT was provided. Emotional neglect was found to be linked to decrease in right frontal pole and left pars triangularis in patients. Moreover, in HC a link between emotional neglect and decrease in right IPC, right LOC and left lingual cortex was shown. Emotional abuse was found to be linked to increase in left PCC and to decrease in right frontal pole in patients. No significant correlation was shown between total scores of CTQ and CT in HC and in patients as well. These findings suggest that CM is generally not related to a particular change in brain structure. Nevertheless, results indicate that specific aspects of CM may lead to alterations in brain structure.

Emotional neglect was found to be correlated to morphological alterations in both patients and HC. In patients emotional abuse was also linked to changes in brain structure. Subscales of sexual and physical abuse and physical neglect showed no significant correlation. In line with evidence, these findings support the notion that emotional neglect and abuse to be are predictive for development of MDD [19, 21].

To date studies investigating changes in brain structure in consequence of CM and MDD have been partly inconsistent and findings were dependent of different methods for brain structure analysis and of duration and onset of MDD in study sample, of intake of antidepressant therapy as well as of which aspect of CM was experienced [32].

5.2.1 Compendium of Findings of Brain Structure in Major Depressive Disorder

Volumetric analysis in patients with MDD resulted in findings of decreased volume in hippocampus, basal ganglia, OFC and subgenual PFC [32]. The hippocampus is a part of the limbic system and is involved in creating short- and longterm and spatial memory [109]. The basal ganglia contain caudate nucleus, putamen, nucleus accumbens, olfactory tubercule, globus pallidus, ventral pallidum, substantia nigra and subthalamic nucleus and are involved in control of voluntary motor movements, cognition and reward [110]. The PFC consists of numerous subregions and is involved in functions such as social and cognitive behavior,
making decisions and expression of personality [111]. The OFC is located in the PFC an involved in decision making and expectation [112]. The subgenual PFC as a part of the cingulate region in the PFC and part of the limbic system is involved in development of physiological negative mood [113].

Findings about volume changes in amygdala were inconsistent while eventually being affected by intake of antidepressant therapy [41, 42]. Amygdala is involved in creating memories of emotional events and in fear conditioning [114].

Meta-analysis of studies investigating patients with MDD in comparison to HC using volumetric analysis of the brain depicted distinct volume reduction in ACC, OFC and PFC and moderate reduction of volume in hippocampus, putamen and caudate nucleus [115].

Another meta-analysis considered the effect of antidepressant therapy and first onset versus recurrence of MDD. An association of MDD with a loss of GMV in PFC and limbic regions was demonstrated [116]. Furthermore, the right thalamus volume was only increased in drug naïve patients with first onset and ACC increase in drug free patients, with antidepressant therapy in the past [116]. As a part of the cingulate cortex the ACC is involved in cognitive and emotional processing [117]. The thalamus is involved in sorting and processing of visual, acoustic and tactile information and in sleep-wake cycle [118].

In addition, studies using CT analysis in patients with MDD and HC reported decrease in right medial OFC, right inferior temporal cortex, right insula and right inferior parietal regions [46]. In patients with MDD changes in brain structure were reported, showing an increase of bilateral middle frontal gyrus, bilateral PCC, left caudal ACC, right lingual gyrus, bilateral fusiform gyrus and precuneus [47, 48]. Early onset of MDD seemed to be associated with enlarged DLPFC, while the DLPFC of patients with relapse was decreased [48, 49].

Meta-analysis of patients with MDD and HC using CT analysis reported different changes in dependence of different stages of life and onset or recurrence of MDD. Decreased CT of OFC, ACC, PCC, insula and temporal lobes were found in adults, most prominent in first onset of MDD. In adults with recurrent MDD decrease of medial OFC, superior frontal gyrus and in visual, somatosensory and motor areas were most prominent [119].

The temporal lobe is separated in superior, middle and inferior temporal gyrus. The temporal lobe is connected to hippocampus and amygdala and is involved in functions such as memory (especially middle frontal gyrus), emotion and language [120, 121]. The superior temporal gyrus is involved in language processing and recognition of emotional facial expression [122, 123]. The inferior temporal gyrus of temporal lobe is involved in memory, more specific in
facial, bodypart, object and scene recognition [124]. Fusiform gyrus is a part of the inferior temporal gyrus and involved in recognition, especially in facial and body recognition [124]. Precuneus is also involved in memory and is connected with hippocampus and the process of learning [125]. The PCC also seems to be involved in memory processing, especially in autobiographical memory [126]. Among other functions, insula is involved in emotional processing [127]. The inferior parietal lobe is like the superior temporal gyrus involved in cognition of facial emotional expressions [123]. The frontal gyrus is sectioned in precentral, superior, middle and inferior frontal gyrus and involved in language processing (IFG), memory (middle and superior frontal gyrus) and voluntary movements (precentral gyrus) [128-131]. In the middle frontal gyrus the DLPFC is located, which is a functional region for memory, planning and voluntary movement [132]. Lingual gyrus is located in the occipital lobe and associated with visual processing and encoding images (see section 5.2.7) [133].

5.2.2 Compendium of Findings of Brain Structure in Childhood Maltreatment

Childhood maltreatment and brain structure were investigated in healthy participants and in patients with MDD or PTSD who experienced sexual abuse in childhood. Results of brain alterations and the relationship to CM differ in respect to investigated aspect of CM, comorbidities of study sample and method of brain structure analysis. Volumetric brain analysis of the impact of sexual abuse in childhood on brain changes without considering comorbidities resulted in decreased volume in hippocampus, corpus callosum and attenuated frontal cortex [60]. Studies providing analysis of brain volumes in respect to CM in patients with MDD reported a loss of volume in hippocampus and IOG and increase in dorsomedial PFC, OFC and cerebellum anterior lobe [74-76]. Childhood maltreatment in HC was reported to be associated with a smaller PCG and anterior lobe of cerebellum. Scores of CTQ and brain volume correlation analysis in MDD and HC showed a negative correlation in left IOG and a positive correlation for right caudate, left dorsomedial PFC and left middle temporal gyrus [76]. Investigations in respect to CM related brain changes including patients with MDD and HC using CT analysis reported a negative correlation in the ACC, precuneus and parahippocampal gyrus with total scores of CTQ. For CTQ subscale emotional abuse a negative correlation in precuneus, left ACC, PCC and face region of somatosensory cortex was reported [77]. In another MRI-study, investigations in male and female adolescent with abuse history, CTQ subscale sexual abuse and physical abuse was associated with decrease in OFC, right IFG, bilateral parahippocampal gyrus, and in temporal gyrus [78].
Corpus callosum is connecting the two hemispheres of the brain and thus provides communication between them [134]. Cerebellum anterior lobe seems to be involved in cognition and emotion [135]. The occipital lobe contains the visual field and enables visual processing [136]. Dorsomedial PFC seems to be involved in self-referential processes [137]. Parahippocampal gyrus is part of the inferior temporal gyrus and seems to be involved in visual memory such as recognition of scenes and objects [124, 138].

Meta-analysis of volumetric analysis including children, adolescent and adults with and without CM-history was performed. Comorbidities were not described for this sample. Childhood maltreatment was associated with a decrease in orbitofrontal gyrus, superior temporal gyrus, amygdala, insula, parahippocampal gyrus, left IFG and postcentral gyrus and with an increase in right superior frontal gyrus and left middle occipital gyrus [61]. Childhood maltreatment related changes in brain structure were also investigated in children. Related to CM a decrease of ACC, OFC and superior frontal gyrus was found [79].

In line with previous findings, we observed changes in frontal regions, inferior parietal regions, lingual gyrus and PCC. Further changes in LOC, IPC and in pars triangularis of middle frontal gyrus were shown.

5.2.3 Frontal Pole

Right frontal pole was positively correlated to emotional abuse and neglect in patients. The frontal pole as part of the frontal lobe is located in the PFC and is also known as the rostral PFC or the Brodmann area 10 [139]. Several theories exist to the function of the humans frontal pole such as control and organisation of behaviour, problem solving, memory and processing and coordination of information [140]. There is also evidence that the frontal pole is involved in multi-task coordination and in social cognition [141]. Frontal pole also seems to be involved in processing pain [142].

5.2.4 Pars Triangularis

Emotional neglect was negatively correlated with CT in left pars triangularis in group of patients. The pars triangularis is located in IFG and also known as Brodmann´s area 45. On left hemisphere Broca’s areal is located in pars triangularis of the IFG [143]. Asymmetry was found with larger volumes in left hemisphere of pars triangularis than in right hemisphere. Therefore the left pars triangularis seems to be involved in language processing [144].
5.2.5 Inferior Parietal Cortex
As mentioned in section 5.2.1, the IPC, as part of the inferior parietal lobe, is involved in processing emotional facial expressions [123]. In fMRI studies, the inferior parietal lobe was co-activated during memory tasks and seemed to be involved in memory retrieval [145, 146]. Increase of right IPC was associated with emotional neglect in HC.

5.2.6 Lateral Occipital Cortex
The LOC as part of the occipital lobe is involved in processing vision and a part of the visual cortex [136, 147]. The LOC seems to be involved especially in visual recognition of objects [148]. Emotion seems to affect attention in respect to visual recognition of objects [149]. Emotional neglect was negatively correlated with CT of LOC in HC.

5.2.7 Lingual Gyrus
The lingual gyrus of left hemisphere was found to be negatively correlated with emotional neglect in HC.
As a part of the occipital lobe the lingual gyrus seems to be activated during visual encoding [133]. Especially in word recognition while reading the lingual gyrus seems to be involved [150]. A fMRI study demonstrated increased activation during resting state, among other regions, in lingual gyrus in participants with resilience to CM. These findings suggest that these brain regions are related to higher ability for processing CM experience [151].

5.2.8 Posterior Cingulate Cortex
The PCC of left hemisphere was positively correlated with emotional abuse in patients. Memory retrieval of autobiographical information and recognition of familiar faces seems to be a function of the PCC [126]. A fMRI study revealed brain activity related to emotional words in the left and right PCC [152].
Our findings of a positive correlation between the PCC and emotional abuse in patients implicates that experiencing emotional abuse in form of repeatedly hearing negative and unpleasant statements during childhood leads to over activation and subsequently to morphological changes in the PCC.

5.3 Volume Based Analysis versus Cortical Thickness Measurement
As mentioned in the introduction, findings of MDD or CM associated changes in brain structure differ depending on type of study sample and on method of structural analysis. For investigating changes in brain structure we used freesurfer CT analysis, which showed high
reliability and statistical power in former analysis [107, 153]. For sufficient power to detect a 10% difference between groups freesurfer's CT analysis requires to test at least 39 participants. In contrast volume based measurements of cortex would require 81 participants for equal sufficient power [153].

Comparing 3T MRI data as used in studies investigating CM to date, with 7T MRI data in respect to CT analysis, results were consistent. This reflects the resistance of this method against potential field strength related falsification [154]. Thus, data of higher resolution 7T showed 1/6th to 1/3rd reduced CT values when compared to lower resolution data, which lets assume that most current studies using 3T MRI and CT analysis might overestimate actual thickness. Conclusive, CT can be analysed more precisely with 7T due to higher resolution [154].

To date, brain structure and CM were not investigated using ultra high field 7T data. This diploma thesis might have shown CM related decrease in new brain regions, which were overestimated in previous studies.

5.4 Limitations

5.4.1 Limitations of Statistical Analysis

Visual inspection of distribution of CT data let suppose a normal distribution, which resulted in using Pearson correlation coefficient for further correlation analysis. One patient scored 99 out of 125 possible points in CTQ, while score of remaining patients ranged from 26 to 53 points, which might be interpreted as an outlier. This might have lead to counterfeit positive correlations with CT as Pearson correlation coefficient was used. Statistical analysis was also limited by small sample size. Common size of sample for neuroimaging studies is $n = 20$ for each group, whereas higher group numbers are suggested. This might have led to underestimation of changes in brain structure related to CM.

5.4.2 Magnetic Resonance Imaging and Cortical Thickness Analysis

Even though ultra high field 7T seems to be a powerful method for data acquisition and CT measurement sample size was reduced by drop outs due to motion artefacts [154]. Small sample size might limit our findings as for CT analysis 39 participants are required for powerful results. In this diploma thesis sample size was only $n = 27$. 
5.4.3 Age and Gender

Evidence for age related decrease of numerous brain regions including amygdala, insula, striatum, precuneus, temporal and parietal cortical areas, PFC, central gyri, midline cortex, cingulate cortex and cerebellum was previously demonstrated. Findings of decrease were found linear to age and in participants older than 50 years [97-99]. In opposite, imaging studies found an age related increase in grey matter in the ACC, OFC and subcallosal cortex [100].

Mean age of study sample was 29.23 (± 10.29; range: 18 and 50 years of age). In consideration of low mean age of study sample and matching for age and gender we set aside a regression model for age correction of structural data. As study sample was matched, also a correction for gender was not conducted.

Moreover, differences between brain structures between men and women was only found in middle aged individuals of age 41 to 57, possibly related to hormonal change by menopause in women [100].

5.4.4 Antidepressant Therapy

Antidepressant therapy has an impact on the central nerve System [56, 96]. Selective serotonine reuptake inhibitors cause higher concentrations of serotonine in the synaptic cleft resulting in greater receptor binging to 5HT which in turn leads to changes in hippocampus, ACC, PCC, posterior inferior temporal cortex, posterior medial temporal cortex, medial occipital cortex, pericalcarine region, ventral precuneus, precentral gyrus, postcentral gyrus and parts of the cerebellum [56, 96].

Not all patients with MDD were drug naïve, though at least 3 months drug free prior MRI scans. The intake of antidepressant medication of patients may have masked changes in regions which would have been affected by CM. According to above mentioned studies possibly biased regions due to SSRI intake in our analysis may be the ACC, PCC, pericalcarine cortex, precuneus, precentral cortex and postcentral cortex [56, 96]. Not only, that some regions might have been significantly correlated to CM if patients were consistent drug naïve, also our finding of positive correlation of PCC and CM in patients might have been generated by potential SSRI intake.

5.4.5 Co-Variables

Co variables like physical act or smoking status of participants were not considered in statistical analysis but might have had an impact on brain structure. There is evidence, that
smoking is associated with changes in PFC, ACC, OFC, frontal cortex, lingual cortex, olfactory gyrus, ventral striatum, thalamus, cerebellum, insula, parahippocampal gyrus and putamen [155-160]. Smoking status might have influenced clinical and imaging results.

5.4.6 Childhood Trauma Questionnaire

Beside five subscales to determine different aspects of CM, the CTQ also includes the minimalization scale. This scale captures the possibility of the denial or minimalization of experienced CM. Overall, 0 to 3 points can be scored. Scoring 3 points is interpreted as a sign, that experienced CM might be denied [26]. One participant in group of patients with MDD scored 3 points for minimalization and a total score of 26, which is almost the least attainable score of the CTQ. In group of HC one participant scored 3 points in minimalization scale and a total of 25 points. Also 3 HC scored each 1 point for minimalization and almost the least attainable score of CTQ. This might be indicative to false low total score of CTQ in participants of both groups, which in turn may limit accuracy and validity of statistical analysis.

As the CTQ is constructed as a retrospective self reporting questionnaire, results may be also biased by false memories.

5.4.7 Genetic Analysis

There is evidence that correlations of CM with brain structure are also influenced by genetical factors. BDNF met allele carrier with experienced CM showed more prominent loss of amygdala than other participants with CM-history. Furthermore, CM related decrease in ACC was found in participants with val/val BDNF genotype [161]. Mediating effects of BDNF gene were also found in hippocampal subfields when examining in respect to CM [90]. Also the FKBP5 gene, involved in glucocorticoid regulation, was found to interact in CM related brain changes [92].

Genotyping was not investigated and therefore not considered interacting effects of specific genes limit the findings in this diploma thesis.
6. Conclusion

We found correlation between CTQ subscales and frontal pole, PCC, pars triangularis, IPC, LOC and lingual gyrus. In patients with MDD emotional abuse and neglect was negatively correlated with right frontal pole. Patient’s PCC was negatively correlated with emotional abuse while emotional neglect was negatively linked to patient’s left pars triangularis. These findings suggest that experiencing emotional abuse or neglect in childhood may affect morphology of brain regions involved in cognition, emotional processing and memory. Yet, our findings did not remain significant after correction for multiple testing possibly due to small sample size.

To date, findings about CM related changes in brain structure have been inconsistent. To the best of our knowledge, this is the first study investigating CM related changes using 7T MRI. Further investigations of CM related morphological brain changes with 7T MRI and greater sample size will be needed to confirm our findings and to be conducive to better understanding of the neurological effects of emotional events.
### 7. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived Neurotrophic Factor</td>
</tr>
<tr>
<td>CM</td>
<td>Childhood Maltreatment</td>
</tr>
<tr>
<td>CT</td>
<td>Cortical Thickness</td>
</tr>
<tr>
<td>CTQ</td>
<td>Childhood Trauma Questionnaire</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral Prefrontal Cortex</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
</tr>
<tr>
<td>EA</td>
<td>Emotional Abuse</td>
</tr>
<tr>
<td>EN</td>
<td>Emotional Neglect</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>GMV</td>
<td>Gray Matter Volume</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Rating Scale for Depressive Symptoms</td>
</tr>
<tr>
<td>HC</td>
<td>Healthy Control</td>
</tr>
<tr>
<td>ICD10</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>IFG</td>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>IOG</td>
<td>Inferior Occipital Gyrus</td>
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8. References


Yang, S., et al., Childhood maltreatment is associated with gray matter volume abnormalities in patients with first-episode depression. Psychiatry Res Neuroimaging, 2017. 268: p. 27-34.


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