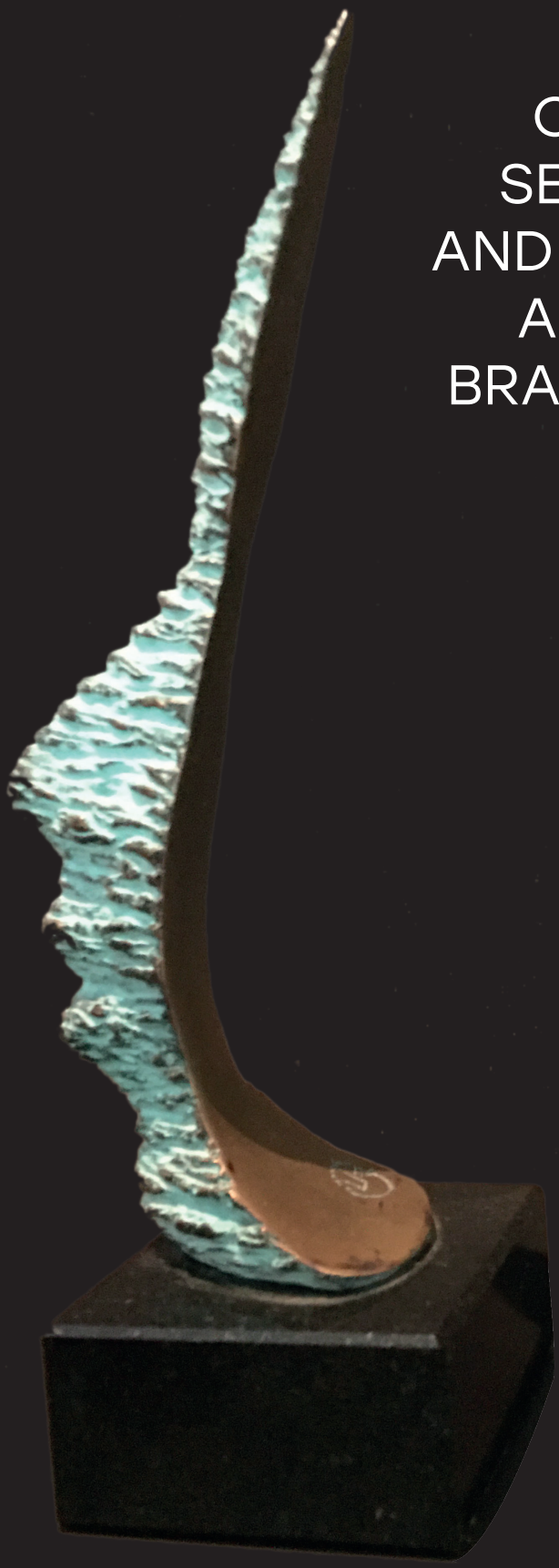
Childhood sexual abuse and its effect on adolescent brain structure

Rinne-Albers, M.A.W.



CHILDHOOD SEXUAL ABUSE AND ITS EFFECT ON ADOLESCENT BRAIN STRUCTURE

MIRJAM RINNE-ALBERS

Childhood sexual abuse and its effect on adolescent brain structure

Mirjam A.W. Rinne-Albers

Promotores:

Prof. dr. R.R.J.M. Vermeiren

Prof. dr. N.J.A. van der Wee

Promotiecommissie

Prof. dr. A.M. van Hemert

Prof. dr. R.J.L. Lindauer

Prof. dr. L.R.A. Alink

Prof. dr. E.A.M. Crone

Prof. dr. P.M. Westenberg

Dr. M. de Leeuw

Childhood sexual abuse and its effect on adolescent brain structure

Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,

op gezag van de Rector Magnificus prof. mr. C.J.J.M. Stolker, volgens besluit

van het College voor Promoties

ter verdediging op woensdag 14 oktober 2020

klokke 10.00 uur

door

Mirjam Aleida Wilhelmina Rinne-Albers

geboren te Den Haag

in 1959

Index

Chapter 1 INTRODUCTION 3
Chapter 2 REVIEW 11
Chapter 3 VOXEL BASED MORPHOMETRY (VBM) 29
Chapter 4 CORTICAL THICKNESS 45
Chapter 5 DIFFUSION TENSOR IMAGING (DTI) 66
Chapter 6 SUMMARY AND GENERAL DISCUSSION 81
Nederlandse samenvatting 98
Dankwoord 103
Curriculum Vitae 104
Publications 105

Chapter 1 INTRODUCTION

Aim of this thesis

The aim of this thesis is to further elucidate characteristics of brain structure in traumatised youth, in order to better understand the way childhood adversity may lead to an increased risk of psychiatric and somatic pathology in later life. To this end, structural neuroimaging techniques were used to explore structural brain characteristics in a group of adolescents who experienced childhood sexual abuse. The findings of the thesis may eventually contribute to the development of optimised treatment and preventative strategies.

1. Background

1.1 Childhood trauma – epidemiology and consequences

Childhood trauma is not a rare phenomenon: In the Netherlands, every year between 90.000 and 127.000 children experience abuse or neglect (De Derde Nationale Prevalentiestudie Mishandeling van Kinderen en Jeugdigen, 2017; www.wodc.nl). When using a broader definition of trauma, i.e. having experienced childhood adversity, Kessler et al. in the 2010 WHO-study showed substantial rates in high as well as low income countries (38,4% versus 39,1%). Thus, around the world, as much as one out of every three children has experienced childhood adversities (1).

Childhood psychological trauma like sexual, physical or emotional abuse, neglect by caregivers or witnessing domestic violence, was shown to cause intense suffering for the child in the immediate or near immediate aftermath (2). Depending on several factors, this suffering typically involves anxiety, depressive symptoms, sleep disturbance, learning disorders or the symptoms of Posttraumatic Stress Disorder (PTSD) (3).

In the long term, the detrimental consequences of childhood adversity outrange these classical trauma sequelae and are impressive in severity as well as pervasiveness, comprising somatic as well as psychiatric disorders. The large scale Adverse Childhood Experience (ACE-) study by Anda and Felitti showed that childhood adversity carries a great threat for general health in later life: childhood adversities do not only predict the onset of psychiatric disorder like anxiety and depression, but also the onset of somatic disorders like cardiovascular disease, chronic lung disorder and diabetes (4;5). Subjects who were persons exposed to six or more ACE, even had a 20-year reduction in lifespan (6). Reviews found the same psychiatric and somatic outcomes across studies (7-9). The WHO-study by Kessler calculated that eradication of childhood adversities would lead to an impressive 22.9 % reduction in mood disorders, 31.0 % in anxiety disorders, 41.6 % in behaviour disorders, 27.5 % in substance disorders and 29.8 % of all psychiatric disorders (1).

Clearly, the impact of childhood adversity on multiple vital processes in the human body underscores the need of broad investigation, including neurobiological trajectories that follow ACE, in order to develop therapeutic avenues that may counteract negative clinical consequences.

1.2 Neurobiology of adversity and the developing brain

Up till far in the third decade of life, developmental anatomic trajectories of the human brain typically involve a massive proliferation of neurons, dendrites and synapses early in life with a peak in late childhood, to differentiation and pruning in adolescence and young adulthood (10). Preclinical research shows that trajectories of brain development are for a large part dependent on experience,

i.e. dependent on the situations the developing person is passing through (11). In their classical study Wiesel and Hubel demonstrated that visual input during a sensitive period early in life is critical for development of the visual cortex and vision (12). In this way the developing brain, adapting to the environment, is thought to maximally facilitate adaptation and survival.

The process of selective pruning, or loss of neurons, their branches and synapses, is at least partly controlled by the neurotoxic effect of stress hormones like cortisol (13;14). This might explain how and why childhood psychological traumas, being intensive threatening and stressful experiences, influence structural developmental brain trajectories that in the end may lead to psychiatric and somatic pathology (11). Interestingly, It has been suggested that pathology in later life after adverse childhood experiences might be the result of an in origin adaptive process (11). Being on guard and hyper vigilant in a threatening situation is an appropriate reaction, however, when the danger is no longer part of the environment these same phenomena can be the manifestation of an anxiety disorder or PTSD in later life. The stress hormone cortisol has shown to play a major role in several psychiatric disorders like depression (15), eating disorders (16) and personality disorders (17).

From a physiological point of view, the neurobiology of adversity is the neurobiology of stress. In the human body the HPA (Hypothalamus – Pituitary – Adrenal)-axis, or stress-axis, consists of a chain of hormonal substances produced in and outside the brain where one hormone stimulates the production of the next and the level of the total chain is regulated by a negative feedback mechanism. The end product of the chain, cortisol, supports the energy supply necessary for the stress reaction by stimulating the breaking down of carbohydrates, fat and proteins. It ends the stress reaction when the trigger for stress has disappeared or has returned below threshold.

During the long phase of development, brain regions can successively increase (in the early stages) as well as decrease (in adolescence and young adulthood) in size and have their own developmental pathway in time (10). Therefore, taking into account the developmental stage an individual is in, is important when studying the neurobiology of adversity. Especially earlier neuroimaging studies with minors who experienced adversity, however, often have included heterogenous groups of children as well as adolescents with regard to developmental stage and not taken this into account (18-20).

More recently, gene environment interaction studies have shown the impact of ACE on gene expression patterns (21). Childhood traumatic experiences are now thought to have a strong impact on epigenetic patterns via processes like DNA-methylation, histone modification and non-coding RNA signalling, leading to vulnerability for many psychiatric disorders (22;23). These disorders vary from psychosis (24), behavioural disorders (25), and eating disorders (26), to alcohol, heroin and cocaine dependence (27). Through epigenetic mechanisms, vulnerability might even be expressed in the offspring of trauma survivors. Research suggests that the effect of treatment also can be transferred to the next generation in this way (22).

1.3 Neurobiology of childhood adversity – neuroimaging

Findings on brain structure and mechanisms related to traumatisation due to ACE are far from consistent, particularly because of the diversity in studies with regard to developmental stages and trauma types. While some neurobiological consequences of ACE as shown with neuroimaging , e.g. decreased volume of the hippocampus, may only become apparent in adulthood (28), other relationships, e.g. decreased corpus callosum volume, seem limited to childhood (29). Additionally, due to the heterogeneity in sequelea of trauma, the relationship between adversity related neuroimaging findings and specific symptomatology is far from clear. Therefore, a review of neuroimaging research investigating structural brain characteristics of minors that experienced adversity was clearly warranted.

Reviews showed that structural changes in the adult brain found to be associated with ACE are mostly reported in emotion and stress regulating structures, for example the hippocampus in adults who experienced childhood abuse (28;29) or the medial prefrontal cortex (mPFC) in adults with childhood emotional maltreatment (30;31). The psychological consequences of trauma, like PTSD, depression and anxiety disorders, i.e. disorders in the affective spectrum, in adults also are predominantly associated with abnormalities in these brain regions which are part of the limbic system or circuit. The limbic system is the affective and alarm circuit in the brain and consists of the afore mentioned hippocampus and the medial prefrontal cortex (mPFC) and also the amygdala, thalamus, hypothalamus, basal ganglia, and cingulate gyrus (11). In this circuit the amygdala is thought to generate emotions (bottom-up) in reaction to external stimuli. The cingulate gyrus, part of the prefrontal cortex (PFC), exerts a top-down inhibitory control over the emotions by cognitive processing. The hippocampus, thalamus, hypothalamus and basal ganglia, each have specific related functions.

At present, much still has to be discovered about the effects of traumatic stress on the developing brain in juveniles who experienced ACE. Deeper insight in these effects is needed in order to understand how affected brain structures or circuits play a pivotal role in the pathogenetic influences of ACE in children (32;33). Knowledge on neurobiological trajectories that lead from childhood adverse experience to vulnerability for psychiatric and somatic disorders, might help to know when and how best to intervene or even prevent negative consequences of ACEs. This ambition formed the foundation of this thesis.

In the empirical, cross-sectional research of this thesis we used various structural neuroimaging techniques to examine a group of sexually traumatised adolescents and a healthy non-traumatised control group. For a better interpretation of the findings, we controlled for age and pubertal development, and try to focus on one type of trauma. So far, neuroimaging studies in traumatised populations have mainly focussed on specific brain regions, while processes in the brain generally exert themselves in circuits: several regions interconnecting with another. For this reason, we planned to study not only grey matter (GM) structure of the cortex of the brain and brain regions, but also the white matter (WM) tracts of neuron fibers connecting different brain regions.

2. Main research questions of this thesis:

- What are the structural characteristics of the adolescent brain associated with adverse childhood experiences, specifically childhood sexual abuse?
- Is there a relationship between structural neuroimaging abnormalities and trauma symptomatology?

3. Methods

First, we conducted a review to get a comprehensive picture of the literature on neuroimaging results in children, adolescents and young adults with psychological trauma. Next, we executed three empirical studies with different structural neuroimaging techniques, as part of the EPISCA-project (see below). The review helped us with the design of our empirical research.

3.1 EPISCA

The studies described in this thesis were part of the EPISCA project: Emotional Pathways' Imaging Study in Clinical Adolescents.
The objective of the EPISCA project was to examine the neural emotion circuitry in adolescents aged 12-18 years with anxiety or depressive disorders (i.e., with internalising disorders), with childhood

sexual abuse, and in healthy non-traumatised controls. The patient groups were compared to controls with regard to emotion regulating skills and the related structure and function of the neural emotion circuitry. Participants underwent structural and functional Magnetic Resonance Imaging (MRI) and performed a face-attention task in a 3T scanner. In the MRI-scanner, the following sequence was applied: fMRI resting state measurements (7 minutes), fMRI assessment of the face-attention task (20 minutes), Anatomical scan measurements (10 minutes) and measurement of white matter characteristics with Diffusion Tensor Imaging (DTI) and magnetic resonance spectroscopy (MRS) of the brain (10 minutes). In this thesis, we present the cross-sectional structural MRI results of the childhood sexual abuse group as compared with the healthy non-traumatised control group before the start of treatment. In the following paragraph we will only mention the part of the imaging procedure that is relevant for this thesis.

For the study of the impact of sexual abuse, we included a specific group of adolescents who had experienced sexual abuse during their lifetime more than once, by one or more perpetrators inside or outside the family. This group of adolescents with childhood sexual abuse was recruited from the two Psychotrauma centers for children and adolescents; in Leiden (part of GGZ Rivierduinen) and Haarlem (KJTC). They were referred for treatment at one of these two psychotrauma centers. Experienced psychotherapists in these specialised psychotrauma centers obtained the trauma histories from the adolescents as well as from their caregivers during clinical interviews. To objectify any abuse or neglect and get an estimate of the severity and impact of problems, as well as the risk for functional impairment and morbidity, we verified police reports, involvement of child welfare, and family custody or other child clinical protection measures. Healthy control adolescents were recruited via advertisements in local newspapers, via the website of the research group of Prof. dr. Crone (http://www.hersenen-in-actie.nl) and the intranet of Curium-LUMC. We determined puberty development by the Puberty Development Scale (PDS), a self-assessment questionnaire that is well validated (35;36). For more details about the behavioural measurements see chapters 3-5.

4. Outline of this thesis

4.1 Review (Chapter 2)

Although childhood psychological trauma is a strong predictor of psychopathology and preclinical research points to the influence of this type of trauma on brain development, the effects of psychological trauma on the developing human brain are less known. The aim of the review was to give an overview of neuroimaging studies in traumatised juveniles and young adults published before the start of our empirical research. We included studies in young adults in the review as well, as brain development is known to continue into the third decade of life. Furthermore, by including young adults we intended to identify developmental differences over time.

4.2 Structural neuroimaging techniques

In order to get a more comprehensive view of brain structure and circuitry in adolescents who have experienced sexual abuse compared to a healthy not traumatised adolescent group, we studied grey as well as white matter. Grey matter (GM) consists mainly of the cell bodies of neurons. Structural connectivity is located in white matter (WM), composed chiefly of long-range myelinated axon tracts constituting the connection between brain regions, shaping circuitry. The myelin sheets around the axons make the tissue look white in contrast to the grey colour of the cell bodies.

4.2.1 Voxel Based Morphometry (Chapter 3)

Voxel Based Morphometry (VBM) is the technique mostly used to study grey matter volume (GMV). The aim of this study was to investigate abnormalities in GMV in a group of adolescents with PTSD due to childhood sexual abuse (CSA) and the relationship between GMV and symptom severity. Using 3T diffusion tensor imaging, we performed a VBM analysis in 21 adolescents with CSA-related PTSD and 25 matched non-traumatised, non-clinical adolescents. Based on the literature we selected hippocampus, amygdala, anterior cingulate cortex (ACC), medial PFC (mPFC) and superior temporal gyrus (STG) as regions of interest (ROIs). Trauma symptomatology was measured with the Trauma Symptom Checklist for Children (TSCC) and dissociation symptoms with the Adolescent Dissociative Experiences Scale (A-DES).

4.2.2 Cortical thickness (Chapter 4)

Cortical thickness is a more recently developed imaging analysis technique for studying aspects of GM. It assesses the thickness of the cortical layer, mostly in combination with surface area. Total volume is calculated by multiplying cortical thickness with surface area. This technique (the Freesurfer pipeline in our research) takes into account cortical folding patterns and therefore uses a specific anatomical segmentation.
The aim of this study was to investigate cortical thickness measures and their relation with clinical data in the group of adolescents with CSA-related PTSD (N=21) and the healthy non-traumatised control group (N=21). The ventromedial PFC (vmPFC), ACC, insula, and middle / superior temporal gyrus were chosen as ROI's due to their respective roles in emotion and information processing and based on earlier research. Trauma symptomatology was measured with the TSCC and dissociation symptoms with the A-DES.

4.2.3 Diffusion Tensor Imaging (Chapter 5)

WM integrity is studied mostly with Diffusion Tensor Imaging (DTI) technique. In DTI, Fractional Anisotropy (FA) is a measure for WM integrity and based on the restriction of movement of the water molecules in the tissue. The architecture of the axons in parallel bundles and their myelin shield facilitates the diffusion of the water molecules along their main direction.
We examined FA in a group of adolescents with CSA-related PTSD (N = 20) and matched healthy controls (N = 20). Based on our review we selected a region of interest consisting of the bilateral uncinate fasciculus (UF), the genu, splenium and body of the corpus callosum (CC), and the bilateral cingulum. In addition, we performed an exploratory whole brain analysis. Trauma symptomatology was measured with the TSCC to enable correlational analyses between FA differences and trauma symptomatology.

- **Chapter 2 Review**
  Neuroimaging in children, adolescents and young adults with psychological trauma
- **Chapter 3 Grey matter – VBM**
  Anterior cingulate cortex grey matter volume abnormalities in adolescents with PTSD after childhood sexual abuse
- **Chapter 4 Grey matter – Cortical thickness**
  Cortical thickness, surface area and volume in adolescents with PTSD after childhood sexual abuse
- **Chapter 5 White matter – DTI**
  Abnormalities of white matter integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study

Reference List

(1) Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, de GG, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu CY, Karam EG, Kawakami N, Lee S, Lepine JP, Ormel J, Posada-Villa J, Sagar R, Tsang A, Ustun TB, Vassilev S, Viana MC, Williams DR. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br.J.Psychiatry 197, 378-385. 2010.

(2) Kalmakis KA, Chandler GE. Health consequences of adverse childhood experiences: a systematic review. J.Am.Assoc.Nurse Pract. 27[8], 457-465. 2015.

(3) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th. 2013. Arlington, VA, American Psychiatric Publishing.

(4) Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur.Arch.Psychiatry Clin.Neurosci. 256[3], 174-186. 2006.

(5) Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am.J.Prev.Med. 14[4], 245-258. 1998.

(6) Brown DW, Anda RF, Tiemeier H, Felitti VJ, Edwards VJ, Croft JB, Giles WH. Adverse childhood experiences and the risk of premature mortality. Am.J.Prev.Med. 37[5], 389-396. 2009.

(7) Herzog JI, Schmahl C. Adverse Childhood Experiences and the Consequences on Neurobiological, Psychosocial, and Somatic Conditions Across the Lifespan. Front Psychiatry 9, 420. 2018.

(8) Meyer-Lindenberg A, Tost H. Neural mechanisms of social risk for psychiatric disorders. Nat.Neurosci. 15[5], 663-668. 4-15-2012.

(9) Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS.Med. 9[11], e1001349. 2012.

(10) Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. Nat.Neurosci. 2[10], 861-863. 1999.

(11) Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. Nat.Rev.Neurosci. 17[10], 652-666. 9-19-2016.

(12) WIESEL TN, HUBEL DH. SINGLE-CELL RESPONSES IN STRIATE CORTEX OF KITTENS DEPRIVED OF VISION IN ONE EYE. J.Neurophysiol. 26, 1003-1017. 1963.

(13) Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: clinical implications. Biol.Psychiatry 48[8], 778-790. 10-15-2000.

(14) Marsh R, Gerber AJ, Peterson BS. Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. J.Am.Acad.Child Adolesc.Psychiatry 47[11], 1233-1251. 2008.

(15) Suzuki A, Poon L, Papadopoulos AS, Kumari V, Cleare AJ. Long term effects of childhood trauma on cortisol stress reactivity in adulthood and relationship to the occurrence of depression. Psychoneuroendocrinology 50, 289-299. 2014.

(16) Monteleone AM, Monteleone P, Serino I, Scognamiglio P, Di GM, Maj M. Childhood trauma and cortisol awakening response in symptomatic patients with anorexia nervosa and bulimia nervosa. Int.J.Eat.Disord. 48[6], 615-621. 2015.

(17) Flory JD, Yehuda R, Grossman R, New AS, Mitropoulou V, Siever LJ. Childhood trauma and basal cortisol in people with personality disorders. Compr.Psychiatry 50[1], 34-37. 2009.

(18) Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol.Psychiatry 50[12], 943-951. 12-15-2001.

(19) De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol.Psychiatry 52[11], 1066-1078. 12-1-2002.

(20) Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. Biol.Psychiatry 56[2], 80-85. 7-15-2004.

(21) Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu.Rev.Neurosci. 24, 1161-1192. 2001.

(22) Provencal N, Binder EB. The neurobiological effects of stress as contributors to psychiatric disorders: focus on epigenetics. Curr.Opin.Neurobiol. 30, 31-37. 2015.

(23) McCrory E, De Brito SA, Viding E. The impact of childhood maltreatment: a review of neurobiological and genetic factors. Front Psychiatry 2, 48. 2011.

(24) van WR, van NM, Myin-Germeys I, van OJ. Childhood trauma as a cause of psychosis: linking genes, psychology, and biology. Can.J.Psychiatry 58[1], 44-51. 2013.

(25) Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. Science 297[5582], 851-854. 8-2-2002.

(26) Stoltenberg SF, Anderson C, Nag P, Anagnopoulos C. Association between the serotonin transporter triallelic genotype and eating problems is moderated by the experience of childhood trauma in women. Int.J.Eat.Disord. 45[4], 492-500. 2012.

(27) Enoch MA, Hodgkinson CA, Yuan Q, Shen PH, Goldman D, Roy A. The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. Biol.Psychiatry 67[1], 20-27. 1-1-2010.

(28) Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. 1. Neuroimaging Clin.N.Am. 17[4], 523-38, ix. 2007.

(29) McCrory E, De Brito SA, Viding E. Research review: the neurobiology and genetics of maltreatment and adversity. J.Child Psychol.Psychiatry 51[10], 1079-1095. 2010.

(30) Hart H, Rubia K. Neuroimaging of child abuse: a critical review. Front Hum.Neurosci. 6, 52. 2012.

(31) van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM. Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biol.Psychiatry 68[9], 832-838. 11-1-2010.

(32) Colvonen PJ, Glassman LH, Crocker LD, Buttner MM, Orff H, Schiehser DM, Norman SB, Afari N. Pretreatment biomarkers predicting PTSD psychotherapy outcomes: A systematic review. Neurosci.Biobehav.Rev. 75, 140-156. 2017.

(33) Schmidt U, Willmund GD, Holsboer F, Wotjak CT, Gallinat J, Kowalski JT, Zimmermann P. Searching for non-genetic molecular and imaging PTSD risk and resilience markers: Systematic review of literature and design of the German Armed Forces PTSD biomarker study. Psychoneuroendocrinology 51, 444-458. 2015.

(34) Davidson RJ, McEwen BS. Social influences on neuroplasticity: stress and interventions to promote well-being. Nat.Neurosci. 15[5], 689-695. 2012.

(35) Bond L, Clements J, Bertalli N, Evans-Whipp T, McMorris BJ, Patton GC, Toumbourou JW, Catalano RF. A comparison of self-reported puberty using the Pubertal Development Scale and the Sexual Maturation Scale in a school-based epidemiologic survey. J.Adolesc. 29[5], 709-720. 2006.

(36) Herting MM, Maxwell EC, Irvine C, Nagel BJ. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb.Cortex 22[9], 1979-1992. 2012.

Chapter 2 REVIEW

Neuroimaging in children, adolescents and young adults with psychological trauma

Mirjam A.W. Rinne-Albers, Nic J.A. van der Wee, Francien Lamers-Winkelman, Robert R.J.M. Vermeiren

European Child and Adolescent Psychiatry, 2013, 22: 745-755

Abstract

Childhood psychological trauma is a strong predictor of psychopathology. Preclinical research points to the influence of this type of trauma on brain development. However, the effects of psychological trauma on the developing human brain are less known and a challenging question is whether the effects can be reversed or even prevented. The aim of this review is to give an overview of neuroimaging studies in traumatized juveniles and young adults up till 2012. Neuroimaging studies in children and adolescents with traumatic experiences were found to be scarce. Most studies were performed by a small number of research groups in the United States and examined structural abnormalities. The reduction of hippocampal volume reported in adults with PTSD could not be confirmed in juveniles. The most consistent finding in children and adolescents who experienced psychological trauma are structural abnormalities of the corpus callosum. We could not identify any studies investigating treatment effects. Neuroimaging studies in traumatized children and adolescents clearly lag behind studies in traumatized adults as well as studies on ADHD and autism.

1. Introduction

In countries all over the world, varying from low to high-income, similar proportions of respondents, as many as one in three, reported adversities in childhood, including psychological trauma (1). This poses an important problem for mental health, as childhood adversity is known to be a strong predictor for both child and adult affective psychopathology such as anxiety disorders, posttraumatic stress disorders and depression (1;2).

The maturation of the human brain is a complex process which lasts into early adulthood and can be strongly influenced by experiences (3);(4). Differentiation of brain structures during development takes place through the formation of new neurons, dendrites and synapses, the selective 'pruning' of neurons, dendrites and synapses, and the myelinisation of neurons. These processes are influenced by neuronal hormones like the stress hormones cortisol and catecholamines (5).

Preclinical science has shown that structure and functioning of the developing brain are highly vulnerable to the effects of adversity, particularly in certain critical time windows. An extensive body of animal research in rodents, as well as in non-human primates, has demonstrated that childhood adversity - like prolonged maternal separation or maternal stress - has profound immediate and long lasting (into adulthood) effects on functioning of the HPA axis (3;6). In general, HPA axis effects are more profound after earlier and repeated exposure to adversity. The sequelae of exposure to adversity are not limited to disturbances in HPA axis functioning, but typically also involve increases in anxiety related behaviour and impairment in cognitive functioning (7);(8). In animal studies, childhood adversity was found to be associated with changes in brain structures involved in stress and emotion regulation, such as the hippocampus and certain prefrontal regions (9;10), probably underlying vulnerability to the impact of stressors later in life. In humans too, a history of chronic traumatization during childhood and adolescence was found to be associated with structural and functional damage in emotion and stress regulating brain structures, for example in the hippocampus in adults reporting childhood abuse or in the medial prefrontal cortex in adults reporting childhood emotional maltreatment (11);(12). Interestingly, in animal studies compensatory fostering partially reversed several changes in the brain, while treatment with an SSRI was shown to have a similar effect in both animals and adult human studies (13). Also, cognitive behavioural treatment was found to normalize brain activity patterns in adults with post-traumatic stress disorder (14);(15). Taken together, data from studies in animals and adult humans show that childhood adversity can have a long lasting impact on brain structure and functioning, but animal data also suggest that interventions may reduce these effects not only in the mature, but also in the

developing brain. From a clinician's perspective these are intriguing findings and possibilities, raising interest in the current knowledge on the structural and functional effects of childhood adversity at the level of the developing brain, and more importantly, their malleability by treatment. This type of data could help identifying targets and time-windows for early intervention, treatment or perhaps prevention by enhancing resilience mechanisms in humans (11;16). We therefore performed a review of recent structural and functional neuroimaging studies in children and adolescents with a history of trauma or maltreatment.

2. Methods

The databases PubMed and Web of Science were searched on the keywords: *neuroimaging, MRI, fMRI* and crossed one by one with the terms *PTSD, trauma, psychotrauma, abuse* and again crossed with *children, adolescents, youth, young adults.* We also checked the references from the resulting articles to identify manuscripts not identified in the PubMED and Web of Science searches. Furthermore, we screened relevant review and meta-analysis articles for additional studies.

3. Results

Literature search

Of the 27 articles we found, 26 were studies including a control group, published between 1999 and 2012. All studies, except for two, were conducted in the USA. The number of subjects varied between five and 61. Thirteen articles reported on findings in PTSD patients, the other articles on findings in persons with PTSD-symptoms (N=2) or various forms of psychological trauma: sexual abuse (N=2), interpersonal trauma (N=1), physical abuse/maltreatment (N=2, one with / without PTSD) (17), harsh corporal punishment (N=1), early deprivation (N=2), abuse (physical or sexual) or neglect (N=1) and parent verbal abuse (N=2). Age of participants ranged from 4 to 25 years. Two studies included only females, the other 25 mentioned a male/female ratio.

Most studies (N=24) were structural MRI studies, of which four were Diffusion Tensor Imaging studies (DTI); only three studies used functional MRI. There were three longitudinal studies, all of them structural. Nineteen studies were performed on a 1.5 Tesla scanner, the other eight on a 3 T scanner.

In nine articles Michael D. De Bellis was one of the authors, six articles were from Victor G. Carrion and his group at Stanford and seven came from the Harvard group of Martin H. Teicher . The De Bellis group published three studies on the volumes of different brain regions (total brain, lateral ventricle, hippocampus, pituitary) but all examined in the same group of 61 children and adolescents. (18-20)

Table 1. Reviewed studies

	Study	N	M/F	inclusion	contr	age	proc	task	long	med	Tesla
1	De Bellis MD, Pittsburgh, 1999	44	25/19	PTSD	+	6-17	struct		-	-	1.5
2	Carrion VG, Stanford, 2001	24	14/10	PTSD	+	7-14	struct		-	?	1.5
3	De Bellis MD, Pittsburgh, 2001	9	5/4	PTSD	+	10-13	struct		+	-	1.5
4	De Bellis MD, Pittsburgh, 2002	43	25/18	PTSD	+	6-17	struct		-	-	1.5
5	De Bellis MD, Pittsburgh, 2002	28	14/14	PTSD	+	4-16	struct		-	-	1.5
6	De Belis MD, Pittsburgh, 2003	61	31/30	Chron PTSD	+	4-17	struct		-	-	1.5
7	Yang P, Taiwan, 2004	5	1/4	Earthquake PTSD	+	12-14	funct	Visual / imaginary recollection of trauma	-	-	1.5
8	Thomas LA, Pittsburgh, 2004	61	31/30	Chronic PTSD	+	4-17	struct		-	-	1.5
9	Teicher MA, Harvard, 2004	28	13/15	Abuse / neglect	+	9-16	struct		-	?	1.5
10	Richert KA, Stanford, 2005	23	13/10	Trauma + PTSD-symptoms	+	7-14	struct		-	-	1.5
11	Tupler LA, Pittsburgh, 2006	61	31/30	Chron PTSD	+	4-17	struct		-	-	1.5
12	Eluvathingal TJ, Detroit, 2006	7	2/5	Early deprivation	+	7-13	struct (DTI)		-	-	1.5
13	De Bellis MD, Pittsburgh, 2006	58	30/28	PTSD	+	10--13	struct		-	-	1.5

14	Carrion VG, Stanford, 2007	15	6/9	Maltreatment	-	7-13	struct		+	-	1.5
15	Carrion VG, Stanford, 2008	24	14/10	PTSD	+	7-14	struct		-	-	1.5
16	Carrion VG, Stanford, 2008	16	7/9	PTSD	+	10-16	funct	Response inhibition	-	-	3
17	Jackowski AP, Yale, 2008	17	7/10	PTSD	+	6-14	struct (DTI)		-	-	1.5
18	Andersen SL, Harvard, 2008	26	0/26	Childh Sex Abuse	+	18-22	struct		-	-	1.5
19	Mehta MA, London, 2009	14	6/8	Early deprivation	+	16.2 +/- 0.72	struct		+	-	1.5
20	Choi J, Harvard, 2009	16	4/12	Parent Verb Abuse	+	21.9 +/- 2.4	struct (DTI)		-	-	3
21	Tomoda A, Harvard, 2009	23	0/23	Childh Sex Abuse	+	18-22	struct		-	-	1.5
22	Tomoda A, Harvard, 2009	23	15/8	Harsh Corp Punishment	+	18-25	struct		-	-	3
23	Carrion VG, Stanford, 2010	16	6/10	PTSD sympt	+	10-17	funct	Verbal declarative memory	-	No auton/ HPA effect	3
24	Hanson, JL, Wisconsin, 2010	31	19/12	Physical abuse	+	12,0 +/- 0,2	struct		-	?	3
25	De Bellis MD, North Carolina, 2010	49/49	38/60	Maltreatment +/- PTSD	+	3-17	struct		-	?	3
26	Tomoda A, Harvard, 2011	21	9/12	Parent Verb Abuse	+	18-25	struct		-	-	3
27	Choi J, Harvard, 2011	20	4/16	Witnessing Domestic Violence	+	22,4 +/- 2,5	struct (DTI)		-	?	3

M/F= male / female ratio
Contr= controlled study
Proc= structural MRI / (DTI) / functional MRI
Task= functional MRI paradigm
Long= longitudinal study
Med= medication use during study
Tesla= 1.5 / 3 Tesla scanner

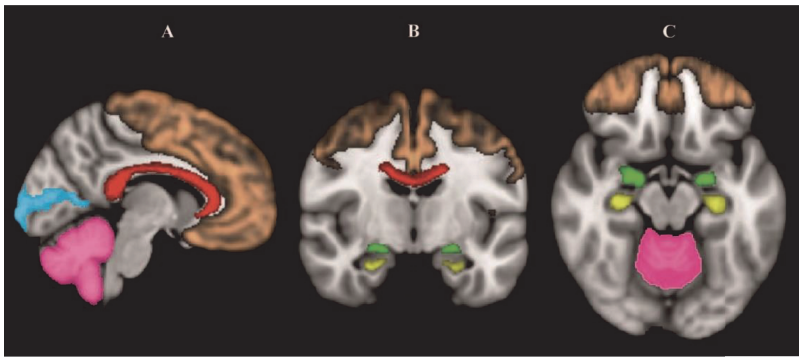


Figure 1. Summary of brain regions showing abnormalities in traumatized individuals superimposed on the MNI-152 standard brain (grey). **(A)** Sagittal section, **(B)** Coronal section, **(C)** Transversal section of the brain in which the frontal cortex (brown), corpus callosum (red), cerebellum (pink), visual cortex (blue), amygdala (green), hippocampus (yellow). In all depicted brain regions structural abnormalities were found. The few functional imaging studies found abnormalities in the cerebellum and the prefrontal, hippocampal and visual cortices. For details see table 2.

Structural Neuroimaging

Structural MRI studies in traumatized children and adolescents have found abnormalities in a number of brain regions, with the hippocampus, corpus callosum, prefrontal cortex, total brain, sensory cortex, and cerebellum being the most frequently reported.

Hippocampus

The hippocampus is an important part of the limbic system and plays a critical role in declarative memory, working memory, memory for episodic events and stress regulation. (21) The disturbances of verbal declarative memory in PTSD patients are related to the consistent finding of reduction in eleven of the 27 studies identified in the present review reported on the hippocampus, of which one DTI study and one functional MRI study (see table 2). In children most studies (N=6) found no change in hippocampal volume after exposure to psychological trauma. (17;23;24;24-27;27;27) These studies included prepubertal children as well as postpubertal adolescents. One larger matched controlled study (N=61) in children and adolescents with PTSD, aged 4-17 years, found even an increase in specific white matter volume. Here, hippocampal volume was positively related to age of trauma onset and level of psychopathology (20). The remaining two volumetric structural studies report a decrease in volume. In a study in young female adults (N=26), Andersen et al. found decreased hippocampal volume to be associated with sexual abuse at ages 3-5 years and 11-13 years. (28).

Choi, in a DTI study, found reduced fractional anisotropy (FA) in the cingulum bundle by the posterior tail of the left hippocampus in young adults (N=14) exposed to parental verbal abuse (29).

In a longitudinal study (N=15) in 7-13 year olds with a history of maltreatment, posttraumatic stress symptoms and cortisol at baseline predicted hippocampal volume reduction over a 12-18 month interval (30). The volumetric results seem to confirm the hypothesis that stress-induced prolonged exposure to glucocorticoids leads to cell death and a reduction in hippocampal volume over time. Experimental research in animals shows a link between early-life stress and later hippocampal anatomical abnormalities (3). However, De Bellis et al. did not find smaller

hippocampal volume in a longitudinal study with a two-year follow up in nine sexually abused children with PTSD (24).

In summary, findings about hippocampal volume in traumatized children are inconsistent and the reduction in hippocampal volume seen in adults with PTSD can not be confirmed in juveniles. As mentioned, it might be hypothesized that the reduction in volume appears over time and is therefore only visible in adulthood (31). Furthermore, findings from a study in adult patients comparing patients who developed PTSD in reaction to a single psychological trauma with patients who developed PTSD after multiple trauma and the results from a twin study in traumatised and non-traumatized adult patients (32) suggest that smaller hippocampal volume could be a sign of vulnerability instead of a consequence of psychological trauma, a sign that might appear only at later age (33)), Moreover, both theories might be true: a smaller hippocampus may be a vulnerability factor for PTSD and after trauma exposure PTSD can result in a smaller hippocampus .

Corpus callosum

The corpus callosum (CC) connects the two hemispheres of the brain. Seven studies presented results on the corpus callosum, six structural and one DTI study. (see table 2) Of the six structural studies five found a reduction in cross sectional areas and one found no difference compared to controls. The DTI study reported localised reduced FA in the corpus callosum.

In the first MRI study in children with PTSD (N=44) (25) De Bellis et al. found a reduction in size of the midsaggital, middle and posterior regions of the corpus callosum. Symptoms of PTSD and dissociation correlated negatively with total and regional CC volumetric measurements. De Bellis et al. in later studies confirmed these findings (18;27). Mehta et al (N=14) found no difference in midsaggital CC area between early deprived Romanian adoptees and controls (26). Teicher et al. in a group of 28 abused or neglected child psychiatric inpatients found a significant reduction in cross sectional area of the corpus callosum compared to healthy controls, and to a lesser degree in comparison to psychiatric inpatients with other diagnoses (34). In this study the association in girls was strongest with sexual abuse, with the reduction in cross sectional area more located in the rostral part of the CC, whereas in boys the stronger association was with neglect and the reduction in the caudal part. The authors suggest that this can be explained by the fact that myelinization in the CC follows a rostral-caudal pattern and neglect usually takes place in an earlier phase of development. De Bellis et al. also found that the corpus callosum was more affected by early maltreatment in male than in female children (18).

Jackowski et al. (N=17), studying cerebral connectivity in a DTI study, found reduced fractional anisotropy in the medial and posterior corpus, pointing to less connectivity (35).

In traumatized children and adolescents most studies show reduced cross sectional area and connectivity of the CC (36). The structural findings seem to be gender specific and possibly also related to the period in the development that the abuse or neglect took place. The findings in children and adolescents seem to be in line with the results from studies in adults and preclinical data.

The reduction in cross sectional area of the CC was also found in two studies with adults with PTSD (37);(38). Preclinical research in rhesus monkeys showed a relationship between early life stress and a reduction of the CC (9). As the corpus callosum is crucial for cortical communication and individuals with a commissurotomy show discontinuities between perception, comprehension and response, PTSD symptoms like dissociation might be related to abnormalities in CC structure (25).

Prefrontal Cortex

In the emotional circuit of the brain areas in the prefrontal cortex (PFC) are thought to exert control over the limbic system. Lesion studies showed that the medial prefrontal cortex modulates emotional responses through inhibition of the amygdala, where emotions are generated (22).

Six of the 23 structural articles identified found structural consequences of early psychological trauma in the prefrontal cortex, although the findings were equivocal.. Four studies found a decrease in volume: One study in children and adolescents with PTSD (N=28) reported a smaller volume of the prefrontal cortex and the prefrontal white matter (14). Andersen et al. reported decreased frontal cortex volume in young female adults (N=26) related to sexual abuse at ages 14-16 years, corresponding with a period of intensive cortical development in late adolescence (28). In physically abused children (N=31) Hanson et al. found a reduced volume of the orbitofrontal cortex. (39) Tomoda (40), using voxel based morphometry (VBM), found reduced prefrontal cortical gray matter volume (GMV) in the medial and dorsolateral frontal cortex in young adults (N=23) who experienced harsh corporal punishment during childhood.

In contrast, Carrion et al. found increased GMV in the prefrontal cortex (inferior and superior quadrants) of children 7-14 years of age (N=14) with PTSD (41) . Finally, in a study by Richert and Carrion (N=23), children with PTSD symptoms showed a larger gray matter volume in the middle inferior and ventral regions of the PFC. The decreased volume of gray matter in the dorsal PFC correlated with increased functional impairment scores (42).

In line with the findings of reduced volume in some of the studies in children and adolescents, van Harmelen et al. (12) showed an association between maltreatment and a reduction in predominantly left dorsal medial prefrontal cortex volume in a study with adults reporting childhood emotional maltreatment.

Remarkably, in a cross-sectional review (43) reporting on neuroimaging findings in children and adolescents with mental disorders from 2005 to 2008, the frontal cortex was the region that showed the most structural and functional abnormalities in children and adolescents with anxiety disorders. In line with findings in adults (22) the group of children and adolescents with anxiety or depressive disorders (the affective cluster) was characterized by abnormalities of the frontal-limbic regions. In the same review the frontal cortex was also identified as the region where the structural and functional abnormalities were consistently found in the group of disorders with ‘cognitive deficits’ (ADHD, autism spectrum disorders, schizophrenia, anorexia nervosa, addiction).

The majority of structual studies in children and adolescents included in our review did not find structal abnormalites in the PFC associated with maltreatment or psychological trauma. This may be related to the inclusion of subjects based on exposure to a form of psychological trauma without the presence of psychopathology in a number of studies, the small numbers of subjects or differences in scanner resolution.

Total brain

Total cerebral volume is examined as some consider it to be a marker for more diffuse cerebral damage. Four larger, also older (18;23;25;27;27) studies and one more recent study (26) reported a decrease in total cerebral volume in addition to other findings in youths with PTSD or a history of chronic psychological trauma. In traumatized adults, decreased total brain volume has not been reported. Results from animal studies showed that stress has a negative effect on brain development through the mechanisms of accelerated loss of neurons, delays in myelinization of neurons and inadequate ways of pruning of neurons. These developmental processes are likely to be

controlled by the stress hormone cortisol and catecholamines (25). Through these mechanisms the stress and disturbances of stress regulation generated by psychological trauma are thought to influence brain development.

Sensory cortex

Recently, three different studies from the group of Teicher found a relationship between certain types of maltreatment and alterations in the volume or FA (DTI) of parts of the sensory cortex in young adults (18-25 year), traumatized during childhood. Because brain development continues until the third decade of life, these results are relevant to our topic.. Especially in late adolescence and early adulthood, major changes still take place in the brain and data on this period may shed light on the differences in findings between children and adults with a history of psychological trauma.

The first study by Tomoda et al. found a relationship between the duration of sexual abuse before age 12 and a reduction in GMV in the primary and secondary visual cortex (VBM) of young women (N=23) (44). Choi et al. used DTI and found reduced fractional anisotropy in the visual limbic pathway (the inferior longitudinal fasciculus of the left lateral occipital lobe) in 20 young adults who witnessed domestic violence in childhood, compared to controls (45). In the third study by Tomoda et al. (N=21), exposure to parental verbal abuse was associated with an increase in GMV in the superior temporal gyrus (the auditory association cortex) (46). Taken together, these data suggest that parts of the sensory cortex involved in perception processing may be affected by exposure to extreme impressions during early development. Alternatively, it could also be the case that differences in structure and functioning of the sensory cortex influence the vulnerability to traumatization.

Cerebellum

The cerebellum has a coordinating function in motor action, while more recent research suggests a similar role for the cerebellum in cognitive and emotional processes through its connection with limbic structures and the HPA axis (10);(47).

Two structural studies reported on the cerebellum and both found a decrease in volume.
In the study of De Bellis et al. (N=58) the left, right and total cerebellum volume were smaller in children and adolescents with maltreatment related PTSD than in youngsters with generalized anxiety disorder and healthy controls. Cerebellar volume positively correlated with age of onset of the psychological trauma and negatively with the duration (48). Carrion et al. found a reduced volume of the pons and cerebellar vermis in 24 patients with paediatric PTSD. (41)
Interestingly, a recent study in adult patients (N=42) (49) revealed a correlation between PTSD and reduced left cerebellar hemisphere and vernal volume in comparison to resilient controls who experienced psychological trauma but did not develop PTSD. Moreover, in the PTSD group vermal volume correlated negatively with traumatic symptoms and early traumatic life events.

Amygdala

The amygdala plays an important role in emotional circuitry, especially in fear conditioning and threat appraisal (7). Abnormalities in the amygdala are strongly associated with affective disorders and probably also with vulnerability for psychopathology (43). To our knowledge, only three studies report on structural abnormalities of the amygdala in traumatized children and adolescents. One found an increase in volume compared to controls, the other two found no difference in volume.
The study by Mehta (26) found increased amygdala volumes in a study (N = 14) in severe early deprived Romanian adoptees. Left amygdala volume was related to the time spent in the institutions in Romania.

De Bellis et al (24) in a longitudinal pilot study (N=9) found no difference in amygdala volume between children with maltreatment related PTSD and healthy controls at baseline, after at least two years' follow up and across time. In a more recent and somewhat larger (N=28) study by De Bellis et al. (27) in children and adolescents that had maltreatment related PTSD, the authors again found no differences in amygdala volume.

In adults, almost all functional MRI studies in PTSD show increased activation or reactivity of the amygdala (22). Structural findings concerning amygdala volume in adults with PTSD are mixed, with some studies showing smaller volumes and other no abnormalities. This is also true for adults with PTSD and a history of childhood maltreatment (21;31). Animal data show that the amygdala play a central role in the neurocircuits activated by early adverse experience like maternal separation causing dysregulation of the neuroendocrine stressresponse. (3)

Pituitary

Thomas and De Bellis in one study specifically examined the pituitary gland because of its function in the HPA axis, controlling cortisol production in reaction to stress (19). In this larger study (N=61) the researchers did not find overall group differences in pituitary volume between the maltreatment related PTSD patients and healthy controls, but there was a significant age-by-group effect in the PTSD subjects. In the PTSD subjects pituitary volume increased more with age than in control subjects. This is an interesting finding as HPA axis abnormalities are known to be associated with PTSD. To our knowledge there are no specific MRI studies on the pituitary in adult traumatized patients.

Uncinate fasciculus

The uncinate fasciculus (UF) connects parts of the prefrontal cortex (orbitofrontal) with the temporal lobe and the amygdala. Among the 24 reviewed structural articles there is only one small DTI study (N=7) of this structure. This connectivity study was a follow up of an earlier PET study in which a decreased glucose metabolism in limbic and paralimbic structures was found in neglected adopted children. The DTI study found a decreased fractional anisotropy in the left UF of adopted children who were subjected to early socio-emotional deprivation, compared to matched healthy controls. (50). The authors linked these DTI findings to the disturbances in neurocognitive and behavioral functioning, like a relative deficit in verbal memory. This in accordance with earlier studies that found a correlation between quantitative DTI measures of the left UF and neurocognitive variables such as general intelligence, visual and verbal memory and executive function in various patient populations. A recent review on DTI in anxiety disorders found three studies in adults in which the UF was identified as a structure where FA correlated negatively with anxiety traits, implicating the structure also in emotional functioning (51)

Summary of structural findings

Because of the limited number of studies, the small sample size of many of the structural studies and the fact that some studies examined the same population, conclusions can only be tentative. The most robust findings seem to be a reduction in size of several regions of the corpus callosum and a decrease in total brain volume in traumatized children and adolescents. Recent research in young adults seems to point in the direction of an influence of early traumatization on the sensory cortex (visual and auditory cortex) and its connection to limbic areas. The reduction in hippocampal volume found in adults with PTSD is not found in children and adolescents. Findings on abnormalities in the PFC and the amygdala are limited or unequivocal .

Functional Neuroimaging

Surprisingly, we could identify only three functional neuroimaging studies in children and youth with a history of psychological trauma or maltreatment.

Yang et al published a very small study (N=5) in which child earthquake survivors with PTSD were matched with non-PTSD survivors (52). Functional scans were made during visual perception and imaginary recollection of traumatic reminders and neutral pictures. Contrary to the control group, the PTSD group showed activation in the bilateral visual cortex, bilateral cerebellum and left parahippocampal gyrus. Under the same conditions the control group showed activation in the anterior cingulate cortex while the PTSD group did not. Although this is only one, very small study, the results may point in the direction of involvement of the visual cortex and the cerebellum, as Tomoda et al (44) and De Bellis et al. (48) suggested based on their structural studies of these regions.

In the second functional MRI study by Carrion et al. (53), 16 youths with PTS symptoms (PTSS) performed a response-inhibition Go/no-Go task. The 14 age and gender matched control subjects showed greater middle frontal cortex activation (Brodman area 9/46) than the PTSS subjects. The PTSS subjects had greater medial frontal activation (Brodman area 8/9, 17/18/19, 32/24, 37). A sub-group of seven youths with PTSS and a history of self injurious behaviour demonstrated increased insula and orbitofrontal activation. Insula activation correlated positively with PTSS severity.

Research in adult traumatized patients mostly shows a decreased activation in the PFC (22). The paradigms used in adults usually consist of exposure to visual or auditory stimuli related to a specific type of psychological trauma.

In the third fMRI study Carrion et al. found reduced activity in the hippocampus of 16 adolescents with PTS symptoms during a verbal declarative memory task in the scanner (54). This is in line with similar findings of reduced hippocampal activity in adults with PTSD during a verbal declarative memory task (22)

Table 2. Results reviewed studies

Structural (volumetric)		
Structure	Study	Results
Hippocampus	De Bellis MD, Pittsburgh, 1999	=
	Carrion VG, Stanford, 2001	=
	De Bellis MD, Pittsburgh, 2001	=
	De Bellis MD, Pittsburgh, 2002	=
	Tupler LA, Pittsburgh, 2006	↑ WMV↑ GMV =
	Carrion VG, Stanford, 2007	↓
	Andersen SL, Harvard, 2008	↓
	Mehta MA, Southampton, 2009	=
	De Bellis MD, Durham, 2010	=
Corpus callosum	De Bellis MD, Pittsburgh, 1999	CSA↓
	De Bellis MD, Pittsburgh, 2002	CSA↓
	De Belis MD, Pittsburgh, 2003	CSA↓
	Teicher MH, Harvard, 2004	CSA↓
	Andersen SL, Harvard, 2008	CSA↓

	Mehta MA, Southampton, 2009	=
Frontal cortex	De Bellis MD, Pittsburgh, 2002	↓ WMV↓
	Richert KA, Stanford, 2005	GMV ↓/↑
	Carrion VG, Stanford, 2008	GMV↑
	Andersen SL, Harvard, 2008	↓
	Tomoda A, Harvard, 2009	GMV↓
	Hanson, JL, Wisconsin, 2010	↓
Total brain	De Bellis MD, Pittsburgh, 1999	↓
	Carrion VG, Stanford, 2001	↓
	De Bellis MD, Pittsburgh, 2002	↓
	De Belis MD, Pittsburgh, 2003	↓
	Mehta MA, Southampton, 2009	GMV↓ WMV↓
Amygdala	De Bellis MD, Pittsburgh, 2001	=
	De Bellis MD, Pittsburgh, 2002	=
	Mehta MA, Southampton, 2009	↑
Visual cortex	Tomoda A, Harvard, 2009	GMV↓
Sup temp gyrus	De Bellis MD, Pittsburgh, 2002	GMV↑ WMV↓
	Choi J, Harvard, 2009	WMT↓
	Tomoda A, Harvard, 2011	GMV↑
Cerebellum	De Bellis MD, Pittsburgh, 2006	↓
	Carrion VG, Stanford, 2009	GMV↓ vermis
Pituitary	Thomas LA, Pittsburgh, 2004	=/↑

GMV= Grey Matter Volume
WMV= White Matter Volume
CSA= Cross Sectional Area

Diffusion Tensor Imaging (DTI)		
Structure	Study	Results
Hippocampus	Choi J, Harvard, 2009	FA↓ Cingulum bundle post tail left hippocampus
Corpus callosum	Jackowski AP, Yale, 2008	FA ↓ med + post corpus
Visual cortex	Choi J, Harvard, 2011	FA↓ Visual limbic pathway
Uncinate fasciculus	Eluvathingal TJ, Detroit, 2006	FA↓ Left

FA = fractional anisotropy

Functional		
Structure	Study	Results
Hippocampus	Carrion VG, Stanford, 2010	↓
Frontal cortex	Carrion VG, Stanford, 2008	Medial PFC↑ Middle PFC↓
Visual cortex	Yang P, Taiwan, 2004	↑
Cerebellum	Yang P, Taiwan, 2004	↑
Parahippocampal gyrus	Yang P, Taiwan, 2004	↑

Discussion

Neuroimaging is considered an important tool to study the effects of psychological trauma on the brain. As a large body of evidence points at the immediate and long-term sequelea of traumatic experiences in childhood it is remarkable, however, that so few neuroimaging studies in traumatized juveniles have been published. With the exception of two studies, neuroimaging research in traumatized juveniles was conducted in the USA and by a limited number of groups. Most studies examined structural aspects and we could not identify studies on the effect of psychotherapy or farmacotherapy. Neuroimaging research in traumatized children and adolescents lags behind research in other child and adolescent disorders like ADHD and autism, both in number and approach. For example , a review by Konrad and Eickhoff in 2010 about ADHD mentioned already 18 studies on connectivity alone. (55) A review by Williams in the same year on neuroimaging studies that helped explaining the nature of autism and related disorders, included almost 40 studies. (56) There are limited or no data available on structural and functional connectivity in traumatized children and adolescents, on brain activation patterns during cognitive and emotional tasks, on longitudinal effects, and on the effects of psychotherapy or pharmacotherapy.

There can be different explanations for this relative scarcity of neuroimaging studies in traumatized children and adolescents, such as difficulty of inclusion, high number of drop-outs, or the idea that this type of research is especially burdensome for these children and youngsters. In our own and others experience inclusion can be difficult for several reasons, for example because of obtaining parental consent when abuse takes place in the family circle or reluctance of professionals and parents to let this group of patients participate in research..

Given the limited number of studies, often conducted by the same groups, the small sample sizes and the often disparious findings, conclusions of our review must be considered tentative.

The most consistent structural finding seems to be a reduced volume of parts of the corpus callosum in traumatized juveniles. No clear picture emerges from the three functional studies. Several structural and functional findings are in line with results found in adult trauma patients, in juvenile and adult patients with affective disorders, and in animal studies. The reduction in size of brain structures, especially total brain and PFC, in traumatized children and adolescents is considered to be the result of deviant brain development caused by stress, in line with animal studies showing negative effects of stress on brain development. Active brain development is characterized by loss of neurons which is thought to be a process of controlled differentiation. As this controlled differentiation is at least partly under the influence of stress hormones, it can be hypothesized that psychological trauma, especially in critical time windows, overstimulates this process. Animal data have confirmed this hypothesis for early stress in relation to hippocampal atrophy, reduced fibre innervation and fibre density in some regions of the prefrontal cortex and the corpus callosum (9). The influence of severe stress can lead to long lasting changes in brain structure and function. In this light it is important to mention the strong relationship between childhood adverse experience and

later psychopathology in general as was recently reconfirmed by a large WHO survey in 21 countries (1) (See also: (57)).

Remarkably, some abnormalities, like the consistent finding of reduced volume of the hippocampus in adult psychological trauma patients are not found in traumatized children and adolescents. This underscores the importance of continued research into the interaction between psychological trauma and the developing brain. In addition, research in adults with PTSD and mood and anxiety disorders has shown changes in brain function and structure after successful psychotherapy (58-60). Children and youth with psychological trauma related psychopathology are typically treated with psychotherapy, but data on the malleability of their brain structure and function by therapy, or on critical neurobiological windows of opportunity for treatment are still lacking.

Research in developmental psychopathology and affective neuroscience has come a long way in describing the neurobiological basis of important cognitive and emotional processes and their disturbances, but more research efforts to unravel the neurobiology of the traumatized juvenile brain, and especially its potential for change, is clearly warranted (61;62).

Reference List

1. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, de GG, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu CY, Karam EG, Kawakami N, Lee S, Lepine JP, Ormel J, Posada-Villa J, Sagar R, Tsang A, Ustun TB, Vassilev S, Viana MC, Williams DR (2010) Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br J Psychiatry 197:378-385

2. MacMillan HL, Fleming JE, Streiner DL, Lin E, Boyle MH, Jamieson E, Duku EK, Walsh CA, Wong MY, Beardslee WR (2001) Childhood abuse and lifetime psychopathology in a community sample. Am J Psychiatry 158:1878-1883

3. Sanchez MM, Ladd CO, Plotsky PM (2001) Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev Psychopathol 13:419-449

4. Teicher MH (2002) Scars that won't heal: the neurobiology of child abuse. Sci Am 286:68-75

5. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP (2002) Developmental neurobiology of childhood stress and trauma. Psychiatr Clin North Am 25:397-viii

6. Vermetten E, Bremner JD (2002) Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. Depress Anxiety 16:14-38

7. Pine DS (2003) Developmental psychobiology and response to threats: relevance to trauma in children and adolescents. Biol Psychiatry 53:796-808

8. Nock MK, Kaufman J, Rosenheck RA (2001) Examination of predictors of severe violence in combat-exposed Vietnam veterans. J Trauma Stress 14:835-841

9. Kaufman J, Plotsky PM, Nemeroff CB, Charney DS (2000) Effects of early adverse experiences on brain structure and function: clinical implications. Biol Psychiatry 48:778-790

10. McCrory E, De Brito SA, Viding E (2010) Research review: the neurobiology and genetics of maltreatment and adversity. J Child Psychol Psychiatry 51:1079-1095

11. Bremner JD, Vermetten E (2001) Stress and development: behavioral and biological consequences. Dev Psychopathol 13:473-489

12. van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM (2010) Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biol Psychiatry 68:832-838

13. Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD (2003) Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry 54:693-702

14. Felmingham K, Kemp A, Williams L, Das P, Hughes G, Peduto A, Bryant R (2007) Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. Psychol Sci 18:127-129

15. Roy MJ, Francis J, Friedlander J, Banks-Williams L, Lande RG, Taylor P, Blair J, McLellan J, Law W, Tarpley V, Patt I, Yu H, Mallinger A, Difede J, Rizzo A, Rothbaum B (2010) Improvement in cerebral function with treatment of posttraumatic stress disorder. Ann N Y Acad Sci 1208:142-149

16. Newport DJ, Stowe ZN, Nemeroff CB (2002) Parental depression: animal models of an adverse life event. Am J Psychiatry 159:1265-1283

17. De Bellis MD, Hooper SR, Woolley DP, Shenk CE (2010) Demographic, maltreatment, and neurobiological correlates of PTSD symptoms in children and adolescents. J Pediatr Psychol 35:570-577

18. De Bellis MD, Keshavan MS (2003) Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. Neurosci Biobehav Rev 27:103-117

19. Thomas LA, De B (2004) Pituitary volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry 55:752-758

20. Tupler LA, De B (2006) Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. Biol Psychiatry 59:523-529

21. Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A (2006) A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev 30:1004-1031

22. Bremner JD (2007) Neuroimaging in posttraumatic stress disorder and other stress-related disorders. Neuroimaging Clin N Am 17:523-38, ix

23. Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL (2001) Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiatry 50:943-951

24. De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G (2001) A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry 50:305-309

25. De Bellis, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND (1999) A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. Biol Psychiatry 45:1271-1284

26. Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, Rutter M, Sonuga-Barke EJ (2009) Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. J Child Psychol Psychiatry 50:943-951

27. De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G (2002) Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry 52:1066-1078

28. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH (2008) Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci 20:292-301

29. Choi J, Jeong B, Rohan ML, Polcari AM, Teicher MH (2009) Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. Biol Psychiatry 65:227-234

30. Carrion VG, Weems CF, Reiss AL (2007) Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. Pediatrics 119:509-516

31. Woon FL, Hedges DW (2008) Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 18:729-736

32. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242-1247

33. Yehuda R, Golier JA, Tischler L, Harvey PD, Newmark R, Yang RK, Buchsbaum MS (2007) Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: relation to risk and resilience factors. J Psychiatr Res 41:435-445

34. Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL (2004) Childhood neglect is associated with reduced corpus callosum area. Biol Psychiatry 56:80-85

35. Jackowski AP, Douglas-Palumberi H, Jackowski M, Win L, Schultz RT, Staib LW, Krystal JH, Kaufman J (2008) Corpus callosum in maltreated children with posttraumatic stress disorder: a diffusion tensor imaging study. Psychiatry Res 162:256-261

36. Jackowski AP, de Araujo CM, de Lacerda AL, Mari JJ, Kaufman J (2009) Neurostructural imaging findings in children with post-traumatic stress disorder: brief review. Psychiatry Clin Neurosci 63:1-8

37. Kitayama N, Brummer M, Hertz L, Quinn S, Kim Y, Bremner JD (2007) Morphologic alterations in the corpus callosum in abuse-related posttraumatic stress disorder: a preliminary study. J Nerv Ment Dis 195:1027-1029

38. Villarreal G, Hamilton DA, Graham DP, Driscoll I, Qualls C, Petropoulos H, Brooks WM (2004) Reduced area of the corpus callosum in posttraumatic stress disorder. Psychiatry Res 131:227-235

39. Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ, Pollak SD (2010) Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. J Neurosci 30:7466-7472

40. Tomoda A, Suzuki H, Rabi K, Sheu YS, Polcari A, Teicher MH (2009) Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. Neuroimage 47 Suppl 2:T66-T71

41. Carrion VG, Weems CF, Watson C, Eliez S, Menon V, Reiss AL (2009) Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric posttraumatic stress disorder: an MRI study. Psychiatry Res 172:226-234

42. Richert KA, Carrion VG, Karchemskiy A, Reiss AL (2006) Regional differences of the prefrontal cortex in pediatric PTSD: an MRI study. Depress Anxiety 23:17-25

43. Mana S, Paillere Martinot ML, Martinot JL (2010) Brain imaging findings in children and adolescents with mental disorders: a cross-sectional review. Eur Psychiatry 25:345-354

44. Tomoda A, Navalta CP, Polcari A, Sadato N, Teicher MH (2009) Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. Biol Psychiatry 66:642-648

45. Choi J, Jeong B, Polcari A, Rohan ML, Teicher MH (2012) Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. Neuroimage 59:1071-1079

46. Tomoda A, Sheu YS, Rabi K, Suzuki H, Navalta CP, Polcari A, Teicher MH (2011) Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. Neuroimage 54 Suppl 1:S280-S286

47. Durston S (2008) Converging methods in studying attention-deficit/hyperactivity disorder: what can we learn from neuroimaging and genetics? Dev Psychopathol 20:1133-1143

48. De Bellis, Kuchibhatla M (2006) Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry 60:697-703

49. Baldacara L, Jackowski AP, Schoedl A, Pupo M, Andreoli SB, Mello MF, Lacerda AL, Mari JJ, Bressan RA (2011) Reduced cerebellar left hemisphere and vermal volume in adults with PTSD from a community sample. J Psychiatr Res 45:1627-1633

50. Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M (2006) Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 117:2093-2100

51. Ayling E, Aghajani M, Fouche JP, van der Wee N (2012) Diffusion tensor imaging in anxiety disorders. Curr Psychiatry Rep 14:197-202

52. Yang P, Wu MT, Hsu CC, Ker JH (2004) Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: a functional MRI study. Neurosci Lett 370:13-18

53. Carrion VG, Garrett A, Menon V, Weems CF, Reiss AL (2008) Posttraumatic stress symptoms and brain function during a response-inhibition task: an fMRI study in youth. Depress Anxiety 25:514-526

54. Carrion VG, Haas BW, Garrett A, Song S, Reiss AL (2010) Reduced hippocampal activity in youth with posttraumatic stress symptoms: an FMRI study. J Pediatr Psychol 35:559-569

55. Konrad K, Eickhoff SB (2010) Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Hum Brain Mapp 31:904-916

56. Williams DL, Minshew NJ (2007) Understanding autism and related disorders: what has imaging taught us? Neuroimaging Clin N Am 17:495-509, ix

57. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS (1998) Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14:245-258

58. Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L (2008) Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol Med 38:555-561

59. Frewen PA, Dozois DJ, Lanius RA (2008) Neuroimaging studies of psychological interventions for mood and anxiety disorders: empirical and methodological review. Clin Psychol Rev 28:228-246

60. Nardo D, Hogberg G, Looi JC, Larsson S, Hallstrom T, Pagani M (2010) Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J Psychiatr Res 44:477-485

61. Pine DS (2007) Research review: a neuroscience framework for pediatric anxiety disorders. J Child Psychol Psychiatry 48:631-648

62. Shonkoff JP (2011) Protecting brains, not simply stimulating minds. Science 333:982-983

Chapter 3 VOXEL BASED MORPHOMETRY (VBM)

Anterior cingulate cortex grey matter volume abnormalities in adolescents with PTSD after childhood sexual abuse

Mirjam A. Rinne-Albers, J. Nienke Pannekoek, Marie-José van Hoof, Natasja D. van Lang, Francien Lamers-Winkelman, Serge A. Rombouts, Ph.D. Nic J. van der Wee, Robert R. Vermeiren

European Neuropsychopharmacology, 2017, 27: 1163-1171

Abstract

Adverse childhood experiences (ACE) substantially increase the risk of later psychiatric and somatic pathology. While neurobiological factors are likely to play a mediating role, specific insights are lacking. The scarce neuroimaging studies in traumatised pediatric populations have provided inconsistent results, potentially due to the inclusion of different types of trauma. To further improve our understanding of the neurobiology of pediatric psychotrauma, this study seeks to investigate abnormalities in grey matter volume (GMV) in a homogeneous group of adolescents with posttraumatic stress disorder (PTSD) due to childhood sexual abuse (CSA) and the relationship between GMV and symptom severity. We performed a voxel based morphometry (VBM) analysis in 21 adolescents with CSA-related PTSD and 25 matched non-traumatised, non-clinical adolescents. Hippocampus, amygdala, anterior cingulate cortex (ACC), medial PFC (mPFC) and superior temporal gyrus (STG) were chosen as regions of interest (ROIs). Trauma symptomatology was measured with the Trauma Symptom Checklist for Children (TSCC) and dissociation symptoms with the Adolescent Dissociative Experiences Scale (A-DES). The ROI analysis showed that the CSA-related PTSD group had significant smaller volumes of the dorsal ACC as compared to healthy controls. However, no correlations were found between GMV and scores on the TSCC and A-DES. The smaller ACC volume is partly in line with previous studies in traumatised youth and is a consistent finding in traumatised adults. Taken together our results suggest that the dorsal ACC is implicated in the neurobiological sequelae of CSA, potentially associated with an altered evaluative processing of emotion, but not directly with PTSD severity.

1. Introduction

An abundant number of studies have established the role of adverse childhood experiences (ACE), like abuse or neglect, as a risk factor for the development of psychiatric and somatic disorders (Gilbert et al., 2009;Kessler et al., 2010;Scott et al., 2013;Shonkoff & Garner, 2012). As ACE exceed normal experience, it is hypothesized that through the influence of an excess of stress hormone on synapse formation and pruning of neurons, developmental pathways in the brain are altered, leading to structural and functional changes that predispose to psychopathology (Kaufman et al., 2000;Marsh et al., 2008). Therefore, neuroimaging studies in traumatised children and adolescents are crucial to increase our insight in altered developmental trajectories and the associated neurobiological mechanisms. Preclinical research and studies in human adults have shown ACE to be associated with structural changes in the brain. Most prominently abnormalities in emotion and stress regulating structures have been reported, like the hippocampus in adults who experienced childhood abuse (Bremner, 2007;Woon & Hedges, 2008) or the medial prefrontal cortex (mPFC) in adults with childhood emotional maltreatment (Hart & Rubia, 2012;McCrory et al., 2011;van Harmelen et al., 2010).

To date, studies on brain structure in traumatised pediatric populations are still scarce, and have yielded divergent results, while neuroimaging findings in traumatised minors also seem to differ substantially from those in adults reporting childhood adversity (Rinne-Albers et al., 2013).

Research in adults with ACE consistently reports decreased grey matter volume (GMV) in the hippocampus (Bremner, 2007;O'Doherty et al., 2015;Woon & Hedges, 2008). In minors, however, only one out of nine studies in traumatised populations found a smaller hippocampal volume (Carrion et al., 2007). One study of adolescents with maltreatment-related PTSD even found a larger (white matter) volume compared to healthy non-abused controls (Tupler & De Bellis, 2006). Interestingly, Andersen reports smaller volumes of the hippocampus in a group of young women in transition to adulthood (aged 18-22 years), correlated with sexual abuse at ages 11-13 years

(Andersen et al., 2008;McCrory et al., 2010;Woon & Hedges, 2008), suggesting that the decrease in hippocampal volume is already visible from early adulthood.
Notwithstanding the key role of the amygdala in emotion processing, earlier reviews concluded that childhood maltreatment does not affect amygdala volume in adults (McCrory et al., 2010;Woon & Hedges, 2008). Recently, the meta-analysis by O'Doherty et al. (McCrory et al., 2010;O'Doherty et al., 2015) of structural MRI measurement in adults with PTSD, showed mixed results in 14 studies investigating amygdala volume. Six studies investigating amygdala volumes in minors also yielded inconsistent results. Two studies report smaller amygdala volumes (Carrion et al., 2001;De Bellis et al., 1999), two studies report no differences in amygdala volume (De Bellis et al., 2001;De Bellis et al., 2002b) and two recent studies report larger amygdala volumes (Mehta et al., 2009;Tottenham et al., 2010). The larger amygdala volumes were reported in children and adolescents with early institutional deprivation, while studies with PTSD subjects, with or without maltreatment, report smaller or no change in amygdala volume.

Because the PFC, an area central to higher cognitive functioning and involved in emotion regulation, matures relatively late and continues to develop into adulthood (Marsh et al., 2008), this structure is thought to be especially vulnerable for the effects of ACE (Pine, 2003). The six studies examining PFC volume in traumatised minors, however, showed inconsistent results (Rinne-Albers et al., 2013). Larger (N=1) and smaller (N=3) volumes as well as mixed results for the PFC (N=2) were reported, but it should be noted that different subdivisions of the PFC were studied. Remarkably, smaller frontal volumes were reported in cases of maltreatment with or without PTSD and larger volumes or mixed results came from studies on PTSD not based on maltreatment. Of special interest to emotion regulation is the medial PFC (mPFC), which encompasses the ACC. The ACC modulates emotional responsiveness by inhibition of the amygdala (Morgan et al., 1993). In adults, studies consistently report smaller ACC volumes in patients with PTSD (Kuhn & Gallinat, 2013;Meng et al., 2014;O'Doherty et al., 2015). In minors, two recent studies report abnormalities in GMV of the ACC in adolescents with childhood adversity. Ahmed et al. (Ahmed et al., 2012) found reduced GMV in the right cingulate gyrus in a PTSD group. In contrast, Walsh et al. (Walsh et al., 2014) reported recent negative life events at age 14 to be associated with increased anterior cingulate GMV. Finally, the superior temporal gyrus, an area involved in social cognition, has been studied in both minors and adults. Only one study in minors specifically focussed on the STG. DeBellis et al. found larger STG GMV and smaller STG white matter volume (WMV) in a group of maltreated children and adolescents with PTSD compared to non-maltreated healthy controls (De Bellis et al., 2002a). The human brain is known to develop well into the third decade of life. Two structural neuroimaging studies in traumatised young adults report changes in the STG. In studies with young adults (age 18 to 25 y), all exposed to parental verbal abuse but no other form of maltreatment, Tomoda et al. report larger grey matter volume in the STG (Tomoda et al., 2011) and Choi et al. in a DTI study report reduced fractional anisotropy (FA, a measure for white matter integrity) in the white matter tract of the STG (Choi et al., 2012). In a voxel-wise meta-analysis Lim et al. (Lim et al., 2014) concluded that relative to unexposed comparison subjects, individuals exposed to childhood maltreatment showed significantly smaller GMV in the right STG. This conclusion was based on twelve whole brain morphometry datasets from adults as well as youth with childhood maltreatment.

Most of the pediatric studies on ACE not only included heterogeneous groups regarding type of childhood adversity; they also often combined different age groups of children and adolescents, further contributing to inconsistency in neuroimaging findings. To further improve the understanding of the impact of trauma on adolescent brain structure, we therefore studied GMV in a homogeneous group of adolescents with childhood sexual abuse (CSA) related PTSD and in a group of matched non-traumatised, healthy controls.

Based on the literature, we focused on GMV in the amygdala, hippocampus, mPFC, ACC and STG. We hypothesized GMV in frontal regions to be decreased compared to healthy non-traumatised controls. For the amygdalar, hippocampal, and STG GMV, we had no a priori hypothesis about the directionality of the findings. We also planned an exploratory whole brain analysis to detect aberrant GMV in areas outside our a priori defined ROIs. Furthermore, we explored a correlation of structural abnormalities with trauma symptomatology.

2. Experimental procedures

2.1 Participants

Participants were selected from the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA). EPISCA is a longitudinal MRI study in which adolescents with clinical depression, adolescents with a history of sexual trauma and healthy controls were followed over a six-month period in which they received treatment. The adolescents were assessed and underwent scanning at three time points: upon inclusion at baseline, three months after baseline, and six months after baseline (Aghajani et al., 2016;van Hoof et al., 2015). The current study reports on cross-sectional baseline data from the adolescents with a history of sexual trauma and healthy non-traumatised controls. Inclusion criteria for the adolescents with a history of sexual trauma were: having experienced sexual abuse during their lifetime more than once by one or more perpetrators inside or outside the family, and being referred for treatment at the psychotrauma center of mental health institute GGZ Rivierduinen in Leiden or the child psychotrauma center KJTC in Haarlem, the Netherlands. Experienced psychotherapists in these specialised Psychotrauma Centers obtained the trauma histories from the adolescents as well as from their caregivers during clinical interviews. To objectify any abuse or neglect as well as risk for functional impairment and morbidity, we verified police reports, involvement of child welfare, and family custody or other child protection measures as to have an estimate of the severity and impact of problems. (For more details about the participants in the CSA-related PTSD group see van Hoof et al., 2015. (van Hoof et al., 2015))

Presence of PTSD was not an inclusion criterion, although clinical assessments (see below) showed that all patients but one were having PTSD related to CSA. Inclusion criteria for the control group were: no current or past DSM-IV classifications, no clinical scores on validated mood and behavioural questionnaires, no history of traumatic experiences, and no current psychotherapeutic and/or psychopharmacological intervention of any kind. Exclusion criteria for all participants were: primary DSM-IV clinical diagnosis of attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), pervasive developmental disorders, Tourette's syndrome, obsessive–compulsive disorder, bipolar disorder, and psychotic disorders; current use of psychotropic medication other than stable use of SSRI's, or amphetamine medication, but not on the day of scanning; current substance abuse; history of neurological disorders or severe head injury; age <12 or >21 years; pregnancy; left-handedness; IQ score <80 as measured by the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1997) or adults (Wechsler, 1991); and general MRI contraindications.

Fifty-four participants were included in the study: 32 healthy non-traumatised controls and 22 patients with a history of sexual trauma. From this group, one participant (control) was excluded due to anomalies found on the anatomical scans upon inspection of the structural scans by a neuroradiologist, five participants (four controls, one CSA) were excluded because of technical problems during scanning or poor imaging data quality, one control was excluded due to high scores on rating scales, and one control was excluded due to a history of sexual trauma that was not reported until the scanning day. The resulting sample that was used in the current study consisted of 46 adolescents (25 controls and 21 CSA). Of the 21 CSA participants, 20 fulfilled all PTSD criteria on

the ADIS, while one had sufficient PTSD symptoms, but with limited interference. Since earlier research showed that persons with sub threshold PTSD in many aspects resemble PTSD patients, we decided to include this patient in the PTSD group (Cukor et al., 2010).

The study was approved by the Medical Ethics Committees of the Leiden University Medical Center and written informed assent and consent was obtained from the participants and their parents respectively.

2.2 Clinical assessment

A standardized set of instruments was used to assess symptomatology in both groups of adolescents.
The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS-C/P) (Silverman & Ollendick, 2005) are semi structured interviews for the classification of DSM-IV anxiety and depressive disorders in children. Classification is reached by a minimal interference score of 4 obtained by trained examiners based on the ADIS-C and ADIS-P. The ADIS is known to have good reliability and validity (Silverman et al., 2001) with reported strong test–retest reliability statistics for the ADIS-C/P for combined diagnoses (.80–.92) and individual diagnoses (.62–.88).

The Trauma Symptom Checklist for Children (TSCC) (Briere, 1996) is a 54-item self-report for children and adolescents aged 8 through 18 but often used up to 21 years (Barakat et al., 1997;Gustafsson et al., 2009) which measures trauma-related symptoms. On a 4-point scale (never to almost all of the time), the adolescent indicates how often a thought, a feeling or a behavior occurs. The items are grouped into six clinical scales. The clinical scales are Anxiety (Anx), Depression (Dep), Post-traumatic Stress (Pts), Sexual Concerns (Sc), Dissociation (Dis) and Anger (Ang). The TSCC total score is used as the main measure on post-traumatic symptomatology. Cronbach's alpha coefficients reported range from .77 to .89 for subscales and .84 for the total scale. The questionnaire has extensively been studied, which has confirmed its good psychometric qualities (Lanktree et al., 2008;Nilsson et al., 2008). The internal consistency of the TSCC subscales varied between .85 and .94, except for the Sexual Concerns subscale that measured .68.

The Adolescent Dissociative Experiences Scale (A-DES) (Armstrong et al., 1997) contains 30 items to assess adolescents of 11-18 years of age for pathological dissociation. The A-DES items inquire about four domains reflecting basic aspects of dissociation: experiences of dissociative amnesia, depersonalisation/derealisation, absorption/imaginative involvement and passive influence. The items are rated by the adolescent on an 11-point Likert-scale ranging from 0 = "never" to 10 = "always" with no midpoint scores. The total A-DES score is based on the mean of all item scores. A mean score of 4 or above on the A-DES signifies pathological dissociation (Kisiel & Lyons, 2001). The scale has good internal reliability and validity (Farrington et al., 2001).

As brain development is known to be influenced by sexual development, corporal sexual development was measured with the self-report Puberty Development Scale (Petersen, 1988). The PDS consists of 5 items that are measured on a 5-point scale by the examiner: 1= pre-pubertal, 2= early pubertal, 3= mid-pubertal, 4= late pubertal, 5= post-pubertal. The PDS is considered a valuable instrument determining pubertal stage (Bond et al., 2006;Herting et al., 2012).

Six subscales from the Wechsler Intelligence scales scores (picture completion, similarities, picture concepts, arithmetic, block design and comprehension) were converted into FIQ estimates.

2.3 Image data acquisition

Images were acquired on a Philips 3T magnetic resonance imaging system (Philips Healthcare, Best, The Netherlands), equipped with a SENSE-8 head coil. Scanning took place at the Leiden University Medical Centre. Prior to scanning, all participants were introduced to the scanning situation by lying in a dummy scanner and hearing scanner sounds. For each subject, a sagittal 3-dimensional gradient-echo T1-weighted image was acquired (repetition time = 9.8 ms; echo time = 4.6 ms; flip angle = 8°; 140 sagittal slices; no slice gap; field of view =256 × 256 mm; 1.17 × 1.17 × 1.2 mm voxels; duration = 4:56 min) as part of a larger, fixed imaging protocol.

2.4 Statistical analysis

Structural MRI data was analyzed with FSL-VBM (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxel-wise general linear model (GLM) was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space. A correction for total intracranial volume is integrated in the standard VBM procedure of FSL.

The Harvard–Oxford Cortical and Subcortical Structural Atlases implemented in FSL were used to create masks for our regions of interest (ROIs): the hippocampus, amygdala, ACC, mPFC and STG. Probability range was set to 50–100% for all structures. FSL was then used to create one mask encompassing the five structures, which was applied to the grey matter image from the study-specific template. Finally, groups were compared using a GLM including age, gender and IQ as confound regressors. PDS scores were not included as confound regressor because the PDS score was missing for several subjects and there was a correlation of PDS scores with age in both groups. A voxel-wise GLM was applied using permutation-based (5000 permutations) non-parametric testing, correcting for multiple comparisons across space. First, volumes were compared voxel-wise in our regions of interest, using the created mask. Second, an exploratory whole-brain analysis was done; using the grey matter image from the study-specific template to investigate whether any non-predicted differences existed between adolescents with a history of sexual trauma and healthy controls. Threshold-Free Cluster Enhancement was used as a method for finding clusters in the data (Smith & Nichols, 2009) with thresholds for the ROI comparison, as well as the whole-brain analysis set on $p < .05$, corrected. The t-statistics in FSL are family-wise corrected for multiple comparisons with a p-value of $< .05$.

Additional correlational analyses were conducted in the patient group to examine voxel-wise correlations of clinical characteristics with grey matter volume in the structural effects found in the VBM analyses.

3. Results

3.1 Sample characteristics

Of the included 46 adolescents (25 controls, 21 CSA-related PTSD), six were male, with three in each group. In the CSA-related PTSD group two adolescents were on stable SSRI use (one fluoxetine, one sertraline) and two adolescents used methylphenidate but abstained from taking medication on the day of the scan. Demographic and clinical characteristics of the sample are displayed in Table 1. The CSA-related PTSD group was significantly older than the controls (t (44) = -2.04, p = .047). Also, the CSA-related PTSD group had a significantly lower FIQ than the controls (t (44) = -3.06, p < .01). Scatterplots did not show significant outliers.

Table 1. Sample characteristics: Means and SD of age, FIQ, total scores of ADES, total scores of TSCC, and numbers per gender and PDS ratings.

		PTSD (N=21)	SD	CNTR (N=25)	SD	Group comparisons p
Gender (f : m)		18:3		22:3		
Age (years)		16.4	2.1	15.3	1.6	.047
FIQ		99.3	8.8	106.8	7.8	.004
PDS[1]	Pre/mid pubertal	1		6		.026*
	Late pubertal	7		11		
	Post pubertal	10		5		
A-DES[2,3]	Total score	72.62	58.8	22.50	20.3	.002
TSCC[2,3]	Total score	47.94	23.5	16.66	13.1	.000

Abbreviations: PTSD, Post Traumatic Stress Disorder; CNTR, control group; FIQ, Full Scale Intelligence Quotient; PDS, Puberty Development Scale; A-DES, Adolescent Dissociative Experiences Scale; TSCC, Trauma Symptom Checklist for Children. Because less than 20% of the data in ADES and TSCC were missing, expectation maximization as regression method was used to calculate the scale scores.
* crosstab chi-square test.
[1] : Six did not complete the PDS (three PTSD and three CNTR)
[2,3] : Three (all PTSD) did not complete the ADES and TSCC.

3.2 VBM Results

The VBM ROI analyses showed a cluster of 403 voxels with smaller GM volume in the ACC in the CSA-related PTSD group compared to healthy non-traumatised controls (TFCE, FWE corrected for multiple comparisons across space, thresholded at p < 0.05, see Figure 1). Peak voxel X=43, Y=75, Z=47; t = 3.64814, p = .0078.

On average, adolescents with CSA-related PTSD showed a 14.8% smaller volume of grey matter in the dorsal ACC compared to the healthy non-traumatised controls. A scatterplot did not show any outliers (figure 2.). We found no group differences in the ROIs for the amygdala, hippocampus, mPFC and STG.

In a post hoc analysis we checked our assumption of high multicollinearity of age and PDS, but found multicollinearity to be low and therefore added pubertal development (PDS) as a covariate next to age in an new analysis. This analysis showed no effect in the ACC, but we now found a small significant negative effect in the right amygdala (TFCE, FWE corrected for multiple comparisons across space, tresholded at $p < 0.05$, see supplemental material). Six subjects (three in the CSA-related PTSD group, three in the control group) were not included in this analysis because of missing PDS scores (see table 1).
The exploratory whole-brain analysis did not reveal any grey matter volume differences between patients and controls. No correlations were found between GMV in the effect and scores on the TSCC and A-DES. Excluding the two subjects on stable medication use (SSRI) from the analysis did not change the results. Also, omitting the one CSA participant who met all PTSD criteria except for interference did not change our findings.

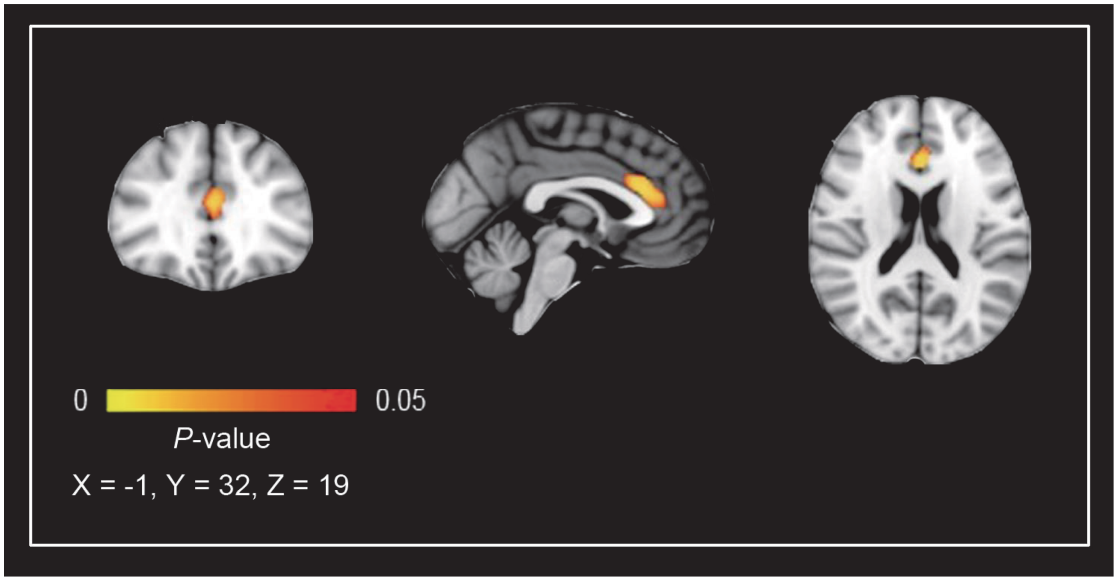


Figure 1.
Reduced ACC gray matter in the CSA-related PTSD group compared with non-traumatised, non-clinical controls. Results are displayed at $p < .05$, TFCE, FWE corrected for multiple comparisons across space. The cluster of 403 voxels is presented on the MNI-152 1 mm standard brain, 2 mm isotropic. The left hemisphere corresponds with the right side of the image. Brighter colour indicates higher corrected thresholds.

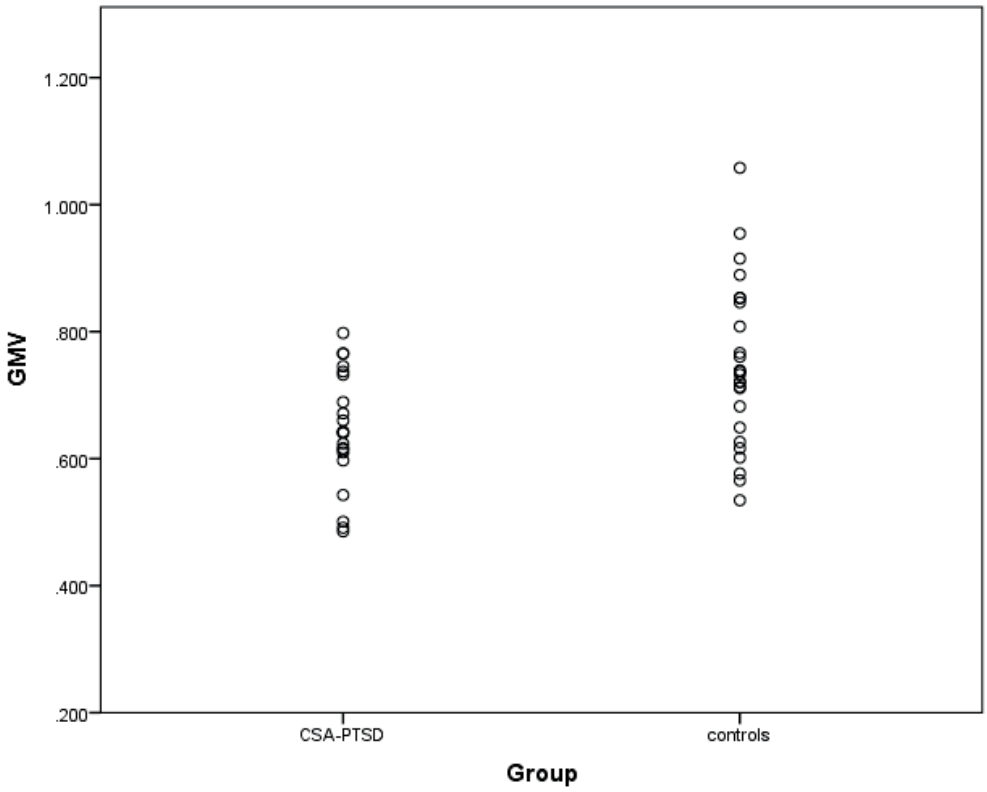


Figure 2. Scatterplot. Grey Matter Volume (GMV) of the CSA-related PTSD group and control group.

Discussion

We examined GMV in a sample of adolescents with CSA related PTSD, using a ROI and an additional exploratory whole brain approach. To our knowledge, this VBM study is the first to focus on a group of adolescents who had all experienced CSA. We focused on GMV in a number of relevant brain structures: hippocampus, amygdala, mPFC, ACC, and STG. While we hypothesized lower volumes in several frontal regions of our adolescent CSA-related PTSD group, this group showed smaller GMV in the dorsal ACC only. Similar to findings in earlier studies in minors, hippocampus GMV was not different. The other structures, for which we had no a priori hypothesis because of mixed results in earlier studies, showed no differences compared to the healthy non-traumatised control group. The whole brain analysis revealed no GMV differences outside our a priori defined ROIs.

Our finding of smaller GMV in the ACC is consistent with studies in adults with PTSD (Kuhn & Gallinat, 2013;Meng et al., 2014), as well as some groups experiencing adversity without PTSD (Ansell et al., 2012;Cohen et al., 2006;Dannlowski et al., 2011). Two studies in traumatised adolescents report GMV abnormalities in the ACC. Ahmed et al. (Ahmed et al., 2012) investigating traumatised adolescents with and without PTSD, found reduced grey matter in the right anterior cingulate gyrus, left insula and right precuneus in the PTSD group, compared to the adolescents without PTSD. This suggests a specific relationship of smaller ACC volume with having developed PTSD, which parallels our finding. In contrast, Walsh et al. (Walsh et al., 2014) studied the association of early life psychosocial adversities (but not severe abuse) with grey matter volume in healthy adolescents (mean age 18 y). Exposure to childhood adversity was only associated with smaller GMV in the vermis, while reported recent negative life events at age 14 were associated with larger anterior cingulate and lateral cerebellar GMV. A possible hypothesis could be that in healthy adolescents milder adverse events lead to increases of ACC volumes, while severe traumatisation with PTSD leads to smaller ACC volumes. Increases of prefrontal areas have also been found in primate studies investigating the resilience effects of exposure to mild stressors during adulthood (Katz et al., 2009).

Different functions are attributed to the dorsal versus the ventral part of the ACC. A recent review of human and animal neuroimaging, electrophysiology and lesion studies on the role of the ACC and the mPFC in the processing of fear and anxiety, concluded that the dorsal ACC in combination with the mPFC has an evaluative function, while the ventral ACC together with the mPFC has a more regulatory function (Etkin et al., 2011). However, since we did not assess these higher order cognitive and executive functions, we can only speculate on a possible relationship with the finding in our study of a reduced dorsal ACC volume. Future longitudinal research is needed to unravel whether the result of our study of reduced dorsal ACC volume is a consequence of CSA, PTSD or both, or related to vulnerability.

Our finding of normal hippocampal GMV adds to the results of many earlier studies in traumatised minors. This is in contrast to consistent findings of smaller hippocampal volume in traumatised adults with or without PTSD, even when traumatisation took place during childhood (O'Doherty et al., 2015;Rinne-Albers et al., 2013;Woon & Hedges, 2008). As studies on amygdala and STG volume in traumatised child and adolescent as well as adult populations are scarce and the studied populations differ in several aspects (e.g. age, kind of trauma) and results are mixed, it is hard to interpret our finding of no abnormalities in GMV of these structures in the context of this earlier research.

While the CSA-related PTSD group showed a smaller ACC GMV, there was no correlation of symptom severity measured with the TSCC. A first possible explanation could be the small variation in severity,

as almost all subjects in our CSA-related PTSD group report severe trauma related symptomatology. Another potential explanation could be that a correlation only becomes visible in a later phase of brain maturation. Adult studies found a correlation of ACC activation but not volume with PTSD symptom severity (Nardo et al., 2010) and cumulative adversity (Ansell et al., 2012). A final explanation for the absence of a significant correlation with clinical data could be the relatively small sample size.

Reviews about neuroimaging in PTSD have emphasized that methodological differences hamper comparing studies (Meng et al., 2014;O'Doherty et al., 2015). The homogeneous sample is undoubtedly a strength of our study, although some limitations should be taken into account. The CSA-related PTSD group was significantly older than the control group and also more advanced in pubertal development. As normal development is accompanied by thinning of the ACC this could perhaps partly explain our result, but we controlled for age in our analysis. (Luciana, 2013;Vijayakumar et al., 2014). A post hoc analysis with PDS as covariate next to age and with smaller groups because of subjects with missing PDS data, yielded a small negative effect in the right amygdala and no effect in the ACC (see supplemental material). Clearly, this needs to be replicated in larger samples. Further, although we know that gender influences brain development and the reaction to trauma, we could not address this topic because our participants were mainly girls. Full-scale IQ measures differed significantly between the CSA-related PTSD group and controls. However, as PTSD is known to depress IQ values, the CSA-related PTSD group might originally have been more equal to the control group with respect to intellectual ability (Pechtel & Pizzagalli, 2011).
Finally, timing, frequency and severity of trauma are highly relevant when studying childhood trauma. However, as in our study several of the perpetrators of the CSA were family members, it was not possible to reliably assess these aspects retrospectively.

In conclusion, our study in adolescents with PTSD after CSA suggests smaller GMV in the dorsal ACC, a region implicated in the evaluative processing of emotion, compared to healthy non-traumatised controls. Smaller GMV might be related to CSA or the subsequent development of PTSD, but was not related to severity of PTSD symptoms. While our findings suggest a pattern that might be more specific to CSA, this needs to be corroborated in studies directly comparing different types of maltreatment.

Clearly, further research, especially with longitudinal designs, is warranted to unravel the relationships between developmental trajectories and vulnerability and resilience for childhood trauma.

Supplemental Material

Post hoc analysis

The CSA-related PTSD group and the control group differed significantly in pubertal development as assessed with the Puberty Development Scale (PDS). (See table 1.)

In both the CSA-related PTSD group and the control group, PDS scores and age were significantly positively correlated, but not very strongly (Pearson's r .633; p<.001). The variance inflation factor (VIF), ($1/(1-R^2)$), an indicator of multicollinearity, was 1.67 and the tolerance (1/VIF) 0.6. This indicates that there was low multicollinearity. Therefore, we added pubertal development (PDS) as a covariate to a post hoc analysis, thereby losing six participants (three in the CSA-related PTSD group, three in the control group). The effect in the Anterior Cingulate Cortex (ACC) disappeared and instead we found a significant (p<.05) 4.5% smaller volume of grey matter in the right amygdala (TFCE, FWE corrected for multiple comparisons across space, tresholded at p < 0.05, see figure Supplemental Material). Peak voxel X=30, Y=61, Z=25; t = 4.30418, p = .017774.

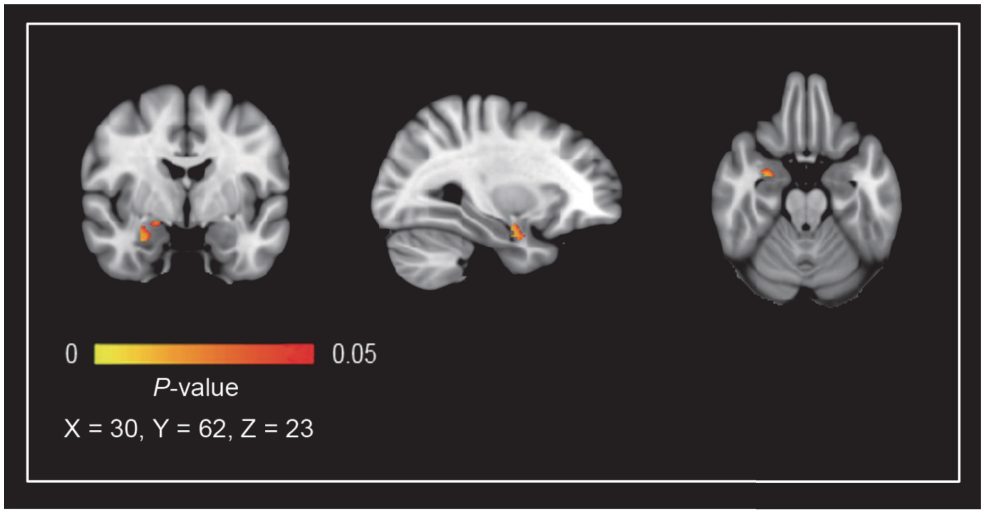


Figure 1. Supplemental material
Reduced right amygdala gray matter in the CSA-related PTSD group compared with non-traumatised, non-clinical controls, with pubertal development (PDS) added as a covariate next to age. Six subjects (three in the CSA-related PTSD group, three in the control group) are not included because of missing PDS scores. Results are displayed at p < .05, TFCE, FWE corrected for multiple comparisons across space. The cluster of 99 voxels is presented on the MNI-152 1 mm standard brain, 2 mm isotropic. The left hemisphere corresponds with the right side of the image. Brighter colour indicates higher *t*-scores.

Reference List

Aghajani M, Veer IM, van Hoof MJ, Rombouts SA, van der Wee NJ, Vermeiren RR. Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. Hum.Brain Mapp. 2016; 37:1120-1135.

Ahmed F, Ras J, Seedat S. Volumetric structural magnetic resonance imaging findings in pediatric posttraumatic stress disorder and obsessive compulsive disorder: a systematic review. Front Psychol. 2012; 3:568.

Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J.Neuropsychiatry Clin.Neurosci. 2008; 20:292-301.

Andersson M, Jenkinson M, Smith S. *Non-linear registration, aka Spatial normalisation. FMRIB technical report TR07JA2* . In: Oxford: FMRIB Software Library, 2007.

Ansell EB, Rando K, Tuit K, Guarnaccia J, Sinha R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol.Psychiatry 2012; 72:57-64.

Armstrong JG, Putnam FW, Carlson EB, Libero DZ, Smith SR. Development and validation of a measure of adolescent dissociation: the Adolescent Dissociative Experiences Scale. J.Nerv.Ment.Dis. 1997; 185:491-497.

Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. J.Pediatr.Psychol. 1997; 22:843-859.

Bond L, Clements J, Bertalli N, Evans-Whipp T, McMorris BJ, Patton GC, Toumbourou JW, Catalano RF. A comparison of self-reported puberty using the Pubertal Development Scale and the Sexual Maturation Scale in a school-based epidemiologic survey. J.Adolesc. 2006; 29:709-720.

Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders

1. Neuroimaging Clin.N.Am. 2007; 17:523-38, ix.

Briere J. Trauma Symptoms Checklist for Children (TSCC), Professional Manual. Odessa, FL: Psychological Assessment Resources, 1996.

Brooks-Gunn J, Warren MP, Rosso J, Gargiulo J. Validity of self-report measures of girls' pubertal status. Child Dev. 1987; 58:829-841.

Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol.Psychiatry 2001; 50:943-951.

Carrion VG, Weems CF, Reiss AL. Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. Pediatrics 2007; 119:509-516.

Choi J, Jeong B, Polcari A, Rohan ML, Teicher MH. Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. Neuroimage. 2012; 59:1071-1079.

Cohen RA, Grieve S, Hoth KF, Paul RH, Sweet L, Tate D, Gunstad J, Stroud L, McCaffery J, Hitsman B, Niaura R, Clark CR, McFarlane A, Bryant R, Gordon E, Williams LM. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. Biol.Psychiatry 2006; 59:975-982.

Cukor J, Wyka K, Jayasinghe N, Difede J. The nature and course of subthreshold PTSD. J.Anxiety.Disord. 2010; 24:918-923.

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, Domschke K, Hohoff C, Ohrmann P, Bauer J, Lindner C, Postert C, Konrad C, Arolt V, Heindel W, Suslow T, Kugel H. Limbic Scars: Long-Term Consequences of Childhood Maltreatment Revealed by Functional and Structural Magnetic Resonance Imaging. Biol.Psychiatry 2011.

De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol.Psychiatry 2001; 50:305-309.

De Bellis MD, Keshavan MS, Frustaci K, Shifflett H, Iyengar S, Beers SR, Hall J. Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. Biol.Psychiatry 2002a; 51:544-552.

De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol.Psychiatry 2002b; 52:1066-1078.

De Bellis, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. Biol.Psychiatry 1999; 45:1271-1284.

Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci. 2011; 15:85-93.

Farrington A, Waller G, Smerden J, Faupel AW. The adolescent dissociative experiences scale: psychometric properties and difference in scores across age groups. J.Nerv.Ment.Dis. 2001; 189:722-727.

Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. Lancet 2009; 373:68-81.

Good CD, Ashburner J, Frackowiak RS. Computational neuroanatomy: new perspectives for neuroradiology. Rev.Neurol.(Paris) 2001; 157:797-806.

Gustafsson PE, Nilsson D, Svedin CG. Polytraumatization and psychological symptoms in children and adolescents. Eur.Child Adolesc.Psychiatry 2009; 18:274-283.

Hart H, Rubia K. Neuroimaging of child abuse: a critical review. Front Hum.Neurosci. 2012; 6:52.

Herting MM, Maxwell EC, Irvine C, Nagel BJ. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb.Cortex 2012; 22:1979-1992.

Katz M, Liu C, Schaer M, Parker KJ, Ottet MC, Epps A, Buckmaster CL, Bammer R, Moseley ME, Schatzberg AF, Eliez S, Lyons DM. Prefrontal plasticity and stress inoculation-induced resilience. Dev.Neurosci. 2009; 31:293-299.

Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: clinical implications. Biol.Psychiatry 2000; 48:778-790.

Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, de GG, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu CY, Karam EG, Kawakami N, Lee S, Lepine JP, Ormel J, Posada-Villa J, Sagar R, Tsang A, Ustun TB, Vassilev S, Viana MC, Williams DR. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br.J.Psychiatry 2010; 197:378-385.

Kisiel CL, Lyons JS. Dissociation as a mediator of psychopathology among sexually abused children and adolescents. Am.J.Psychiatry 2001; 158:1034-1039.

Kuhn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol.Psychiatry 2013; 73:70-74.

Lanktree CB, Gilbert AM, Briere J, Taylor N, Chen K, Maida CA, Saltzman WR. Multi-informant assessment of maltreated children: convergent and discriminant validity of the TSCC and TSCYC. Child Abuse Negl. 2008; 32:621-625.

Lim L, Radua J, Rubia K. Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. Am.J.Psychiatry 2014; 171:854-863.

Luciana M. Adolescent brain development in normality and psychopathology. Dev.Psychopathol. 2013; 25:1325-1345.

Marsh R, Gerber AJ, Peterson BS. Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. J.Am.Acad.Child Adolesc.Psychiatry 2008; 47:1233-1251.

McCrory E, De Brito SA, Viding E. Research review: the neurobiology and genetics of maltreatment and adversity. J.Child Psychol.Psychiatry 2010; 51:1079-1095.

McCrory E, De Brito SA, Viding E. The impact of childhood maltreatment: a review of neurobiological and genetic factors. Front Psychiatry 2011; 2:48.

Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, Rutter M, Sonuga-Barke EJ. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. J.Child Psychol.Psychiatry 2009; 50:943-951.

Meng Y, Qiu C, Zhu H, Lama S, Lui S, Gong Q, Zhang W. Anatomical deficits in adult posttraumatic stress disorder: a meta-analysis of voxel-based morphometry studies. Behav.Brain Res. 2014; 270:307-315.

Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci.Lett. 1993; 163:109-113.

Nardo D, Hogberg G, Looi JC, Larsson S, Hallstrom T, Pagani M. Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J.Psychiatr.Res. 2010; 44:477-485.

Nilsson D, Wadsby M, Svedin CG. The psychometric properties of the Trauma Symptom Checklist For Children (TSCC) in a sample of Swedish children. Child Abuse Negl. 2008; 32:627-636.

O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res. 2015; 232:1-33.

Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl) 2011; 214:55-70.

Petersen AC. Adolescent development. Annu.Rev.Psychol. 1988; 39:583-607.

Pine DS. Developmental psychobiology and response to threats: relevance to trauma in children and adolescents. Biol.Psychiatry 2003; 53:796-808.

Rinne-Albers MA, van der Wee NJ, Lamers-Winkelman F, Vermeiren RR. Neuroimaging in children, adolescents and young adults with psychological trauma. Eur.Child Adolesc.Psychiatry 2013.

Scott KM, Koenen KC, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, Benjet C, Bruffaerts R, Caldas-de-Almeida JM, de GG, Florescu S, Iwata N, Levinson D, Lim CC, Murphy S, Ormel J, Posada-Villa J, Kessler RC. Associations between lifetime traumatic events and subsequent chronic physical conditions: a cross-national, cross-sectional study. PLoS.One. 2013; 8:e80573.

Shonkoff JP, Garner AS. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012; 129:e232-e246.

Silverman WK, Ollendick TH. Evidence-based assessment of anxiety and its disorders in children and adolescents. J.Clin.Child Adolesc.Psychol. 2005; 34:380-411.

Silverman WK, Saavedra LM, Pina AA. Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: child and parent versions. J.Am.Acad.Child Adolesc.Psychiatry 2001; 40:937-944.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De LM, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De SN, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23 Suppl 1:S208-S219.

Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 2009; 44:83-98.

Tomoda A, Sheu YS, Rabi K, Suzuki H, Navalta CP, Polcari A, Teicher MH. Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. Neuroimage. 2011; 54 Suppl 1:S280-S286.

Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti IM, Thomas KM, Freed PJ, Booma ES, Gunnar MR, Altemus M, Aronson J, Casey BJ. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev.Sci. 2010; 13:46-61.

Tupler LA, De B. Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. Biol.Psychiatry 2006; 59:523-529.

van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM. Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biol.Psychiatry 2010; 68:832-838.

van Hoof MJ, van Lang ND, Speekenbrink S, van IJzendoorn MH, Vermeiren RR. Adult Attachment Interview differentiates adolescents with Childhood Sexual Abuse from those with clinical depression and non-clinical controls. Attach.Hum.Dev. 2015; 17:354-375.

Vijayakumar N, Whittle S, Yucel M, Dennison M, Simmons J, Allen NB. Prefrontal structural correlates of cognitive control during adolescent development: a 4-year longitudinal study. J.Cogn Neurosci. 2014; 26:1118-1130.

Walsh ND, Dalgleish T, Lombardo MV, Dunn VJ, van Harmelen AL, Ban M, Goodyer IM. General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. Neuroimage.Clin. 2014; 4:308-318.

Wechsler D. Wechsler Adult Intelligence Scale. San Antonio, TX: The Psychological Corporation, 1991.

Wechsler D. Wechsler Intelligence Scale for Children. San Antonio, TX: The Psychological Corporation, 1997.

Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 2008; 18:729-736.

Chapter 4 CORTICAL THICKNESS

Preserved cortical thickness, surface area and volume in adolescents with PTSD after childhood sexual abuse

Mirjam A. Rinne-Albers, Charlotte P. Boateng, Steven J. van der Werff, Francien Lamers-Winkelman, Serge A. Rombouts, Robert R. Vermeiren, Nic J. van der Wee

Scientific Reports, 2020, 20: 3266

Abstract

Exposure to childhood adverse events is associated with severe consequences for general health and structural and functional changes in the brain of its survivors. In order to unravel and in the end influence the pathway linking adversity and pathology, neuroimaging research is crucial. Up till now studies in minors are scarce and differ in type of adversity or methodology. Almost all studies report lower cortical thickness, but in a broad variety of regions. In this study we investigated cortical thickness measures and clinical data in a well circumscribed group of adolescents with PTSD related to childhood sexual abuse (CSA) (N=21) and a healthy non-traumatised control group (N=21). The ventromedial PFC (vmPFC), ACC, insula, and middle / superior temporal gyrus were chosen as ROI's due to their respective roles in emotion and information processing. No significant effect of group was found for cortical thickness, surface area or volume in any of the ROIs. This is in line with the results of research in adult women with sexual abuse related PTSD, suggesting that this may be specific to this group, independent of age. Recent research points to differential biological and pathological consequences of different types of childhood adversity.

1. Introduction

The experience of traumatic events in childhood is a strong predictor of psychiatric and somatic pathology later in life[1-3], with substantial consequences for general health[4,5]. Recent epigenetic research further demonstrated the substantial impact of stress and trauma on the next generation[6]. In order to counter the negative effects of childhood psychological trauma, it is necessary to understand the neurobiological processes related to these trajectories. Results from preclinical and human studies link stress hormones like cortisol to structural changes in the brain, reflecting underlying alterations in neuron density and microstructure[7-9]. Psychological processes like threat processing, heightened emotional reactivity and altered emotional learning are thought to mediate between trauma exposure , structural changes in the brain and later psychopathology[10]. Understanding the developing and still malleable child or adolescent brain after trauma could provide an approach for thwarting negative consequences, particularly because even the adult brain is considered to be susceptible for structural changes after therapeutic interventions[11,12]. Structural neuroimaging research in traumatised children and adolescents may help to elucidate the effects of childhood adverse events on brain development, however, up till this moment such studies are scarce[13].

Meta-analyses of structural MRI studies in adults with PTSD have reported smaller gray matter volume (GMV) in emotion and threat processing structures like the hippocampus, the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC)[14,15]. Apart from a smaller corpus callosum (CC), results of structural MRI studies in traumatised C&A however, are mixed and inconclusive[16]. Results from neuroimaging studies in adult victims of childhood trauma thus differ from findings in traumatised minors. While studies in adults with a history of childhood abuse or neglect consistently report smaller volume of the hippocampus compared to non-traumatised controls, this has not been replicated in minors[17,18]. In contrast, the decrease in volume of the corpus callosum, has consistently been reported in children and adolescents, but not in adults who have experienced childhood trauma[19,20]. Clearly, more research is needed in order to understand the neurodevelopmental trajectories related to trauma leading to the negative consequences in adulthood.

This study is part of the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA) project. Earlier research with the same groups, using VBM (Voxel Based Morphometry), DTI (Diffusion Tensor Imaging) and functional MRI techniques, have been published [20-27] Cortical thickness is a

relatively new neuroimaging analysis technique, which is considered complementary to VBM in studying grey mater integrity[28].

Smaller cortical thickness in adult traumatised populations, mostly PTSD patients, has been reported in various brain regions like the mPFC, the ACC, the insula, and the superior and middle temporal gyrus[29-32]. Some studies even found an inverse correlation between cortical thickness and symptom severity[29,33]. A study in adult women with sexual abuse related PTSD, similar to our adolescent group, showed normal cortical thickness compared to healthy controls[34]. Greater cortical thickness has been associated with resilience in adults[35,36]. For those reasons, it is relevant to study cortical thickness in traumatised children and adolescents as well.

Cortical thickness studies in traumatised minors are, however, limited and show little concordance. To our knowledge there are only ten studies on cortical thickness in traumatised minors, almost all adolescents. In contrast to adult trauma research only two of these ten studies report about PTSD patients[37,38], the others included minors having experienced different types of adversity. Studies found smaller cortical thickness, but not consistently, in several regions including the mPFC[39-43], ACC[37,44,45], insula[37,38,46] temporal regions[39,40,42], other frontal regions[40,43-46] parahippocampal regions [40] and parietal regions [42,43] Exceptions are reported by Whittle et al.[43] who compared maltreated with non-maltreated adolescents and found an association of maltreatment with accelerated as well as less thinning in frontal and precentral regions, and by Ahmed et al.[37] who compared traumatised adolescents with and without PTSD and reported no significant difference in cortical thickness between groups in the insula, ACC, amygdala, CC and hippocampus using Freesurfer technique and a reduction in insula thickness when using Qdec. No clear distinction can be made between results from studies with inclusion based on the presence of PTSD or the presence of different types of trauma. Results of studies may vary due to differences in age and type of adversity.

In order to further elucidate the impact of trauma on the developing brain, we decided to examine cortical thickness, surface area and volume in our EPISCA sample, a well-defined group of adolescents with posttraumatic stress disorder based on childhood sexual abuse (CSA) with measures in non-traumatised controls. Based on the literature, we hypothesized differences in the following regions of interest (ROIs): the ventromedial PFC (vmPFC), ACC, insula, and middle / superior temporal gyrus, regions that are considered to play a role in emotion and information processing.

2. Methods

2.1 Participants

Participants were selected from the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA). EPISCA is a longitudinal MRI study in which adolescents with clinical depression, adolescents with a history of sexual trauma and healthy controls were followed over a six-month period in which they received treatment. The adolescents were assessed and underwent scanning at three time points: upon inclusion at baseline, three months after baseline, and six months after baseline[21,47]. The current study reports on cross-sectional baseline data from the adolescents with a history of sexual trauma and healthy non-traumatised controls. See also previous reports from neuroimaging research with the same population[20-27]. Inclusion criteria for the adolescents with a history of sexual trauma were: having experienced sexual abuse during their lifetime more than once by one or more perpetrators inside or outside the family, and being referred for treatment to the Psychotrauma Center of mental health institute GGZ Rivierduinen in Leiden or the child and adolescent psychotrauma center KJTC in Haarlem, both located in the Netherlands. Experienced psychotherapists in these specialised psychotrauma centers obtained the trauma histories from the

adolescents as well as from their caregivers during clinical interviews. To objectify any abuse or neglect as well as risk for functional impairment and morbidity, we verified police reports, involvement of child welfare, and family custody or other child protection measures as to have an estimate of the severity and impact of problems. (For more details about the participants in the CSA-group see van Hoof et al., 2015[47].)

Presence of PTSD was not an inclusion criterion, although clinical assessments (see below) showed that all patients but one were diagnosed with PTSD related to CSA. Inclusion criteria for the control group were: no current or past DSM-IV classifications, no clinical scores on validated mood and behavioural questionnaires, no history of traumatic experiences, and no current psychotherapeutic and/or psychopharmacological intervention of any kind. Exclusion criteria for all participants were: primary DSM-IV clinical diagnosis of attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), pervasive developmental disorders, Tourette's syndrome, obsessive–compulsive disorder, bipolar disorder, and psychotic disorders; current use of psychotropic medication other than stable use of SSRI's, or amphetamine medication, but not on the day of scanning; current substance abuse; history of neurological disorders or severe head injury; age <12 or >21 years; pregnancy; left-handedness; IQ score <80 as measured by the Wechsler Intelligence Scale for Children (WISC) [48]or adults[49]; and general MRI contraindications.
Fifty-four participants were included in the study: 32 healthy non-traumatised controls and 22 patients with a history of sexual trauma. From this group, two controls were excluded because of technical problems during scanning or poor imaging data quality, one participant with CSA because of complete segmentation failure. One control was excluded due to high scores on clinical symptom rating scales, and one control was excluded due to a history of sexual trauma that was not reported until the day of scanning. This resulted in a final sample of 21 adolescents with CSA and 28 controls. Of the 21 CSA-participants, 20 fulfilled all PTSD criteria on the ADIS, while one had sufficient PTSD symptoms, but with limited interference. Since earlier research showed that persons with sub threshold PTSD in many aspects resemble PTSD patients, we decided to include this patient in the (CSA-related) PTSD group[50].
The study was approved by the Medical Ethics Committees of the Leiden University Medical Center and written informed assent and consent was obtained from the participants and their parents respectively.

2.2 Clinical Assessment

A standardized set of instruments was used to assess symptomatology in both groups of adolescents.

The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS-C/P)[51] are semi structured interviews for the classification of DSM-IV anxiety and depressive disorders in children. Classification is reached by a minimal interference score of 4 obtained by trained examiners based on the ADIS-C and ADIS-P. The ADIS is known to have good reliability and validity[52] with reported strong test–retest reliability statistics for the ADIS-C/P for combined diagnoses (.80–.92) and individual diagnoses (.62–.88). The Trauma Symptom Checklist for Children (TSCC)[53] is a 54-item self-report for children and adolescents aged 8 through 18 but often used up to 21 years[54,55] which measures trauma-related symptoms. On a 4-point scale (never to almost all of the time), the adolescent indicates how often a thought, a feeling or a behaviour occurs. The items are grouped into six clinical scales. The clinical scales are Anxiety (Anx), Depression (Dep), Post-traumatic Stress (Pts), Sexual Concerns (Sc), Dissociation (Dis) and Anger (Ang). The TSCC total score is used as the main measure on post-traumatic symptomatology. Cronbach's alpha coefficients reported range from .77 to .89 for subscales and .84 for the total scale. The questionnaire has extensively been studied, which has confirmed its good psychometric qualities[56,57]. The internal consistency of the TSCC subscales varied between .85 and .94, except for the Sexual Concerns subscale that measured .68.

The Adolescent Dissociative Experiences Scale (A-DES) contains 30 items to assess adolescents of 11-18 years of age for pathological dissociation. The A-DES items inquire about four domains reflecting basic aspects of dissociation: experiences of dissociative amnesia, depersonalization /derealisation, absorption/imaginative involvement and passive influence. The items are rated by the adolescent on an 11-point Likert-scale ranging from 0 = "never" to 10 = "always" with no midpoint scores. The total A-DES score is based on the mean of all item scores. A mean score of 4 or above on the A-DES signifies pathological dissociation[58]. The scale has good internal reliability and validity.
As brain development is known to be influenced by sexual development, corporal sexual development was measured with the self-report Puberty Development Scale[59]. The PDS consists of 5 items that are measured on a 5-point scale by the examiner: 1= pre-pubertal, 2= early pubertal, 3= mid-pubertal, 4= late pubertal, 5= post-pubertal. The PDS is considered a valuable instrument determining pubertal stage[60,61].
Six subscales from the Wechsler Intelligence scales scores (picture completion, similarities, picture concepts, arithmetic, block design and comprehension) were converted into Full IQ estimates[21,47].
All methods were performed in accordance with the relevant guidelines and regulations.

2.3 MRI data acquisition

Images were acquired on a Philips 3T magnetic resonance imaging system (Philips Healthcare, Best, The Netherlands), equipped with a SENSE-8 head coil. Scanning took place at the Leiden University Medical Center. Prior to scanning, all participants were introduced to the scanning situation by lying in a dummy scanner and hearing scanner sounds. For each subject, a sagittal 3-dimensional gradient-echo T1-weighted image was acquired (repetition time = 9.8 ms; echo time = 4.6 ms; flip angle = 8°; 140 sagittal slices; no slice gap; field of view =256 x 256 mm; 1.17 x 1.17 x 1.2 mm voxels; duration = 4:56 min) as part of a larger, fixed imaging protocol.

2.4 Image processing and analysis

Cortical parcellations of 68 cortical grey matter regions, 34 regions in each cerebral hemisphere, were performed using FreeSurfer (Software version 5.3.0) based on the Desikan-Killiany atlas. In addition, two whole-hemisphere measures were extracted using FreeSurfer. The segmentations of all 68 cortical grey matter regions and the two whole-hemisphere measures were followed by a statistical outlier assessment and a visual inspection for artefacts and abnormal clinical findings, which was done independently by three different researchers using standardized ENIGMA-protocol: http://enigma.ini.usc.edu/protocols/imaging-protocols/protocol-for-quality-control-and-summary-statistics/ After visual inspection, both the left and right insula were excluded from further analyses due to frequent inadequate or complete failure of segmentation.

2.5 Statistical analyses

Statistical analyses for all data were performed with the Statistical Package for Social Sciences Software (SPSS, version 25). Demographic and clinical characteristics were analysed using independent-sample t-tests. If the data did not meet the assumptions necessary for parametric analyses, which was the case for the total scores on the A-DES and TSCC, the non-parametric Mann-Whitney U-test was used. Categorical variables were assessed with the Chi-square test. All tests were performed with the significance set at $p < 0.05$.
Total volume for each ROI was calculated by multiplying cortical thickness with surface area. The effect of PTSD on cortical morphometric measures in all ROIs was tested using a multivariate analyses of covariance (MANCOVA). Considering that age and intracranial volume are strongly correlated with cortical measures, both were included as covariates[62]. In line with previous research, puberty development (PDS score) was also accounted for in the model[20]. Three separate MANCOVAs

were used to assess group differences, one for cortical thickness, one for surface area and one for volume of the selected ROI as dependent factors. Therefore, we corrected for multiple testing by dividing the p-value of .05 by 3 (p <.017). The ROIs included left and right ACC (caudal and rostral ACC in Freesurfer) , middle temporal gyrus, superior temporal gyrus, vmPFC (medial orbitofrontal cortex in FreeSurfer). (Figure 1.) Post-hoc, between-group effects were correlated with symptom severity scores within the CSA-related PTSD group. Post-hoc, between-group effects were correlated with symptom severity scores within the CSA-related PTSD group.

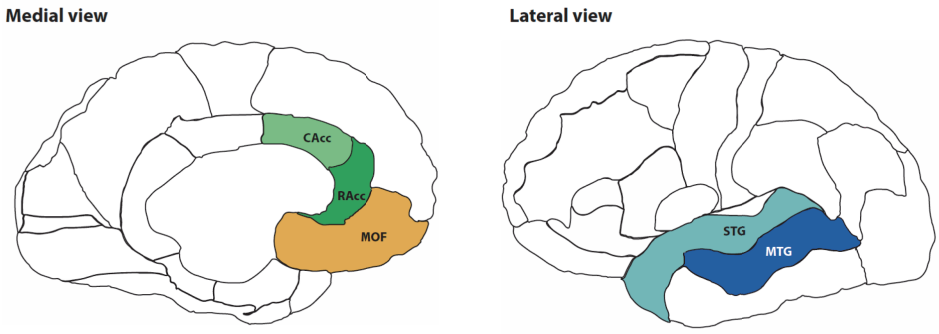


Figure 1. Regions of Interest (ROIs): medial orbitofrontal (MOF), caudal anterior cingulate cortex (CAcc), rostral anterior cingulate cortex (RAcc), superior temporal gyrus (STG), middle temporal gyrus (MTG). The left and right insula were excluded from further analyses due to frequent inadequate or complete failure of segmentation.

3. Results

3.1 Sample characteristics

The means and standard deviations of demographic and clinical characteristics are presented in table 1. The majority of participants was female (85.7%). The adolescents with CSA-related PTSD had a significantly lower TIQ (mean 99.3, SD 8.8) than controls (mean 107.0, SD 8.3) [t(47)= -3.120, p= 0.003]. In addition, adolescents with PTSD (mean 16.4, SD 2.0) were significantly older than controls (mean 15.2, SD 1.6) [t (47)=-2.338, p= 0.024]. As expected, there was a significant difference between the total scores on the A-DES and TSCC between adolescents with CSA-related PTSD and healthy non-traumatised controls, with a higher mean total score for CSA-participants. There was one adolescent in the CSA-related PTSD group with comorbid anxiety disorder not otherwise specified. Among the adolescents with CSA, 2 adolescents were on SSRI treatment and 2 used amphetamines, the latter were not used on the day of the MRI scan.

Table 1. Sample characteristics: Means and SD of age, TIQ, total scores of ADES, total scores of TSCC, and numbers per gender and PDS ratings.

		CSA-related PTSD		Controls		Group comparison
		N= 21		N = 28		
			SD		SD	p
Gender (f : m)		18:3		24:4		
Age (years)		16.4	2.1	15.2	1.6	0.024
TIQ		99.3	8.8	107.0	8.3	0.003
PDS	Pre/mid pubertal	1		8		0.020
	Late pubertal	10		14		
	Post pubertal	10		6		
A-DES[1]	Total score	72.6	58.8	22.3	19.7	0.001
TSCC[1]	Total score	47.9	2.5	17.4	13.6	0.000 0,000002

Abbreviations: CSA, Childhood Sexual Abuse; PTSD, Post Traumatic Stress Disorder; TIQ, Total Intelligence Quotient; PDS, Puberty Development Scale; A-DES, Adolescent Dissociative Experiences Scale; TSCC, Trauma Symptom Checklist for Children.
[1]4 did not complete the A-DES and TSCC.

3.2 Cortical thickness, surface area and volume

Differences in cortical thickness, surface area and volume between adolescents with CSA-related PTSD and non-traumatised controls were assessed in the selected ROI. Overall, no significant effect of group was found in the MANCOVAs for cortical thickness ($F(10,35) = 1.130$, $p=0.369$) (Table 2.), surface area ($F(10,35) = 0.850$, $p=0.586$) (Table 3.) or volume ($F(10,35) = 1.050$, $p=0.425$) (Table 4.). Excluding the 2 CSA-participants that were using medication from the analyses did not change the results.

Also, excluding the one CSA-participant with sufficient PTSD symptoms, but limited interference from the analyses, did not change the results. As the CSA-related PTSD group had a significant lower TIQ than the controls, we report correlations with IQ within groups in the Supplementary Material Table S1. There were no significant correlations.
There were significant correlations between PDS scores and age (Pearson's r.632; p .001) and between PDS scores and ICV age (Pearson's r-.298; p .005). There was no significant correlation between age and ICV (Pearson's r-.250). The variance inflation factor (VIF) between these three variables varied between 1.07 and 1.66, which indicates that there was low multicollinearity. As age, ICV and PDS were all included as covariates in the primary model, we did not perform any post hoc analysis in which one of these covariates was omitted. In addition, in post hoc analysis we tested for associations between structural brain measures and TSCC and ADES scores. These analyses only showed a significant overall correlation between regional volume and TSCC score. However, this result failed to reach significance when correcting for multiple comparisons. (Supplementary Material Table S2.) Post hoc, we performed a power analysis based on comparable studies in the literature and concluded that the effect size is in the range of comparable studies. (Suplementary Material Analysis A1.)

3.3 Whole brain analysis

The exploratory whole-brain analysis did not reveal any overall differences in cortical thickness, surface area and volume between CSA-related PTSD and controls (cortical thickness ($F(1,44) = 1.093$, $p=0.656$), surface area ($F(1,44) = 0.885$, $p=0.706$) or volume ($F(1,44) = 3.596$ $p=0.339$)). Also, there were no significant regional differences when corrected for multiple comparisons.

Table 2. Contributions of each ROI's cortical thickness

ROI	Cortical thickness (mm)		F-value	P-value
	CSA-related PTSD	Controls		
Left hemisphere				
Caudal anterior cingulate cortex	3.13 (0.32)	3.10 (0.23)	0.872	0.355
Rostral anterior cingulate cortex	3.26 (0.20)	3.25 (0.21)	0.043	0.837
Middle temporal gyrus	3.03 (0.20)	3.12 (0.13)	2.495	0.121
Superior temporal gyrus	2.94 (0.22)	3.00 (0.15)	0.186	0.668
Medialorbitofrontal cortex	2.70 (0.23)	2.76 (0.13)	1.337	0.254
Right hemisphere				
Caudal anterior cingulate cortex	2.92 (0.32)	3.05 (0.27)	1.334	0.254
Rostral anterior cingulate cortex	3.21 (0.26)	3.28 (0.23)	0.473	0.495
Middle temporal gyrus	3.17 (0.21)	3.24 (0.12)	0.366	0.548
Superior temporal gyrus	2.98 (0.18)	3.06 (0.20)	1.405	0.242
Medialorbitofrontal cortex	2.79 (0.25)	2.83 (0.19)	0.387	0.537

Abbreviations: CSA, Childhood Sexual Abuse; PTSD, Post Traumatic Stress Disorder

Table 3. Contributions of each ROI's surface area

ROI	Surface area (mm^2)		F-value	P-value
	CSA-related PTSD	Controls		
Left hemisphere				
Caudal anterior cingulate cortex	586.05 (78.39)	697.79 (186.17)	6.041	0.018
Rostral anterior cingulate cortex	774.38 (124.50)	844.39 (135.67)	2.078	0.156
Middle temporal gyrus	2962.71 (431.81)	2972.75 (310.94)	0.408	0.526
Superior temporal gyrus	3667.33 (492.02)	4776.43 (438.840)	1.375	0.247
Medialorbitofrontal cortex	1872.00 (249.75)	1918.14 (241.51)	0.083	0.774
Right hemisphere				

Caudal anterior cingulate cortex	707.00 (199.30)	789.61 (207.27)	3.424	0.071
Rostral anterior cingulate cortex	634.71 (149.35)	672.39 (133.16)	0.735	0.396
Middle temporal gyrus	3301.52 (416.79)	3370.64 (410.00)	0.176	0.677
Superior temporal gyrus	3657.48 (453.63)	3706.11 (369.80)	0.316	0.577
Medialorbitofrontal cortex	1815.00 (179.90)	1851.89 (212.56)	0.230	0.634

Abbreviations: CSA, Childhood Sexual Abuse; PTSD, Post Traumatic Stress Disorder

Table 4. Contributions of each ROI's volume

ROI	Volume (mm^3)		F-value	P-value
	CSA-related PTSD	Controls		
Left hemisphere				
Caudal anterior cingulate cortex	1837.66 (329.66)	2153.61 (542.50)	3.548	.066
Rostral anterior cingulate cortex	2518.97 (400.07)	2737.07 (443.40)	1.720	.196
Middle temporal gyrus	8976.41 (1450.26)	9268.04 (1009.68)	0.994	.324
Superior temporal gyrus	11329.50 (1454.24)	10792.39 (1716.97)	0.070	.793
Medialorbitofrontal cortex	5029.51 (659.21)	5290.88 (701.20)	1.294	.261
Right hemisphere				
Caudal anterior cingulate cortex	2055.94 (382.21)	2391.11 (575.40)	4.574	.038
Rostral anterior cingulate cortex	2016.65 (391.04)	2196.90 (407.44)	1.879	.177
Middle temporal gyrus	10430.92 (1342.12)	10950.74 (1531.57)	0.558	.459
Superior temporal gyrus	10894.72 (1387.98)	11353.58 (1475.05)	0.611	.439
Medialorbitofrontal cortex	5072.61 (688.89)	5248.09 (633.89)	1.548	0.220

Abbreviations: CSA, Childhood Sexual Abuse; PTSD, Post Traumatic Stress Disorder

Discussion

This study investigated cortical thickness, surface area and volume in a group of adolescents with CSA-related PTSD and a group of healthy non-traumatised controls. In contrast to our hypothesis, we found no significant difference between the two groups on any cortical morphometric measure in the ventromedial prefrontal cortex, anterior cingulate gyri, middle temporal gyri and superior temporal gyri.

To our knowledge this is the first study investigating cortical thickness in a group of minors with childhood sexual abuse. Up to this moment, cortical thickness studies in traumatised children and adolescents are scarce and mostly report smaller cortical thickness, but in a broad variety of regions. There are many methodological differences that hamper direct comparison of these studies, including selection of participants and controls, type of abuse, imaging parameters and methodology. There is one other study in minors, investigating traumatised adolescents with and without PTSD, which reported no abnormalities in cortical thickness in the insula, ACC, amygdala, CC and hippocampus[37]. However, in contrast to our study, this study included various types of trauma. Our previous VBM study in the same population of the EPISCA project found smaller volumes of the dorsal ACC compared to healthy controls[23]. The current study does not implicate the ACC, but has used a different technique with a different delineation of cortical areas, which might explain the discrepancy in results.

Studies in traumatised adults, mostly in male war veterans with PTSD, consistently show reduced cortical thickness in several regions, such as the ACC and mPFC. In traumatised minors smaller ACC volume is not consistently reported[13]. Remarkably, however, the only study in a sample of adult women with sexual abuse related PTSD by Landré et al, similar to our study found normal cortical thickness compared to healthy controls[34]. The authors hypothesize that apart from gender, the specific type of trauma (i.e. sexual abuse versus combat related) might explain this difference with most other studies on trauma in adults. Interestingly, Heim et al. studied the cortical thickness in a sample of adult women with different forms of childhood abuse. They found in their adult sample that childhood sexual abuse was specifically associated with thinning of the somatosensory cortex representing the clitoris and the surrounding female genital area. In contrast to our study, they used a vertex based whole brain analysis and their sample consisted of adult women with CSA with and without depression or PTSD, potentially including resilient women[63].

Apart from the methodological heterogeneity of studies, the dynamics of growth and development typically appearing in the brains of children and adolescents may in part explain the equivocal results in the literature. (See for example Weems et al. for the development of the amygdala in youth in relation to stress[64]).

In general, there is a growing awareness that different types of adversity may have different neurobiological sequelae and subsequent psychiatric and somatic disorders[65,66]. For instance, dysregulation of the immune system has been suggested by recent research as a possible biological mediator between adverse childhood experiences (ACE) and adulthood pathology. Baumeister et al., in a recent meta-analysis, conclude that there is strong evidence for the impact of ACE on the inflammatory immune system, where specific types of trauma (sexual, physical or emotional abuse) differentially impact on specific inflammatory markers and potentially pathogenic pro-inflammatory phenotypes associated with physical and mental illnesses[67]. The increased immune activation might be caused by changes in epigenetic regulation of gene expression. This appears plausible because of the considerable evidence for association of modifications of HPA- and neuroplasticity-related methylation patterns with childhood trauma[68]. Trauma specific research could thus contribute to

more explicit implementation of interventions that reduce long term risks of childhood adversity and help defining specific treatments for children and adult survivors with psychopathology.
We believe that our study has several strengths. Although this was not an inclusion criterion, all participants in our study met DSM-IV criteria for PTSD, signalling that it is a clinically robust group. This study is part of the EPISCA project, in which we investigated the same groups with other structural and functional neuroimaging techniques that yielded results that were in line with the existing literature[20-25]. The homogeneous and well circumscribed sample of adolescents with CSA-related PTSD is a strength of this study. Some limitations should be mentioned. The CSA-related PTSD group in this study was significantly older than the control group and also more advanced in pubertal development. Longitudinal studies of typical adolescent brain development, however, show little change in most of our ROIs (mPFC, ACC, middle / sup temp gyrus) within the age range of participants of both groups[69]. Furthermore, we controlled for age and pubertal development in our analyses. In the statistical analysis we also controlled for total intracranial volume. Full-scale IQ measures were significantly lower in the CSA-related PTSD group than in the control group. As PTSD has been shown to supress IQ values, groups might originally have been more equal with respect to intellectual ability[70]. Brain development as well as the reaction to trauma is known to be susceptible to gender influences . We could not address this topic because our participants were mainly girls. Finally, as in our study several of the perpetrators of the CSA adolescents were family members, it was not possible to reliably assess timing and frequency of the traumatic experience retrospectively.

In conclusion, we found no differences in cortical measures between a group of adolescents with CSA-related PTSD and healthy non-traumatised controls. These findings support the suggestion that different types of adversity may have different neurobiological sequelae and subsequent psychiatric and somatic disorders. As childhood trauma is a highly relevant issue for society with severe consequences for psychological and general health, more and preferably longitudinal research into the neurobiological sequelae is needed.

Supplementary Material

Supplementary Material Table S1. **MANCOVA: Correlation of IQ**
CSA Group: 21
Thickness (F(10,10) =1.917, p=0.160) (Wilks' Lambda)
SA (F(10,10) = 1.755, p=0.194) (Wilks' Lambda)
Volume (F(10,10) = 1.324, p=0.333) (Wilks' Lambda)

Thickness	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,049	,827
Rostral anterior cingulate cortex	1,182	,290
Middle temporal gyrus	2,824	,109
Superior temporal gyrus	5,717	,027
Medialorbitofrontal cortex	,267	,611
Right hemisphere		
Caudal anterior cingulate cortex	1,247	,278
Rostral anterior cingulate cortex	2,009	,173
Middle temporal gyrus	12,388	,002
Superior temporal gyrus	2,620	,122
Medialorbitofrontal cortex	,689	,417

Surface area	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,474	,499
Rostral anterior cingulate cortex	,044	,835
Middle temporal gyrus	,124	,729
Superior temporal gyrus	,036	,852
Medialorbitofrontal cortex	,067	,799
Right hemisphere		
Caudal anterior cingulate cortex	1,632	,217
Rostral anterior cingulate cortex	,018	,896
Middle temporal gyrus	,383	,543
Superior temporal gyrus	,014	,907
Medialorbitofrontal cortex	,159	,694

Volume	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,453	,509
Rostral anterior cingulate cortex	,475	,499
Middle temporal gyrus	,457	,507
Superior temporal gyrus	1,062	,316
Medialorbitofrontal cortex	1,400	,251
Right hemisphere		
Caudal anterior cingulate cortex	3,597	,073
Rostral anterior cingulate cortex	,770	,391
Middle temporal gyrus	,043	,838
Superior temporal gyrus	,573	,458
Medialorbitofrontal cortex	,460	,506

Control group: 28
Thickness (F(10,17) =0.747, p=0.811) (Wilks' Lambda)
SA (F(10,17) = 1.399, p=0.261) (Wilks' Lambda)
Volume (F(10,17) = 0.998, p=0.482) (Wilks' Lambda)

Thickness	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	1,653	,210
Rostral anterior cingulate cortex	,006	,940
Middle temporal gyrus	,180	,675
Superior temporal gyrus	,013	,911
Medialorbitofrontal cortex	2,138	,156
Right hemisphere		
Caudal anterior cingulate cortex	,799	,380
Rostral anterior cingulate cortex	4,186	,051
Middle temporal gyrus	,030	,865
Superior temporal gyrus	,057	,814
Medialorbitofrontal cortex	,270	,608

Surface area	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	1,023	,321
Rostral anterior cingulate cortex	1,640	,212
Middle temporal gyrus	1,264	,271
Superior temporal gyrus	2,347	,138
Medialorbitofrontal cortex	,129	,723
Right hemisphere		
Caudal anterior cingulate cortex	,008	,927
Rostral anterior cingulate cortex	,525	,475
Middle temporal gyrus	,624	,437
Superior temporal gyrus	,010	,922
Medialorbitofrontal cortex	,001	,970

Volume	**F-value**	**P-value**
Left hemisphere	,403	,531
Caudal anterior cingulate cortex	1,921	,177
Rostral anterior cingulate cortex	,009	,926
Middle temporal gyrus	,861	,362
Superior temporal gyrus	1,856	,185
Medialorbitofrontal cortex	,055	,817
Right hemisphere		
Caudal anterior cingulate cortex	2,293	,142
Rostral anterior cingulate cortex	,081	,779
Middle temporal gyrus	,510	,482
Superior temporal gyrus	,037	,850
Medialorbitofrontal cortex	,403	,531

Supplementary Material Table S2. **MANCOVA: Correlation with ADES/TSCC within CSA group**

ADES: subjects = 18
Thickness (F(10,7) =0.503, p=0.843) (Wilks' Lambda)
SA (F(10,7) = 0.549, p=0.812) (Wilks' Lambda)
Volume (F(10,7) = 0.878, p=0.588 (Wilks' Lambda)

Thickness	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	4,565	,048
Rostral anterior cingulate cortex	4,418	,052
Middle temporal gyrus	,102	,754
Superior temporal gyrus	,175	,681
Medialorbitofrontal cortex	2,216	,156
Right hemisphere		
Caudal anterior cingulate cortex	,015	,903
Rostral anterior cingulate cortex	,248	,625
Middle temporal gyrus	,133	,720
Superior temporal gyrus	,632	,438
Medialorbitofrontal cortex	,172	,684

Surface area	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,028	,869
Rostral anterior cingulate cortex	1,559	,230
Middle temporal gyrus	7,195	,016
Superior temporal gyrus	,875	,363
Medialorbitofrontal cortex	3,560	,077
Right hemisphere		
Caudal anterior cingulate cortex	2,959	,105
Rostral anterior cingulate cortex	,653	,431
Middle temporal gyrus	3,568	,077
Superior temporal gyrus	2,994	,103
Medialorbitofrontal cortex	2,478	,135

Volume	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,783	,389
Rostral anterior cingulate cortex	,233	,636
Middle temporal gyrus	,815	,380
Superior temporal gyrus	4,315	,054
Medialorbitofrontal cortex	,384	,544
Right hemisphere		
Caudal anterior cingulate cortex	2,146	,162
Rostral anterior cingulate cortex	1,156	,298
Middle temporal gyrus	,699	,415
Superior temporal gyrus	2,792	,114
Medialorbitofrontal cortex	1,548	,231

TSCC: subjects = 18
Thickness (F(10,7) = 0.758, p=0.666) (Wilks' Lambda)
SA (F(10,7) = 2.069, p=0.173) (Wilks' Lambda)
Volume (F(10,7) = 4.790, p=0.025) (Wilks' Lambda) (multiple comparisons = 0.05/3)

Thickness	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	8,370	,011
Rostral anterior cingulate cortex	2,858	,110
Middle temporal gyrus	,250	,624
Superior temporal gyrus	,055	,817
Medialorbitofrontal cortex	,451	,511
Right hemisphere		
Caudal anterior cingulate cortex	,109	,746
Rostral anterior cingulate cortex	1,014	,329
Middle temporal gyrus	,029	,867
Superior temporal gyrus	,003	,957
Medialorbitofrontal cortex	,180	,677

Surface area	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,604	,448
Rostral anterior cingulate cortex	1,687	,212
Middle temporal gyrus	16,670	,001
Superior temporal gyrus	1,251	,280
Medialorbitofrontal cortex	2,154	,162
Right hemisphere		
Caudal anterior cingulate cortex	5,167	,037
Rostral anterior cingulate cortex	,489	,494
Middle temporal gyrus	6,541	,021
Superior temporal gyrus	3,030	,101
Medialorbitofrontal cortex	4,118	,059

Volume	**F-value**	**P-value**
Left hemisphere		
Caudal anterior cingulate cortex	,568	,462
Rostral anterior cingulate cortex	,383	,545
Middle temporal gyrus	1,035	,324
Superior temporal gyrus	15,345	,001
Medialorbitofrontal cortex	1,194	,291
Right hemisphere		
Caudal anterior cingulate cortex	2,539	,131
Rostral anterior cingulate cortex	1,359	,261
Middle temporal gyrus	3,134	,096
Superior temporal gyrus	7,222	,016
Medialorbitofrontal cortex	2,949	,105

Supplementary Material Analysis A1. **Poweranalysis**

N = 21 CSA, 28 controls (total = 49)

Sensitivity: compute required effect size: given alpha 0.05, power 0.95 and total sample size 49. Number of groups = 2, response variables = 10. Effect size = 0.63.
Meta-analysis by O'Doherty (1), medium to large effect sizes (0.5-0.8) (1). Number of groups =2, response variables = 1. Total sample size: 60.

(1) O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res. 232[1], 1-33. 4-30-2015.

Reference List

1 Anda, R. F. *et al.* The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur. Arch. Psychiatry Clin. Neurosci* **256**, 174-186, doi:10.1007/s00406-005-0624-4 [doi] (2006).

2 Kessler, R. C. *et al.* Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br. J. Psychiatry* **197**, 378-385, doi:10.1192/bjp.bp.110.080499 [doi] (2010).

3 MacMillan, H. L. *et al.* Childhood abuse and lifetime psychopathology in a community sample. *Am. J. Psychiatry* **158**, 1878-1883 (2001).

4 Gilbert, R. *et al.* Burden and consequences of child maltreatment in high-income countries. *Lancet* **373**, 68-81, doi:10.1016/S0140-6736(08)61706-7 [doi] (2009).

5 Shonkoff, J. P. Protecting brains, not simply stimulating minds. *Science* **333**, 982-983, doi:10.1126/science.1206014 [doi] (2011).

6 Provencal, N. & Binder, E. B. The neurobiological effects of stress as contributors to psychiatric disorders: focus on epigenetics. *Curr. Opin. Neurobiol* **30**, 31-37, doi:10.1016/j.conb.2014.08.007 [doi] (2015).

7 Sanchez, M. M., Ladd, C. O. & Plotsky, P. M. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev. Psychopathol* **13**, 419-449 (2001).

8 Kaufman, J., Plotsky, P. M., Nemeroff, C. B. & Charney, D. S. Effects of early adverse experiences on brain structure and function: clinical implications. *Biol. Psychiatry* **48**, 778-790, (2000).

9 McCrory, E., De Brito, S. A. & Viding, E. Research review: the neurobiology and genetics of maltreatment and adversity. *J. Child Psychol. Psychiatry* **51**, 1079-1095, doi:10.1111/j.1469-7610.2010.02271.x [doi] (2010).

10 McLaughlin, K. A. & Lambert, H. K. Child Trauma Exposure and Psychopathology: Mechanisms of Risk and Resilience. *Curr. Opin. Psychol* **14**, 29-34, doi:10.1016/j.copsyc.2016.10.004 [doi] (2017).

11 Davidson, R. J. & McEwen, B. S. Social influences on neuroplasticity: stress and interventions to promote well-being. *Nat. Neurosci* **15**, 689-695, doi:10.1038/nn.3093 [doi] (2012).

12 Thomaes, K. *et al.* Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. *J. Psychiatr. Res* **50**, 1-15, doi:;10.1016/j.jpsychires.2013.11.002 [doi] (2014).

13 Rinne-Albers, M. A., van der Wee, N. J., Lamers-Winkelman, F. & Vermeiren, R. R. Neuroimaging in children, adolescents and young adults with psychological trauma. *Eur. Child Adolesc. Psychiatry* **22**, 745-755, doi:10.1007/s00787-013-0410-1 [doi] (2013).

14 Kuhn, S. & Gallinat, J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. *Biol. Psychiatry* **73**, 70-74, doi:10.1016/j.biopsych.2012.06.029 [doi] (2013).

15 O'Doherty, D. C., Chitty, K. M., Saddiqui, S., Bennett, M. R. & Lagopoulos, J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Res* **232**, 1-33, doi:10.1016/j.pscychresns.2015.01.002 [doi] (2015).

16 Rinne-Albers, M. A., van der Wee, N. J., Lamers-Winkelman, F. & Vermeiren, R. R. Neuroimaging in children, adolescents and young adults with psychological trauma. *Eur Child Adolesc Psychiatry* **22**, 745-755, doi:10.1007/s00787-013-0410-1 [doi] (2013).

17 Bremner, J. D. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. 1. *Neuroimaging Clin. N. Am* **17**, 523-538, ix (2007).

18 Woon, F. L. & Hedges, D. W. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* **18**, 729-736, doi:10.1002/hipo.20437 [doi] (2008).

19 McCrory, E., De Brito, S. A. & Viding, E. The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Front Psychiatry* **2**, 48, doi:10.3389/fpsyt.2011.00048 [doi] (2011).

20 Rinne-Albers, M. A. *et al.* Abnormalities of white matter integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study. *Eur. Child Adolesc. Psychiatry* **25**, 869-878, doi:10.1007/s00787-015-0805-2 [doi] (2016).

21 Aghajani, M. *et al.* Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. *Hum. Brain Mapp* **37**, 1120-1135, doi:10.1002/hbm.23093 [doi] (2016).

22 Riem, M. M. E. *et al.* General psychopathology factor and unresolved-disorganized attachment uniquely correlated to white matter integrity using diffusion tensor imaging. *Behav. Brain Res* **359**, 1-8, doi:10.1016/j.bbr.2018.10.014 [doi] (2018).

23 Rinne-Albers, M. A. *et al.* Anterior cingulate cortex grey matter volume abnormalities in adolescents with PTSD after childhood sexual abuse. *Eur. Neuropsychopharmacol* 27, 1163-1171, doi:10.1016/j.euroneuro.2017.08.432 [doi] (2017).

24 van den Bulk, B. G. *et al.* Amygdala habituation to emotional faces in adolescents with internalizing disorders, adolescents with childhood sexual abuse related PTSD and healthy adolescents. *Dev. Cogn Neurosci* **21**, 15-25, doi:10.1016/j.dcn.2016.08.002 [doi] (2016).

25 van Hoof, M. J. *et al.* Emotional face processing in adolescents with childhood sexual abuse-related posttraumatic stress disorder, internalizing disorders and healthy controls. *Psychiatry Res* **264**, 52-59, doi:10.1016/j.pscychresns.2017.04.006 [doi] (2017).

26 van Hoof, M. J. *et al.* Unresolved-Disorganized Attachment is Associated With Smaller Hippocampus and Increased Functional Connectivity Beyond Psychopathology. *J. Trauma Stress* **32**, 742-752, doi:10.1002/jts.22432 [doi] (2019).

27 van Hoof, M. J. *et al.* Unresolved-disorganized attachment adjusted for a general psychopathology factor associated with atypical amygdala resting-state functional connectivity. *Eur. J. Psychotraumatol* **10**, 1583525, doi:10.1080/20008198.2019.1583525 [doi] (2019).

28 Clarkson, M. J. *et al.* A comparison of voxel and surface based cortical thickness estimation methods. *Neuroimage* **57**, 856-865, doi:10.1016/j.neuroimage.2011.05.053 [doi] (2011).

29 Corbo, V. *et al.* Reduced cortical thickness in veterans exposed to early life trauma. *Psychiatry Res* **223**, 53-60, doi:10.1016/j.pscychresns.2014.04.013 [doi] (2014).

30 Geuze, E. *et al.* Thinner prefrontal cortex in veterans with posttraumatic stress disorder. *Neuroimage* **41**, 675-681, doi:10.1016/j.neuroimage.2008.03.007 [doi] (2008).

31 Ansell, E. B., Rando, K., Tuit, K., Guarnaccia, J. & Sinha, R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. *Biol. Psychiatry* **72**, 57-64, doi:10.1016/j.biopsych.2011.11.022 [doi] (2012).

32 Woodward, S. H., Schaer, M., Kaloupek, D. G., Cediel, L. & Eliez, S. Smaller global and regional cortical volume in combat-related posttraumatic stress disorder. *Arch. Gen. Psychiatry* **66**, 1373-1382, doi:10.1001/archgenpsychiatry.2009.160 [doi] (2009).

33 Lindemer, E. R., Salat, D. H., Leritz, E. C., McGlinchey, R. E. & Milberg, W. P. Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF Veterans and the impact of comorbid TBI. *Neuroimage. Clin* **2**, 601-611, doi:10.1016/j.nicl.2013.04.009 [doi] (2013).

34 Landre, L. *et al.* Preserved subcortical volumes and cortical thickness in women with sexual abuse-related PTSD. *Psychiatry Res* **183**, 181-186, doi:10.1016/j.pscychresns.2010.01.015 [doi] (2010).

35 Dickie, E. W., Brunet, A., Akerib, V. & Armony, J. L. Anterior cingulate cortical thickness is a stable predictor of recovery from post-traumatic stress disorder. *Psychol. Med* **43**, 645-653, doi:10.1017/S0033291712001328 [doi] (2013).

36 Kahl, M., Wagner, G., de la Cruz, F., Kohler, S. & Schultz, C. C. Resilience and cortical thickness: a MRI study. *Eur. Arch. Psychiatry Clin. Neurosci*, doi:10.1007/s00406-018-0963-6 [doi] (2018).

37 Ahmed, F., Spottiswoode, B. S., Carey, P. D., Stein, D. J. & Seedat, S. Relationship between neurocognition and regional brain volumes in traumatized adolescents with and without posttraumatic stress disorder. *Neuropsychobiology* **66**, 174-184, doi:10.1159/000339558 [doi] (2012).

38 Klabunde, M., Weems, C. F., Raman, M. & Carrion, V. G. The moderating effects of sex on insula subdivision structure in youth with posttraumatic stress symptoms. *Depress. Anxiety* **34**, 51-58, doi:10.1002/da.22577 [doi] (2017).

39 Busso, D. S. *et al.* Child Abuse, Neural Structure, and Adolescent Psychopathology: A Longitudinal Study. *J. Am. Acad. Child Adolesc. Psychiatry* **56**, 321-328, doi:10.1016/j.jaac.2017.01.013 [doi] (2017).

40 Gold, A. L. *et al.* Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. *J. Child Psychol. Psychiatry* **57**, 1154-1164, doi:10.1111/jcpp.12630 [doi] (2016).

41 Hodel, A. S. *et al.* Duration of early adversity and structural brain development in post-institutionalized adolescents. *Neuroimage* **105**, 112-119, doi:10.1016/j.neuroimage.2014.10.020 [doi] (2015).

42 McLaughlin, K. A. *et al.* Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biol. Psychiatry* **76**, 629-638, doi:10.1016/j.biopsych.2013.08.016 [doi] (2014).

43 Whittle, S. *et al.* Childhood maltreatment and psychopathology affect brain development during adolescence. *J. Am. Acad. Child Adolesc. Psychiatry* **52**, 940-952, doi:10.1016/j.jaac.2013.06.007 [doi] (2013).

44 Kelly, P. A. *et al.* Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? *Biol. Psychiatry* **74**, 845-852, doi:10.1016/j.biopsych.2013.06.020 [doi] (2013).

45 Kelly, P. A. *et al.* The sexually dimorphic impact of maltreatment on cortical thickness, surface area and gyrification. *J. Neural Transm. (Vienna.)* **123**, 1069-1083, doi:10.1007/s00702-016-1523-8 [doi] (2016).

46 Lim, L. *et al.* Grey matter volume and thickness abnormalities in young people with a history of childhood abuse. *Psychol. Med* **48**, 1034-1046, doi:10.1017/S0033291717002392 [doi] (2018).

47 van Hoof, M. J., van Lang, N. D., Speekenbrink, S., van IJzendoorn, M. H. & Vermeiren, R. R. Adult Attachment Interview differentiates adolescents with Childhood Sexual Abuse from those with clinical depression and non-clinical controls. *Attach. Hum. Dev* **17**, 354-375, doi:10.1080/14616734.2015.1050420 [doi] (2015).

48 Wechsler, D. *Wechsler Intelligence Scale for Children*. (The Psychological Corporation, 1997).

49 Wechsler, D. *Wechsler Adult Intelligence Scale*. (The Psychological Corporation, 1991).

50 Cukor, J., Wyka, K., Jayasinghe, N. & Difede, J. The nature and course of subthreshold PTSD. *J. Anxiety. Disord* **24**, 918-923, doi:10.1016/j.janxdis.2010.06.017 [doi] (2010).

51 Silverman, W. K. & Ollendick, T. H. Evidence-based assessment of anxiety and its disorders in children and adolescents. *J. Clin. Child Adolesc. Psychol* **34**, 380-411, doi:10.1207/s15374424jccp3403_2 [doi] (2005).

52 Silverman, W. K., Saavedra, L. M. & Pina, A. A. Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: child and parent versions. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 937-944, doi:10.1097/00004583-200108000-00016 [doi] (2001).

53 Briere, J. *Trauma Symptoms Checklist for Children (TSCC), Professional Manual*. (Psychological Assessment Resources, 1996).

54 Barakat, L. P. *et al.* Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. *J. Pediatr. Psychol* **22**, 843-859 (1997).

55 Gustafsson, P. E., Nilsson, D. & Svedin, C. G. Polytraumatization and psychological symptoms in children and adolescents. *Eur. Child Adolesc. Psychiatry* **18**, 274-283, doi:10.1007/s00787-008-0728-2 [doi] (2009).

56 Lanktree, C. B. *et al.* Multi-informant assessment of maltreated children: convergent and discriminant validity of the TSCC and TSCYC. *Child Abuse Negl* **32**, 621-625, doi:10.1016/j.chiabu.2007.10.003 [doi] (2008).

57 Nilsson, D., Wadsby, M. & Svedin, C. G. The psychometric properties of the Trauma Symptom Checklist For Children (TSCC) in a sample of Swedish children. *Child Abuse Negl* **32**, 627-636, doi:10.1016/j.chiabu.2007.09.009 [doi] (2008).

58 Kisiel, C. L. & Lyons, J. S. Dissociation as a mediator of psychopathology among sexually abused children and adolescents. *Am. J. Psychiatry* **158**, 1034-1039, doi:10.1176/appi.ajp.158.7.1034 [doi] (2001).

59 Petersen, A. C. Adolescent development. *Annu. Rev. Psychol* **39**, 583-607, doi:10.1146/annurev.ps.39.020188.003055 [doi] (1988).

60 Bond, L. *et al.* A comparison of self-reported puberty using the Pubertal Development Scale and the Sexual Maturation Scale in a school-based epidemiologic survey. *J. Adolesc* **29**, 709-720, doi:10.1016/j.adolescence.2005.10.001 [doi] (2006).

61 Herting, M. M., Maxwell, E. C., Irvine, C. & Nagel, B. J. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. *Cereb. Cortex* **22**, 1979-1992, doi:10.1093/cercor/bhr246 [doi] (2012).

62 Luciana, M. Adolescent brain development in normality and psychopathology. *Dev. Psychopathol* **25**, 1325-1345, doi:10.1017/S0954579413000643 [doi] (2013).

63 Heim, C. M., Mayberg, H. S., Mletzko, T., Nemeroff, C. B. & Pruessner, J. C. Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *Am. J. Psychiatry* **170**, 616-623, doi:10.1176/appi.ajp.2013.12070950 [doi] (2013).

64 Weems, C. F. Severe stress and the development of the amygdala in youth: a theory and its statistical implications. *Developmental Review* **46**, 44-53 (2017).

65 Herzog, J. I. & Schmahl, C. Adverse Childhood Experiences and the Consequences on Neurobiological, Psychosocial, and Somatic Conditions Across the Lifespan. *Front Psychiatry* **9**, 420, doi:10.3389/fpsyt.2018.00420 [doi] (2018).

66 Norman, R. E. *et al.* The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS. Med* **9**, e1001349, doi:10.1371/journal.pmed.1001349 [doi] (2012).

67 Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M. & Mondelli, V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol. Psychiatry* **21**, 642-649, doi:10.1038/mp.2015.67 [doi] (2016).

68 Labonte, B. *et al.* Genome-wide epigenetic regulation by early-life trauma. *Arch. Gen. Psychiatry* **69**, 722-731, doi:10.1001/archgenpsychiatry.2011.2287 [doi] (2012).

69 Giedd, J. N. *et al.* Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci* **2**, 861-863, doi:10.1038/13158 [doi] (1999).

70 Pechtel, P. & Pizzagalli, D. A. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology (Berl)* **214**, 55-70, doi:10.1007/s00213-010-2009-2 [doi] (2011).

Chapter 5 DIFFUSION TENSOR IMAGING (DTI)

Abnormalities of white matter integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study

Mirjam A. Rinne-Albers*, Steven J. van der Werff*, Marie-José van Hoof, Natasja D. van Lang, Francien Lamers-Winkelman, Serge A. Rombouts, Robert R. Vermeiren, Nic J. van der Wee

*Mirjam A. Rinne-Albers and Steven J. van der Werff share first authorship

European Child and Adolescent Psychiatry, 2016, 25: 869-878

Abstract

Objective: The study seeks to determine whether white matter integrity in the brain differs between adolescents with posttraumatic stress disorder (PTSD) due to childhood sexual abuse (CSA) and matched healthy adolescents and if there is a relationship between white matter integrity and symptom severity in the patient group.
Method: A group of 20 adolescents with a history of CSA and related PTSD and a group of 20 healthy matched controls underwent diffusion tensor imaging (DTI) scanning. Fractional anisotropy (FA) values were calculated as a measure for white matter integrity. Trauma symptomatology was measured with the Trauma Symptom Checklist for Children (TSCC). The region of interest consisted of the bilateral uncinate fasciculus (UF), the genu, splenium and body of the corpus callosum (CC) and the bilateral cingulum. Apart from this an exploratory whole brain analysis was done. We also assessed additional DTI parameters to allow further interpretation of DTI abnormalities.
Results: The PTSD group had significantly lower FA values in the genu, midbody and splenium of the CC in comparison with controls. Additional DTI parameters indicates demyelinisation and dysmyelinisation in these areas. We found a negative association between scores on the anger subscale of the TSCC and FA values in the left body of the CC in the patients.
Conclusions: Adolescents with PTSD due to CSA show decreased FA in the CC, which associates with anger symptoms. This altered connectivity might be involved in vulnerability for developing psychiatric symptomatology in later life. Longitudinal treatment effect studies with traumatized juveniles might help to unravel and prevent this pathway.

1. Introduction

Childhood psychotrauma is a prevalent and important predictor of both child and adult psychopathology as well as a number of somatic disorders (1;26;31;45). Preclinical research in rodents and non-human primates has shown that structure and functioning of the developing brain are highly vulnerable to the effects of adversity, especially in certain critical time windows. In animal studies, childhood adversity was found to be associated with changes in brain circuitry involved in stress and emotion regulation, such as the hippocampus and certain prefrontal regions, possibly underlying vulnerability to the impact of stressors later in life (12;25;32;41). In adult humans, a history of chronic traumatization during childhood and adolescence was found to be associated with structural and functional damage in key elements of emotion and stress regulating brain circuitry, for example in the hippocampus in adults reporting childhood abuse or in the medial prefrontal cortex in adults reporting childhood emotional maltreatment (5;56). Bearing in mind the neuroplasticity of the maturing human brain (8), a thorough understanding of the human neurobiology underlying the psychological sequelae of childhood and youth psychotrauma may hold promise for developing appropriate interventions to alter adverse neurodevelopmental trajectories (22). Some recent reviews and meta-analyses have addressed structural brain alterations following childhood trauma in both adolescents and (young) adults with and without psychopathology (11;40;60). The studies included in these reviews and meta-analyses often used different approaches and varied in sample size. Nevertheless, next to findings in the cerebellum and sensory cortex, most of the results from reviews and meta-analyses point towards involvement of the corpus callosum (CC) and corticolimbic circuits in the pathophysiological sequelae of psychotrauma in children and young adults.

Diminished white matter (WM) integrity can constitute one element of abnormalities in corticolimbic and related circuitry. Diminished structural integrity may impede adaptive emotional and cognitive functioning, thereby rendering an individual vulnerable to childhood and adult psychopathology.

A promising tool for examining the structural integrity of WM in children and youth who experienced psychotrauma is diffusion tensor imaging (DTI). Fractional anisotropy (FA) is the most commonly used DTI parameter and reflects the degree of diffusion directionality of water, which in white matter can be influenced by structural properties such as axonal density, organization and myelinization. Smaller FA values are associated with decreased white matter integrity. In order to further interpret differences in FA, additional parameters such as the mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) can be assessed as well.

So far, four studies in children and youth have employed DTI to examine the effects of psychotrauma on white matter integrity in the developing brain and several reported abnormalities in the CC, but also in other areas. The first small study, in children who had been subjected to early socioemotional deprivation (N=7), found decreased FA in the left UF (14). The second study, in a group of children (N=17) with post-traumatic stress disorder (PTSD) following varying forms of maltreatment, found reduced FA in the medial and posterior subregions of the CC (24). The third study looked at the influence of Early Life Stress (ELS) on FA of the genu of the CC across the life span in healthy individuals. The results showed a lower FA in the youngest (8-12 y) and oldest (51-72 y) ELS age groups compared to non-exposed controls, suggesting that the effect is independent from the presence of psychopathology (44). This was corroborated in the fourth study by Huang and Rao, in adolescents exposed to childhood maltreatment but without a history of psychiatric illness, who showed decreased FA values compared to controls in the left and right superior longitudinal fasciculi, right cingulum bundle, left inferior fronto-occipital fasciculus and splenium of the CC (21). None of these studies investigated additional DTI parameters and only a region of interest (ROI) approach was used, which may have led important alterations in WM microstructure outside the ROI to go unobserved. Furthermore, study populations were heterogeneous for type of child adversity, which might have resulted in heterogeneous neuroimaging findings and differences in psychopathological sequelae.

The aim of our study was to investigate white matter integrity in a group of adolescents with psychopathology related to childhood sexual abuse (CSA) and matched healthy controls. We chose CSA as this is a prevalent form of child psychotrauma and a frequent cause of PTSD (15;27). This study is the first to focus on integrity of white matter tracts in a group of adolescents who had all experienced CSA. Based on previous neuroanatomical studies in children and youth as well as in adults, we hypothesized a reduced FA in the CC, the UF and the cingulum, although findings have not been unequivocal. We also aimed to investigate the possible relationship between FA and clinical symptoms in the patient group. Next, we also planned an exploratory whole brain analysis to detect aberrant FA values in areas outside our a priori defined ROIs.

2. Methods

2.1 Participants

We included N=22 adolescents with a history of CSA and related PTSD (further described as PTSD group) and N=30 healthy controls. The current cross-sectional study is part of the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA), a longitudinal MRI study in which adolescents are followed over a six-month period.
Inclusion criteria for the patient group were having experienced sexual abuse during their lifetime more than once by one or more perpetrators in- or outside the family and being referred to a mental health service. Most participants came from specialized psychotrauma centers and had experienced severe and frequent sexual abuse. Presence of PTSD was not an inclusion criterion, but clinical assessments (see below) showed that all patients but one were having PTSD related to the CSA. Exclusion criteria were: (1) primary DSM-IV diagnosis of ADHD, pervasive developmental disorders, Tourette's syndrome, obsessive-compulsive disorder, bipolar disorder, and psychotic disorders, (2) current use of psychotropic medication other than stable use of SSRI's, or amphetamine medication on the day of scanning, and (3) current substance abuse. The healthy control adolescents were recruited through local advertisement, with the following inclusion criteria: no clinical scores on validated mood and behavioral questionnaires, no history of traumatic experiences and no current psychotherapeutic intervention of any kind. All participants met the following inclusion criteria: aged between 12 and 21, estimated full scale IQ (FIQ) ≥ 80 as measured by Dutch versions of the Wechsler Intelligence Scales for Children (WISC-III) (59) or adults (WAIS) (58), being right-handed, normal or corrected-to-normal vision, sufficient understanding of the Dutch language, no history of neurological impairments and no contraindications for MRI testing (e.g. braces, metal implants or possible pregnancy). More extensive description of the clinical group can be found in an earlier report about the EPISCA project (57;57).

The medical ethics committee of the Leiden University Medical Centre approved the study. All anatomical scans were reviewed and cleared by a radiologist. Written informed consent was obtained from all adolescents and their parents. Participants received a financial compensation including travel expenses.

2.2 Clinical assessments

A standardized set of instruments was used to assess symptomatology in both groups of adolescents.

The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS-C/P) (46) are semi structured interviews for the classification of DSM-IV anxiety and depressive disorders in children. The adolescents and at least one of their parents were interviewed. A minimal interference score of 4, obtained by trained examiners based on the ADIS-C and ADIS-P, is necessary for classification. The ADIS is known to have good reliability and validity (47) with reported strong test–retest reliability statistics for the ADIS-C/P for combined diagnoses (.80–.92) and individual diagnoses (.62–.88).
As brain development is known to be influenced by sexual development, physical sexual development was measured with the self-report Puberty Development Scale (PDS) (38). The PDS consists of 5 items that are measured on a 5 point scale by the examiner: 1= pre pubertal, 2= early pubertal, 3= mid pubertal, 4= late pubertal, 5= post pubertal. The PDS is considered a valuable instrument determining pubertal stage (4;19).

The Trauma Symptom Checklist for Children (TSCC) (7) which measures trauma-related symptoms is a 54-item self-report for children and adolescents aged 8 through 18, but is often used up to 21

years (3;18). On a 4-point scale (never to almost all of the time), the adolescent indicates how often a thought, a feeling or a behavior occurs. The items are grouped into six clinical scales. The clinical scales are Anxiety (Anx), Depression (Dep), Post-traumatic Stress (Pts), Sexual Concerns (Sc), Dissociation (Dis) and Anger (Ang). The TSCC total score is used as the main measure on post-traumatic symptomatology. Cronbach's alpha coefficients reported range from .77 to .89 for subscales and .84 for the total scale. The questionnaire has extensively been studied, which has confirmed its good psychometric qualities (29;36).The internal consistency of the TSCC subscales varied between .85 and .94, except for the Sexual Concerns subscale that measured .68.
Six subscales from the Wechsler Intelligence scales scores (picture completion, similarities, picture concepts, arithmetic, block design and comprehension) were converted into FIQ estimates.

2.3 Data Acquisition and Preprocessing

DTI data were collected using a Philips 3.0T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel SENSE (Sensitivity Encoding) head coil. A single-shot echo-planar imaging sequence was used with the following scan parameters: repetition time = 11000 ms, echo time = 56 ms, flip angle = 90°, b-factor = 1000 s/mm^2, voxel dimensions = 2.3 mm isotropic, number of slices = 73, and no slice gap. DTI data were acquired along 32 directions, together with a baseline image having no diffusion weighting (*b*=0). Total scanning time was ~7.5 minutes. Collected DTI data were preprocessed and analyzed, using the Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (49) version 5.0.2. First, DTI data were corrected for distortion and motion artifacts, induced by eddy currents or by simple head motions, using affine registration of each diffusion weighted image to the *b*=0 reference image. Next, non-brain tissue was removed, using the Brain Extraction Tool. Finally, to generate individual FA maps for each participant, the diffusion tensor model was fitted to each voxel, using FMRIB's Diffusion Toolbox. Total brain volume, normalised for subject head size, was estimated using SIENAX (51), part of FSL.

2.4 Tract-based spatial statistics

Tract-based spatial statistics (TBSS) (48) version 1.2 was used for voxelwise analysis of the preprocessed FA data. First, individual FA images were aligned to the FMRIB58_FA standard-space image, using nonlinear registration. Next, the mean FA image was generated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the entire group. The mean FA skeleton was then thresholded at a FA value of ≥0.4, to exclude peripheral tracts and minimize partial voluming. Finally, each participant's aligned FA images were projected onto the mean FA skeleton and the resulting data were fed into voxelwise permutation-based analysis.

2.5 Region of Interest TBSS

To test for regional specific FA alterations, we implemented an ROI-based TBSS. A binary mask, encompassing the bilateral UF, the genu, splenium and body of the CC and the bilateral cingulum, was created as region of interest using the Johns Hopkins University (JHU) white matter atlas provided by FSL (34). The uncincate fasciculus connects subcortical subregions of the limbic system, such as the hippocampus and the amygdala, with the medial prefrontal cortex. The corpus callosum is the largest white matter bundle in the brain and connects left and right cerebral hemispheres. It consists of three subregions, namely the splenium (posterior), the body (middle), and the genu (anterior). The cingulum bundle is situated superior to the corpus callosum, curving around the genu and splenium. It connects prefrontal and subcortical areas, with additional projections to the parietal lobe.

The mask was then applied to the mean FA skeleton, in order to include only voxels comprised in the mean FA skeleton. This confines the statistical analysis exclusively to voxels from the center of the tract, thereby minimizing anatomic inter-subject variability, registration errors, and partial voluming. The resulting study-specific ROI mask was used for voxelwise permutation-based ROI analysis.

2.5 Statistical analysis of demographic and clinical data

We used analysis of variance (ANOVA) to compare the two groups on age, IQ and TSCC total score. Because not all TSCC subscales showed normal distribution we used non-parametric analysis (Mann-Whitney) for the comparison of the TSCC subscales between the two groups.

2.6 MRI analysis

Using FSL's Randomize tool, permutation–based inferences with Threshold-Free Cluster Enhancement (TFCE) were carried out for voxelwise analysis of FA data (50). 5000 random permutations were generated to build up the null distribution of the cluster size statistic, while testing the following contrasts: 1) Controls > PTSD, 2) Controls < PTSD. PDS score, total brain volume, gender and FIQ (demeaned across groups) were included in the analysis as nuisance regressors to correct for between groups variances. The resulting statistical maps were corrected for multiple comparisons across space (p<0.05) and the JHU White Matter and Juelich Histological atlases were used to label clusters with significant FA alterations. This step was first carried out using the ROI mask to test our specific hypotheses. Next, we ran this step a second time using a whole brain mask for our exploratory analysis.

2.7 Post-hoc analyses

The association between FA and symptom severity in the PTSD group was examined using a voxel-wise correlation approach. A mask was created of the voxels that were found to differ significantly on FA based on the between-group ROI analysis.
The TSCC total and subscale scores of the PTSD group were fed into FSL's Randomise tool along with the mask, using permutation–based inferences with TFCE.
Last, we examined how the between-group differences in FA values related to the other DTI measures. Therefore, information on each individuals' AD (the 1st eigenvalue), RD (the average of the 2nd and 3rd eigenvalues), and MD was fed into FSL's Randomise tool along with the mask based on our ROI analysis.

3 Results

Table 1. Demographic and clinical characteristics of participants.

		PTSD (N =20)		CNTR (N = 20)		
		Mean	SD	Mean	SD	p
Gender (f : m)		17:3		18:2		
Age (in months)		198	24	185	19	0.06
FIQ		99	9	107	9	<0.01
PDS[1]	Pre/mid pubertal	1		4		
	Late pubertal	6		9		

	Post pubertal	10		5		
TSCC[2]	Anxiety	9.3	6.0	3.3	2.7	<0.01
	Depression	9.9	4.9	2.6	2.1	<0.001
	Anger	6.2	3.5	2.0	2.2	<0.001
	Posttraumatic stress	11.8	7.2	2.3	2.6	<0.001
	Dissociation	8.6	5.6	2.7	2.3	<0.001
	Sexual concerns	4.7	3.3	1.3	1.6	<0.001
	Total score	48,3	24,2	13,7	10,9	<0.001

(1) Missing data: 2 in control group, 3 in PTSD group

(2) Three PTSD participants did not complete the questionnaire.

From the original total of 22 PTSD and 30 control adolescents, three controls were excluded because of image artefacts in T1-weighted anatomical scans. Further, two adolescents with PTSD were excluded because of image artifacts in the DTI dataset, resulting in a final sample of 20 adolescents with PTSD. From the remaining 27 controls, 20 subjects were group-wise matched on age and gender with the PTSD adolescents. Eventually, 40 participants (20 PTSD and 20 controls) were included. Of the 20 PTSD participants, 19 fulfilled all PTSD criteria on the ADIS, while one had sufficient PTSD symptoms, but with limited interference. Since earlier research showed that persons with subthreshold PTSD in many aspects resemble PTSD patients, we decided to include this patient (10).

The majority of participants was female (88%, see table 1). Of the participants with PTSD, 15 had comorbid anxiety disorders, most often more than one. Eight had a comorbid depressive disorder and one an oppositional defiant disorder (ODD). All controls and 16 adolescents with PTSD were drug- and treatment naïve. Two adolescents with PTSD were on stable SSRI treatment and two used amphetamines (not on the day of scanning).
The PTSD group had a significantly lower FIQ than controls (F (1,38) = 8,14, $p < .01$) and more subjects in the post pubertal phase (50 % versus 25 %). As expected, there was a significant main effect of group on the TSCC scale scores (with and without controlling for age and FIQ; F (7,28) = 6,48, $p < .01$). The PTSD group had significantly higher scores on all TSCC scales (all with $p < .01$).

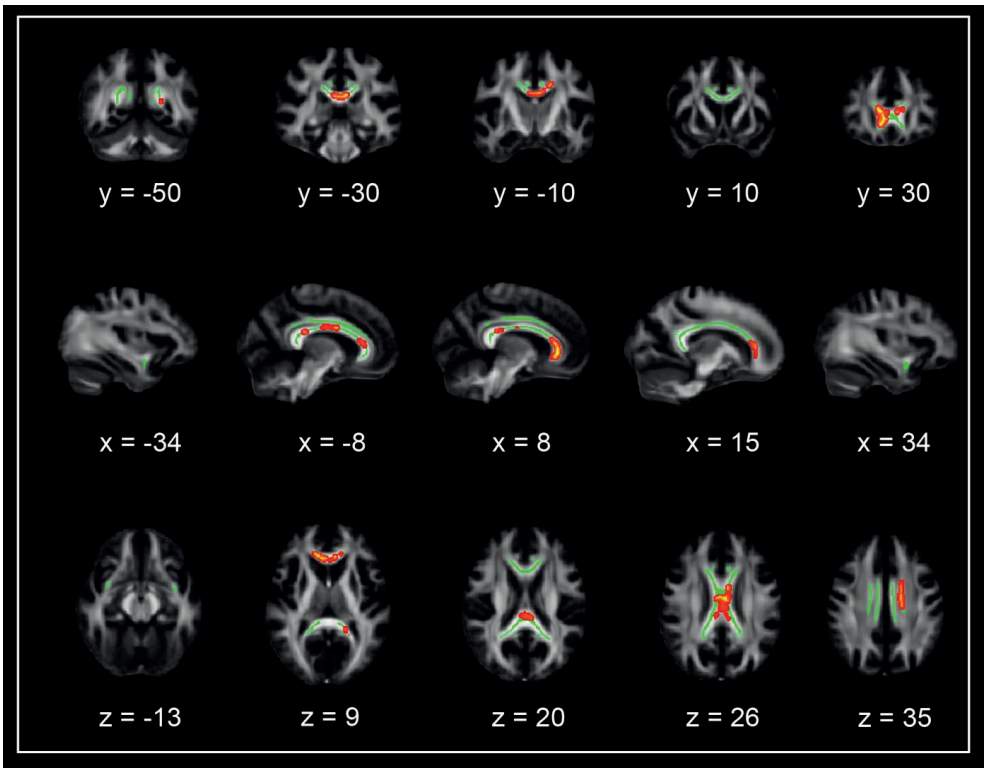


Figure 1: **Region-of-interest analysis results.** Coronal, sagittal and transversal axial sections of the white matter skeleton (green) superimposed on the FMRIB58_FA_1mm standard brain (gray). Depicted in yellow are the regions in which FA values are significantly smaller in patients with PTSD compared to matched healthy controls. For better visibility, the results are thickened using the "tbss-fill" command (red). All TBSS results are corrected for multiple comparisons ($p<0.05$, TFCE corrected), and the axial images are in radiological convention (the right side of the image corresponds with the left hemisphere of the brain and vice-versa).

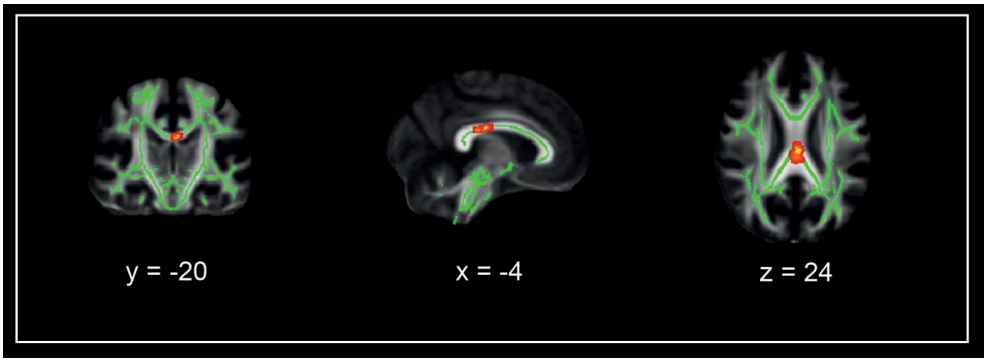


Figure 2. **Whole brain TBSS results.** Coronal, sagittal and transversal axial sections of the white matter skeleton (green) superimposed on the FMRIB58_FA_1mm standard brain (gray). Depicted in yellow are the regions in which FA values are significantly smaller in patients with PTSD compared to matched healthy controls. For better visibility, the results are thickened using the "tbss-fill" command (red) All TBSS results are corrected for multiple comparisons ($p<0.075$, TFCE corrected),

and the axial images are in radiological convention (the right side of the image corresponds with the left hemisphere of the brain and vice-versa).

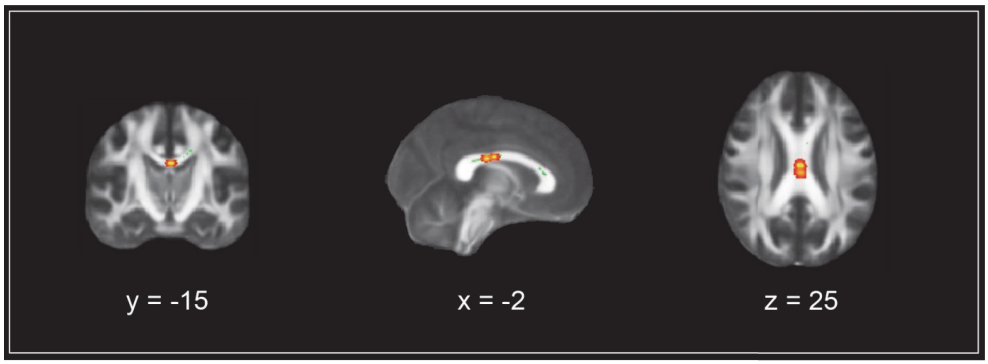


Figure 3: **Voxel-wise correlation between TSCC anger subscale scores and FA values in adolescents with PTSD**. Coronal, sagittal and transversal axial sections of the white matter skeleton (green) superimposed on the FMRIB58_FA_1mm standard brain (gray). FA values in the left CC correlated negatively with TSCC anger subscale scores ($p < .05$) in the adolescents with PTSD (yellow). For better visibility, the results are thickened using the "tbss-fill" command (red). The axial images are in radiological convention (the right side of the image corresponds with the left hemisphere of the brain and vice-versa).

3.1 TBSS Analyses

ROI-based TBSS analysis showed that, in comparison with controls, the PTSD group had lower FA values in the genu, midbody and splenium of the CC ($p< .05$, TFCE corrected) (Figure 1). No FA differences were observed in the bilateral UF and cingulum. The exploratory whole brain TBSS revealed no significant lower FA values. When the threshold was lowered we found lower FA values in the body of the CC in the left hemisphere, adjacent to the splenium ($p< .075$, TFCE corrected; Figure 2). No white matter tracts with lower FA values were found for controls versus PTSD.
Using a voxel-wise correlation approach, we examined the association between the observed smaller FA values from the ROI analysis, and the TSCC total and subscale scores in the patients. We found a significant negative correlation between scores on the anger subscale of the TSCC and FA values in the left body of the CC ($p < .05$; uncorrected, Figure 3.)
Post-hoc analyses of the AD, RD and MD in the voxels that showed FA differences between groups revealed a significant increase ($p< .05$, TFCE corrected) of RD and MD in the PTSD group compared to controls. No significant differences were found between groups in AD. Omitting the one CSA participant who met all PTSD criteria except for interference did not change our findings. Excluding the two participants that were using medication from the analyses did not change the results either.

4 Discussion

We examined white matter integrity in a sample of adolescents with CSA related PTSD, using an ROI and an additional exploratory whole brain approach. We hypothesized reduced FA in a number of relevant white matter tracts: the CC, UF and cingulum. Compared to the control group, our adolescent PTSD group only showed decreased FA in areas of the CC, with additional DTI parameters suggesting demyelinization and dysmyelinization in these areas. We also found a significant correlation (uncorrected) between FA in the CC and Anger scores on the TSCC in the adolescents with CSA related PTSD.

This study is the first to report on white matter integrity in a group of adolescents with CSA related PTSD. The results of our study are in line with the findings of the recent DTI study by Jackowski and colleagues, who examined the CC in a group of children with PTSD following various forms of intrafamilial maltreatment, and also found reduced FA in several subregions of the CC (24). Our findings are in line with recent reviews indicating that the most consisting finding in youth with psychotrauma is structural abnormalities of the CC, in contrast to the reduction of hippocampal volume typically reported in adults with PTSD (5;40).

The CC is known to change throughout life, but most dramatically during childhood and adolescence (2;30). These developmental changes in the CC are the consequence of varying degrees of axonal myelinization, redirection, and pruning, reflecting a permanent adjustment and fine-tuning of fibers connecting homologous cortical areas. The general trend during adolescence is towards increasing FA and decreasing MD (43). This CC maturation parallels puberty development suggesting gonadal hormonal influences (2). For this reason we included PDS scores as regressor. However, we must acknowledge that a simple linear regression of pubertal stage and total brain volume may still not sufficiently account for the results as they are known not to be linear across adolescence.

Early traumatization is likely to have a major influence on the integrity of the CC, as the processes of myelinization and selective pruning are typically influenced by stress hormones (52;54). Of importance, the smaller FA values we found in the CC of the PTSD group were due to increases in RD and MD, known to reflect demyelinization (less development of the myelin sheet) and dysmyelinization (aberrant development of the myelin sheet), linking the abnormalities of the CC integrity to the possible influence of stress hormones. Supporting this possible association, a recent study found that in rhesus monkeys exposed to early maternal abuse, cortisol levels at the time of abuse correlated with abnormalities in white matter connectivity in the CC, brain stem and other brain areas in adolescence (20). Our results are in line with the study of Teicher et al. who, comparing abuse and neglect, found that sexual abuse was the strongest factor influencing CC size in girls (53).

Recent topographic research on the CC is beginning to map the different regions of the CC and their connections. Apart from frontal connections, the body of the CC also has connections with subcortical nuclei (21). Changes in the midbody of the CC in children and adolescents who experienced psychological trauma could be related to disturbances in connectivity with limbic subcortical nuclei, resulting from or underlying the disturbances in emotion regulation.

We found a negative association in the adolescent PTSD group between FA in the CC and the TSCC Anger subscale. This in contrast to the result of the small DTI study in socioemotional deprived children with PTSD (14) in which correlations of FA measures in the CC were found with total anxiety scores, panic scores and separation anxiety scores. This may be due to methodological differences as well as the populations studied. A preclinical study in male non-human primates examined the effects of early life stress on hippocampal volume and CC development and found a significant inverse relationship between CC mid-sagittal area in adult monkeys and the response towards an intruder which typically consists of a mixture of aggressive and anxious behavior (23). In a recent DTI study in male adolescents with conduct disorder, Zhang et al. report increased structural connectivity in the genu and body of the CC (61). Impulsivity correlated positive with WM integrity, which is the opposite pattern of what we found in our study. This suggests that different pathophysiological mechanisms are involved, which is in accordance with the putative mechanisms described in the literature. For instance Raine et al. hypothesize that structural abnormalities in the CC are a consequence of an early arrest of the normal neurodevelopmental process of axonal pruning, while the abnormalities in myelinization following CSA may be more linked to detrimental stress hormone influences (39).

We believe the relatively homogeneous sample and the state-of-the-art DTI approaches are strengths of our study, although several potential limitations should be taken into account. While we know that gender influences brain development and the reaction to psychological trauma, we included gender as a regressor, but could not further explore this issue because our participants are mainly girls. Full scale IQ measures differed significantly between the PTSD group and controls. Several studies report a negative effect of ELS on cognitive function (13;37). In this respect intellectual ability in the PTSD group and the control group might originally have been more equal. The New Zealand longitudinal birth cohort study (28) instead, points to IQ as a risk factor for the development of PTSD. In the discussion about lower IQ being a consequence or a predictor of PTSD, it is suggested that trauma severity overrules IQ as a predictor (33) which could be the case in our study where all included adolescents fulfilled symptom criteria for PTSD diagnosis although this was not an inclusion criterion, but here too results are inconclusive (6). Navas-Sanchez et al. (35) found a positive correlation between IQ and FA in the CC in math gifted adolescents compared to controls matched for age and academic level. Other studies report about correlations, mostly positive, of cognitive function with FA in several WM tracts (17;42). To decrease the potential influence of IQ on the white matter integrity differences we included IQ as a covariate in our analyses, but clearly further research is needed to unravel the exact relationship between childhood adversity, IQ and WM integrity in adolescence.

The normal increase of FA in the CC during adolescence is related to pubertal development. Therefore, the PDS score is chosen as nuisance regressor instead of age. The PTSD group was older and more advanced in pubertal stage. Because of the expected increase, the decrease in FA found in the PTSD group cannot be a consequence of normal (pubertal) development.
Two adolescents with PTSD were on stable SSRI treatment. Omitting these two participants from our analyses didn't have any effect on the results. To our knowledge no influence of SSRIs on the CC is reported (9).

Patients were selected based on the presence of CSA and all except one, who fulfilled PTSD criteria except interference, showed CSA related PTSD. Hence, we cannot differentiate whether the neuroimaging results were a consequence of exposure to trauma or the (development of) PTSD pathology or reflect an underlying vulnerability. Previous research in twins discordant for combat exposure suggests that anatomical abnormalities may indeed represent pre-existing vulnerability factors (16). The ideal cross-sectional design to disentangle the effects of exposure, psychopathology and resilience would have incorporated a CSA group with psychopathology, a CSA group without psychopathology and a non-exposed, healthy control group (55). Furthermore, we could not assess the influence of timing and duration of the CSA in our study, which is thought to be highly relevant in children and youth.

About one-third of the subjects also reported physical abuse, but as we did not assess experiences of other forms of psychotrauma we could have missed other prevalent traumatic experiences, like emotional maltreatment, which might be associated with the presence of DTI abnormalities in our sample.

In conclusion, our DTI findings in this sample of adolescents with CSA related PTSD point at the involvement of the CC in brain alterations associated with juvenile sexual psychotrauma, and together with recent animal data can be taken to point at the influence of stress hormone levels on CC integrity. Clearly, longitudinal studies till mid-adulthood are needed to further elucidate the role of altered CC white matter integrity in the biopsychological consequences of early traumatization and to examine its malleability.

Reference List

1. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH (2006) The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci 256:174-186

2. Asato MR, Terwilliger R, Woo J, Luna B (2010) White matter development in adolescence: a DTI study. Cereb Cortex 20:2122-2131

3. Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML (1997) Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. J Pediatr Psychol 22:843-859

4. Bond L, Clements J, Bertalli N, Evans-Whipp T, McMorris BJ, Patton GC, Toumbourou JW, Catalano RF (2006) A comparison of self-reported puberty using the Pubertal Development Scale and the Sexual Maturation Scale in a school-based epidemiologic survey. J Adolesc 29:709-720

5. Bremner JD (2007) Neuroimaging in posttraumatic stress disorder and other stress-related disorders. Neuroimaging Clin N Am 17:523-38, ix

6. Breslau N, Chen Q, Luo Z (2013) The role of intelligence in posttraumatic stress disorder: does it vary by trauma severity? PLoS One 8:e65391

7. Briere J (1996) Trauma Symptoms Checklist for Children (TSCC), Professional Manual. Psychological Assessment Resources, Odessa, FL

8. Casey BJ, Jones RM, Hare TA (2008) The adolescent brain. Ann N Y Acad Sci 1124:111-126

9. Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, Bullmore E (2007) Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biol Psychiatry 62:407-414

10. Cukor J, Wyka K, Jayasinghe N, Difede J (2010) The nature and course of subthreshold PTSD. J Anxiety Disord 24:918-923

11. Daniels JK, Lamke JP, Gaebler M, Walter H, Scheel M (2013) White matter integrity and its relationship to ptsd and childhood trauma--a systematic review and meta-analysis. Depress Anxiety 30:207-216

12. De Bellis MD, Spratt EG, Hooper SR (2011) Neurodevelopmental biology associated with childhood sexual abuse. J Child Sex Abus 20:548-587

13. De Bellis MD, Woolley DP, Hooper SR (2013) Neuropsychological findings in pediatric maltreatment: relationship of PTSD, dissociative symptoms, and abuse/neglect indices to neurocognitive outcomes. Child Maltreat 18:171-183

14. Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M (2006) Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 117:2093-2100

15. Gibb BE, Chelminski I, Zimmerman M (2007) Childhood emotional, physical, and sexual abuse, and diagnoses of depressive and anxiety disorders in adult psychiatric outpatients. Depress Anxiety 24:256-263

16. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242-1247

17. Glascher J, Rudrauf D, Colom R, Paul LK, Tranel D, Damasio H, Adolphs R (2010) Distributed neural system for general intelligence revealed by lesion mapping. Proc Natl Acad Sci U S A 107:4705-4709

18. Gustafsson PE, Nilsson D, Svedin CG (2009) Polytraumatization and psychological symptoms in children and adolescents. Eur Child Adolesc Psychiatry 18:274-283

19. Herting MM, Maxwell EC, Irvine C, Nagel BJ (2012) The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb Cortex 22:1979-1992

20. Howell BR, McCormack KM, Grand AP, Sawyer NT, Zhang X, Maestripieri D, Hu X, Sanchez MM (2013) Brain white matter microstructure alterations in adolescent rhesus monkeys exposed to early life stress: associations with high cortisol during infancy. Biol Mood Anxiety Disord 3:21

21. Huang H, Zhang J, Jiang H, Wakana S, Poetscher L, Miller MI, van Zijl PC, Hillis AE, Wytik R, Mori S (2005) DTI tractography based parcellation of white matter: application to the mid-sagittal morphology of corpus callosum. Neuroimage 26:195-205

22. Hulvershorn LA, Cullen K, Anand A (2011) Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. Brain Imaging Behav 5:307-328

23. Jackowski A, Perera TD, Abdallah CG, Garrido G, Tang CY, Martinez J, Mathew SJ, Gorman JM, Rosenblum LA, Smith EL, Dwork AJ, Shungu DC, Kaffman A, Gelernter J, Coplan JD, Kaufman J (2011) Early-life stress, corpus callosum development, hippocampal volumetrics, and anxious behavior in male nonhuman primates. Psychiatry Res 192:37-44

24. Jackowski AP, Douglas-Palumberi H, Jackowski M, Win L, Schultz RT, Staib LW, Krystal JH, Kaufman J (2008) Corpus callosum in maltreated children with posttraumatic stress disorder: a diffusion tensor imaging study. Psychiatry Res 162:256-261

25. Kaufman J, Plotsky PM, Nemeroff CB, Charney DS (2000) Effects of early adverse experiences on brain structure and function: clinical implications. Biol Psychiatry 48:778-790

26. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, de GG, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu CY, Karam EG, Kawakami N, Lee S, Lepine JP, Ormel J, Posada-Villa J, Sagar R, Tsang A, Ustun TB, Vassilev S, Viana MC, Williams DR (2010) Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br J Psychiatry 197:378-385

27. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048-1060

28. Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A (2007) Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort. Psychol Med 37:181-192

29. Lanktree CB, Gilbert AM, Briere J, Taylor N, Chen K, Maida CA, Saltzman WR (2008) Multi-informant assessment of maltreated children: convergent and discriminant validity of the TSCC and TSCYC. Child Abuse Negl 32:621-625

30. Luders E, Thompson PM, Toga AW (2010) The development of the corpus callosum in the healthy human brain. J Neurosci 30:10985-10990

31. MacMillan HL, Fleming JE, Streiner DL, Lin E, Boyle MH, Jamieson E, Duku EK, Walsh CA, Wong MY, Beardslee WR (2001) Childhood abuse and lifetime psychopathology in a community sample. Am J Psychiatry 158:1878-1883

32. McCrory E, De Brito SA, Viding E (2010) Research review: the neurobiology and genetics of maltreatment and adversity. J Child Psychol Psychiatry 51:1079-1095

33. McNally RJ, Shin LM (1995) Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam Combat veterans. Am J Psychiatry 152:936-938

34. Mori SWS, Nagae-Poetscher LM, van Zijl PCM (2005) MRI Atlas of Human White Matter. Elsevier, Amsterdam, the Netherlands

35. Navas-Sanchez FJ, Aleman-Gomez Y, Sanchez-Gonzalez J, Guzman-De-Villoria JA, Franco C, Robles O, Arango C, Desco M (2014) White matter microstructure correlates of mathematical giftedness and intelligence quotient. Hum Brain Mapp 35:2619-2631

36. Nilsson D, Wadsby M, Svedin CG (2008) The psychometric properties of the Trauma Symptom Checklist For Children (TSCC) in a sample of Swedish children. Child Abuse Negl 32:627-636

37. Pechtel P, Pizzagalli DA (2011) Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl) 214:55-70

38. Petersen AC (1988) Adolescent development. Annu Rev Psychol 39:583-607

39. Raine A, Lencz T, Taylor K, Hellige JB, Bihrle S, Lacasse L, Lee M, Ishikawa S, Colletti P (2003) Corpus callosum abnormalities in psychopathic antisocial individuals. Arch Gen Psychiatry 60:1134-1142

40. Rinne-Albers MA, van der Wee NJ, Lamers-Winkelman F, Vermeiren RR (2013) Neuroimaging in children, adolescents and young adults with psychological trauma. Eur Child Adolesc Psychiatry

41. Sanchez MM, Ladd CO, Plotsky PM (2001) Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev Psychopathol 13:419-449

42. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK (2005) Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp 26:139-147

43. Schmithorst VJ, Yuan W (2010) White matter development during adolescence as shown by diffusion MRI. Brain Cogn 72:16-25

44. Seckfort DL, Paul R, Grieve SM, Vandenberg B, Bryant RA, Williams LMCCR, Cohen RA, Bruce S, Gordon E (2008) Early Life Stress on Brain Structure and Function Across the Lifespan: a Preliminary Study. Brain Imaging Behav 2:49-58

45. Shonkoff JP (2011) Protecting brains, not simply stimulating minds. Science 333:982-983

46. Silverman WK, Ollendick TH (2005) Evidence-based assessment of anxiety and its disorders in children and adolescents. J Clin Child Adolesc Psychol 34:380-411

47. Silverman WK, Saavedra LM, Pina AA (2001) Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: child and parent versions. J Am Acad Child Adolesc Psychiatry 40:937-944

48. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31:1487-1505

49. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De LM, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De SN, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 Suppl 1:S208-S219

50. Smith SM, Nichols TE (2009) Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44:83-98

51. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De SN (2002) Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 17:479-489

52. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP (2002) Developmental neurobiology of childhood stress and trauma. Psychiatr Clin North Am 25:397-viii

53. Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL (2004) Childhood neglect is associated with reduced corpus callosum area. Biol Psychiatry 56:80-85

54. van der Werff SJ, Andela CD, Nienke PJ, Meijer OC, van Buchem MA, Rombouts SA, van der Mast RC, Biermasz NR, Pereira AM, van der Wee NJ (2014) Widespread reductions of white matter integrity in patients with long-term remission of Cushing's disease. Neuroimage Clin 4:659-667

55. van der Werff SJ, Pannekoek JN, Veer IM, van Tol MJ, Aleman A, Veltman DJ, Zitman FG, Rombouts SA, Elzinga BM, van der Wee NJ (2012) Resting-state functional connectivity in adults with childhood emotional maltreatment. Psychol Med1-12

56. van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM (2010) Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biol Psychiatry 68:832-838

57. van Hoof MJ, van Lang ND, Speekenbrink S, van IJzendoorn MH, Vermeiren RR (2015) Adult Attachment Interview differentiates adolescents with Childhood Sexual Abuse from those with clinical depression and non-clinical controls. Attach Hum Dev 17:354-375

58. Wechsler D (1991) Wechsler Adult Intelligence Scale. The Psychological Corporation, San Antonio, TX

59. Wechsler D (1997) Wechsler Intelligence Scale for Children. The Psychological Corporation, San Antonio, TX

60. Woon FL, Hedges DW (2008) Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 18:729-736

61. Zhang J, Zhu X, Wang X, Gao J, Shi H, Huang B, Situ W, Yi J, Zhu X, Yao S (2014) Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. J Am Acad Child Adolesc Psychiatry 53:466-475

Chapter 6 SUMMARY AND GENERAL DISCUSSION

Aim of this thesis

The aim of this thesis was to further elucidate brain structure in traumatised youth, in order to ultimately better understand the way childhood adversity may lead to an increased risk of psychiatric and somatic pathology in later life. To this end, structural neuroimaging techniques were used to explore structural brain characteristics in a group of adolescents who experienced childhood sexual abuse. The findings of the thesis may eventually contribute to the development of optimal treatment and preventative strategies.

In the general discussion the research questions, the main findings and their clinical implications, the considerations and limitations concerning the studies and directions for future research are discussed.

1. Summary

To address the aim of this thesis, first a literature review was conducted to map the results of earlier neuroimaging studies in children and youth who experienced childhood psychological trauma. Next, three different structural neuroimaging techniques were employed to study the effects of childhood sexual trauma in youth .

1.1 Review

The aim of the review was to discuss the results of neuroimaging studies in traumatised juveniles and young adults, published before the various results of our EPISCA neuro-imaging study.

In a systematic literature search, 27 articles published between 1999 and 2013, were identified which met inclusion criteria. All except two publications were from the United States, and of these 23 manuscripts where from three research groups; De Bellis (Pittsburgh), Carrion (Stanford) and Teicher (Harvard). Structural neuroimaging results were presented in 24 studies, of which four employed diffusion tensor imaging (DTI) and three presented functional MRI findings. The groups of traumatised individuals studied were diverse, which likely has impacted results.

Some (N=10) studies focused on specific types of trauma: i.e. abuse in general (physical or sexual), sexual abuse, interpersonal trauma, physical abuse/maltreatment, harsh corporal punishment, early deprivation or neglect, parent verbal abuse, witnessing an earthquake and rearing in an institution. Others (N=17) selected participants based on the presence of specific pathology as a consequence of trauma: PTSD (N=15) or PTSD-symptoms (N=2), combined with one or several types of trauma. Evidently, the diversity in populations complicates comparison of findings substantially.

The most robust findings across studies were a reduction in size of several regions of the corpus callosum and a decrease in total brain volume in traumatised children and adolescents, findings that are typically not reported in adults. Findings in young adults, studied only by Teicher and his group (N=6 studies), demonstrated an association between early traumatisation and the sensory cortex (visual and auditory cortex) and its connection to limbic areas. A reduction in hippocampal volume, frequently reported in adults with PTSD, was inconsistently found in children and adolescents (no difference between groups N=6 studies; decrease in volume N=2 studies; ambiguous N=1 study). Findings on abnormalities in the PFC and the amygdala were limited or unequivocal. Studies investigating treatment effects could not be identified.

Because of the limited number of studies, the small sample size of many of the studies, the variety in inclusion criteria, and the fact that some studies reported on the same population, conclusions of the review are tentative. Importantly, the number of neuroimaging studies in traumatised children and adolescents was found to clearly lag behind studies in traumatised adults as well as studies on ADHD and autism.

1.2 Chapters on empirical research

The empirical research in this thesis was part of the EPISCA study that included a group of adolescents who experienced childhood sexual abuse. Although not an inclusion criterion, all participants of the traumatised group studied for this thesis were diagnosed with PTSD, while one showed PTSD symptoms with limited interference. Since earlier research showed that persons with sub threshold PTSD in many aspects resemble PTSD patients (1), we included this participant in our childhood sexual abuse (CSA-)related PTSD group. In the analyses of the three empirical studies we checked if inclusion of this patient influenced our results, which was not the case.

1.2.1 Grey matter:

1.2.1.1 Voxel based morphometry (Chapter 3)

The aim of this study was to investigate abnormalities in grey matter volume (GMV) in a group of adolescents with PTSD due to CSA and the relationship between GMV and symptom severity. Based on the review and findings from adult studies, the hippocampus, amygdala, anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC) and superior temporal gyrus (STG) were chosen as regions of interest (ROIs).
Compared to the healthy non-traumatised controls, adolescents with CSA-related PTSD showed a 14.8% smaller grey matter volume in the dorsal ACC. The ACC is a key region in emotion regulation and part of the limbic system (see introduction). Because of low multicollinearity of age and PDS we performed a post-hoc analysis, in which pubertal development (PDS) as well as age were added as covariates. The post-hoc analysis showed no ACC difference between groups, but instead a smaller volume of the right amygdala, also part of the limbic system, appeared. Six subjects (three in the CSA-related PTSD group, three in the control group) were not included in this post-hoc analysis because of missing PDS scores. Our finding of smaller GMV in limbic regions is in line with studies in adults.

1.2.1.2 Cortical Thickness (Chapter 4)

The aim of this study was to investigate cortical thickness measures and their relation with clinical data in the group of adolescents with CSA-related PTSD and the healthy non-traumatised control group. Based on results from earlier research in pediatric and adult populations, we hypothesised differences in the following regions of interest (ROIs): the ventromedial PFC (vmPFC), ACC, insula, and middle / superior temporal gyrus.
No significant effect of group was found for cortical thickness, surface area or volume. These findings are in line with the results of research in adult women with sexual abuse-related PTSD and in contrast to adult studies on other types of trauma, suggesting that this may be specific to females who experienced CSA, independent of age.

1.2.2 White matter

1.2.2.1 Diffusion Tensor Imaging (Chapter 5)

The aim of this study was to examine white matter integrity in youth with CSA-related PTSD and matched healthy controls. Based on our review we selected a region of interest consisting of the bilateral uncinate fasciculus (UF), the genu, splenium and body of the corpus callosum (CC), and the bilateral cingulum. In addition, we performed an exploratory whole brain analysis. Trauma symptomatology was measured with the Trauma Symptom Checklist for Children (TSCC) to enable correlational analyses between measures of white matter integrity and trauma symptomatology.
A ROI-based, tract-based spatial statistics (TBSS) analysis showed that, compared to controls, the PTSD group had lower fractional anisotropy (FA) values in the genu, midbody and splenium of the CC. When we examined the association between FA and symptom severity in the PTSD group, we found a significant negative correlation between scores on the anger subscale of the TSCC and FA values in the left body of the CC. Post-hoc analyses of the additional diffusion parameters in the CC voxels that showed FA differences between groups, revealed a significant increase of radial and mean diffusivity (resp. RD and MD) in the PTSD group compared to controls. As these parameters are known to reflect demyelinisation (less development of the myelin sheet) and dysmyelinisation (aberrant development of the myelin sheet), this links the abnormalities of the CC integrity to the possible influence of stress hormones.
Topographic research on the CC reveals that apart from frontal connections, the body of the CC also has connections with subcortical nuclei (2). The abnormalities in the midbody of the CC indentified in our study might therefore be related to disturbances in connectivity with limbic subcortical nuclei, resulting from or underlying disturbances in emotion regulation.

2. General discussion

Main research questions of this thesis were:

- What are the structural characteristics of the adolescent brain associated with adverse childhood experiences, specifically childhood sexual abuse?
- Is there a relationship between structural neuroimaging abnormalities and trauma symptomatology?

This thesis generated **seven main findings**:

First, neuroimaging studies in traumatised children and adolescents are scarce and heterogeneous in design, in particular with regard to the sample studied and the type of trauma.

Second, the results of structural neuroimaging studies in traumatised minors differ from those in adult traumatised populations, in particular with regard to findings on the hippocampus and the corpus callosum (CC).

Third, paralleling the inconsistent findings on hippocampal volume reduction in traumatised minors, our VBM-study did not show differences between groups for hippocampal volume.

Fourth, VBM showed smaller volumes of key regions of the limbic system (ACC, amygdala) in the CSA-related PTSD group compared to controls.

Fifth, Female adolescents with sexual abuse-related PTSD show no abnormalities in cortical thickness, in line with findings in adults.

Sixth, adolescents with CSA-related PTSD show less integrity of parts of the CC compared to healthy non-traumatised controls.

Seventh, Our structural neuroimaging (VBM, DTI and Cortical Thickness) studies showed limited associations with trauma symptomatology, in line with findings in previous studies in minors

2.1 Discussion of structural findings

2.1.1 Heterogeneity of findings in minors

Remarkably, the conclusions of our review published in 2013 still apply. In a more recent review (Kylllion and Weyandt, 2018) on brain structure in childhood maltreatment-related PTSD across the lifespan, the authors state that neuroimaging studies in traumatised populations still lag behind other fields in juvenile and even in adult populations (3) **(Finding 1.)**. The authors again emphasised the heterogeneity and inconsistency of existing studies **(Finding 1.)**. Their main finding was a pattern of volumetric reductions in hippocampus, corpus callosum, amygdala, and the cerebellum; regions of the brain that are implicated in emotional processing, fear conditioning and memory. However, results do differ substantially across studies. The conclusions of Kyllion and Weyandt are in line with those of our review in 2013. Killion et al. notice that total brain volume, consistently reduced in traumatised minors, has not been investigated in adults.

The reduction in hippocampal volume reported in adults with PTSD could not be confirmed by studies in juveniles while the smaller volume of the CC in traumatised minors is not reported in studies in adults **(Finding 2.)**. The first longitudinal study with structural (GM VBM) and functional (Resting state functional connectivity) MRI data in pediatric PTSD, with an one year follow-up, has only been published recently (4). Youth (8-18 y) with PTSD exhibited sustained reductions in grey matter volume (VBM) in several regions of the PFC, predictive of symptom severity. Further, these youth showed aberrant (increased) longitudinal development of the dorsolateral PFC compared to typically developing youth (normative decrease) between baseline and one year follow-up. Furthermore, PTSD patients showed atypical longitudinal decrease in PFC-amygdala and PFC-hippocampus resting state connectivity, in contrast to an increase in typically developing youths. Sexual abuse, witnessing violence and traumatic accident or death are mentioned as type of trauma. This means that, unfortunately, different types of trauma were included, while recent research suggests an influence of type of trauma on neurobiological trajectories, so different trajectories night be mixed. Again, this makes results hard to compare between studies. There are currently no longitudinal studies spanning juvenile and adult age in populations with ACE, while these studies will be pivotal to map structural changes in the brain following ACE over the total period of development and will help explain differences in structural findings between minors and adults **(Finding 2.)**.

Both our review and the review by Killion and Weyandt (2018), about brain structure in childhood maltreatment-related PTSD across the lifespan, show that inclusion criteria are diverse. Studies can be categorized in those that focus on type of trauma and studies focussing on the consequences of trauma, i.e. pathology (PTSD or PTSD symptoms). Adverse experiences in the studies can be as varied as having been reared in an institution (5) or being the victim of an earthquake (6). In studies focussing on pathology, the type of traumatic experiences is not always specified, but might be decisive.

There is growing interest in the differential neurobiological correlates of different forms of childhood maltreatment and their consequences for pathology and treatment. Growing awareness that different types of adversity may have different neurobiological sequelae is demonstrated for

example by the meta-analysis of Baumeister et al. (7). They conclude that there is strong evidence for the impact of ACE on the inflammatory immune system, and that specific types of trauma (sexual, physical or emotional abuse) differentially impact on specific inflammatory markers and potentially pathogenic pro-inflammatory phenotypes associated with physical and mental illnesses. Changes in epigenetic regulation of gene expression may be responsible for the increased immune activation. This appears plausible in view of the considerable evidence, as mentioned in the introduction, that childhood trauma induces epigenetic modifications of HPA- and neuroplasticity-related methylation patterns (8).

2.1.2 GM – VBM - Limbic circuitry

The absence of group differences in hippocampal volume in the VBM study, is in line with earlier research in traumatised minors **(Finding 3.)** (9). This in contrast to consistent findings of smaller hippocampal volume in traumatised adults with or without PTSD, even when traumatisation took place during childhood **(Finding 2.)** (3;9;10). While the smaller hippocampal volume found in adults might be a consequence as well as a vulnerability factor in relation to childhood trauma, the absence of this finding in youths indicates it is a consequence. However, it is still unresolved whether lower hippocampal volume increases vulnerability for trauma related consequences or retraumatisation. Longitudinal studies could shed more light on this subject.
The finding of smaller volume in the dorsal ACC as well as post-hoc smaller volume in the right amygdala (with PDS as covariate), both implicate the limbic circuit **(Finding 4.)**. In our review, the other regions reported on in juvenile populations besides the CC, with some exceptions (pituitary, superior temporal gyrus), were part of the limbic, emotion regulating circuit: (para-) hippocampus, frontal cortex, amygdala, cerebellum and uncinate fasciculus. This is understandable as psychotrauma is a strong emotional experience. In animal (11-14) as well as adult studies (15;16), early adversity is consistently found to be associated with smaller volumes in the limbic system, specifically the dorsal ACC and amygdala. In minors however, these regions are less often and inconsistently reported **(Finding 2.)**. The VBM-study in this thesis was the first to focus specifically on older adolescents with CSA. The older age of the participants might explain why the results of the VBM study resemble those of traumatised adults, where findings implicate limbic structures. Functional neuro-imaging findings from the EPISCA-project comparing the CSA-related PTSD and control groups, report abnormalities (increased as well as decreased connectivity) in amygdala-centred networks as well (17). Together with our amygdala results from the VBM-study, this suggests impact of childhood traumatisation on amygdala structure and functioning in older adolescents.

2.1.3 GM - Cortical thickness – Type of trauma

This thesis found no CSA-related effects for cortical thickness, surface area or volume in any of the ROIs: ventromedial PFC (vmPFC), ACC, insula, and middle/superior temporal gyrus **(Finding 5.)**. Because cortical thickness (CT) is a relatively new neuroimaging analysis technique, no such studies were included in our initial review. CT is considered a complementary technique to VBM in studying grey mater integrity. The ten previous CT studies with traumatised children and adolescents do not allow firm conclusions because of differences in methodology (e.g. choice of ROI) and samples studied (18-27). While studies with traumatised adults as well as minors almost all show reduced CT, differences were located in a wide variety of regions (10;28).

Remarkably, the only CT study, by Landré et al., in adult women with only sexual abuse-related PTSD, also showed normal CT compared to healthy controls. The authors suggest that apart from gender, the type of trauma (sexual abuse) could explain this negative result compared to the positive CT results in other adult PTSD studies, mostly concerning male veterans (29). The variety in inclusion criteria, specifically type of trauma, found in the studies with traumatised minors described

in our review, contrasts strongly with the research in traumatised adults, which is dominated by studies from the USA in veterans with PTSD. In conclusion, the normal CT measures we found in our study, could be related to the specific form of adversity studied **(Finding 5.)**. In a wider context, this means that the differences reported in the trauma literature between studies including different age groups could not only be related to brain development, but also to the type of adversity included. More research in adults and minors focussing on the role of type of trauma is thus necessary.

Focussing on gender specificity may be relevant as brain development is known to be influenced by sex hormones (30). The role of gender was explicitly investigated by deBellis (31). He concluded that in his group of children and adolescents with chronic PTSD based on abuse, boys more than girls showed smaller cerebral and regional CC volumes and larger lateral ventricle volume compared to healthy controls. In our study we could not properly investigate this topic as the majority of our participants were girls.

2.1.4 WM – DTI - Corpus callosum

The DTI-study in this thesis showed lower FA, indicating decreased integrity, in the genu, midbody and splenium of the CC in the PTSD group compared to healthy controls **(Finding 6.)**. The most consistent finding in our review was a smaller size or lesser integrity of the corpus callosum (CC) in juvenile traumatised populations, which has not been reported in adult populations with psychotrauma, both with or without PTSD **(Finding 2.)**. The review by Killion and Weyandt (which includes our DTI study) confirms this conclusion for the CC (3).

In animal studies and in the growing field of neuroimaging research in traumatised human populations, childhood adversity has found to be associated with circuitry involved in stress and emotion regulation, drawing attention to studies of connectivity (11;14). Therefore, we investigated, in addition to grey matter, white matter tracts connecting different brain regions. At the time we conducted the DTI-study, only four similar studies in children and youth had examined the effects of psychotrauma on white matter integrity in the developing brain. Next to involvement of the CC, these studies found lower FA in the uncinate fasciculus (UF), superior longitudinal fasciculi, cingulum bundle and inferior fronto-occipital fasciculus.

The CC, the largest white matter structure of the brain, with over 190 million axons, connects homotopic and heterotopic regions of the two hemispheres. Surprisingly, in persons with a “split-brain” because of a surgical commissurotomy, typically conducted in adulthood for the treatment of intractable epilepsy, deficits were noted in cognitive processing time, arithmetic, abstract reasoning and short term memory, while speech, verbal intelligence, calculation, motor coordination, verbal reasoning and recall, personality and temperament were all preserved, leading to only subtle behavioural consequences in everyday life (32). Further, agenesis of the CC (AgCC), a failure to develop, occurs in at least 1:4000 live births, resulting from genetic, infectious, vascular or toxic causes. Interestingly, a clinical study reported that about one third of subjects with AgCC developed normally or were only mildly delayed. In general, primary AgCC has a surprisingly limited impact on general cognitive ability (32;33). Of individuals assessed for neurodevelopmental disorders, 3-5% have AgCC and a smaller CC has consistently been reported in populations of patients with schizophrenia (34), autism spectrum disorder (35) and ADHD (36). The CC changes throughout life, but is especially dynamic during brain development (37).

Taken together, the CC dynamically changes during brain development and is involved in the onset of neurodevelopmental disorders, although psychological consequences in later life related to aberrant CC development are not specific and in general unclear. Childhood trauma has profound influence on brain development, including the CC, and increases the risk for psychopathology later in life, but these affective disorders are distinct from those typically mentioned in relation to disturbed

CC development. Remarkably, higher FA values in the CC have been associated with resilience to childhood stress (38). A hypothesis explaining the absence of structural CC abnormalities in adult traumatised populations, in contrast to minors, is that the CC may play an active role during the developmental phase of the brain, possibly related to learning, with the consequence that the CC is susceptible to the neurotoxic influence of stress hormones mainly during this period. Next, the structural changes seem to be compensated in the transition to adulthood. It is remarkable that, apart from connecting the two hemispheres, the precise function of the dynamic CC during brain development, showing increases as well as decreases in volume, is scarcely described in the literature. Clearly, the connection between childhood adversity, its neurobiological consequences and CC structure needs to be studied in more detail. In particular longitudinal studies are warranted.

2.2 Associations with trauma symptomatology

In the three structural neuroimaging studies of this thesis the association of structural abnormalites with measures of trauma symptomatology was limited **(Finding 7.)**. Only the white matter DTI study yielded an association. The FA values in the left body of the corpus callosum showed a significant negative correlation with scores on the anger subscale of the Trauma Symptom Checklist for Children (TSCC). The body of the CC has connections with frontal regions as well as with subcortical nuclei (2). Abnormalities in the midbody of the CC, reported in the DTI study, could be related to disturbances in connectivity with limbic subcortical nuclei, which might explain the relationship with anger symptoms.

As described in our review, earlier neuroimaging research in traumatised minors usually found limited association of neuroimaging findings with symptomatology **(Finding 7.)**. Only two studies reported an association with clinical symptoms. Tupler and DeBellis (39) found trauma severity scores to be correlated with decreased hippocampal volume and Eluvathingal in their very small DTI-study (7 early deprived children, 7 normal controls) for disturbances in neurocognitive and behavioural functioning being correlated with decreased FA in the uncinate fasciculus (40). The lack of association with trauma symptomatology in structural studies might be due to several factors: In our study it could be related to the skewed distribution of the severity of symptomatology (i.e. predominantly severe). Another explanation might well be that structural effects only become visible in the long term. As discussed in relation to our VBM-result, adult trauma research found a correlation of ACC activation, but not volume, with PTSD symptom severity (41) and cumulative adversity (42).

In this light, it is worth mentioning that Aghajani et al. of the EPISCA group found abnormal functional connectivity of amygdala subregional networks in combination with diminished grey matter volume of the basolateral (BLA) and centromedial amygdala subnuclei (CMA) (17). The CMA abnormal connectivity was related to more severe PTSD symptoms, suggesting possible biomarkers and potential therapeutic targets.

2.3 Potential clinical implications

The findings in thesis do not have direct clinical implications. However, a better understanding of the neurobiological trajectories connecting traumatisation in youth to pathology in later life, may help to identify ways to influence the course of these trajectories by prevention and treatment in the still malleable developing brain. Studies in adult populations have already shown that brain changes, structural as well as functional, are related to treatment effect (43).

Adverse childhood experiences (ACE) have an impressive influence on general health. Apart from the suffering of the survivors of childhood trauma in the direct aftermath of this experience, they have much higher chances to develop psychiatric as well as somatic disease in later life. Adverse events

early in life can lead to changes in gene expression through epigenetic mechanisms that alter stress reactivity, brain function, and behaviour (44). This vulnerability might even be transmitted to the next generation and it is suggested that also the therapeutic effect can be passed down to the following generation, which adds even more value to finding the treatment strategies to mitigate the consequences of childhood abuse and neglect (45).

Knowledge about normal and abnormal structure and function of specific brain circuits, like the limbic system implicated in our VBM study and in many adult studies (10;28), opens the possibility of linking malleability of specific brain regions and circuitry to the influence of the psychological processes that are part of trauma therapy. As an example in children, sensitivity to positive stimuli has shown to be an important protective factor and is also associated with reduced risk for psychopathology following child trauma exposure (46). Sensitivity to positive stimuli corresponds with activation in the basal ganglia, part of the reward circuitry. Interestingly, Trauma focused CBT, the regular treatment for childhood trauma, was found to target sensitivity to positive stimuli and other psychobiological processes that could potentially be monitored before and after treatment by MRI (47).

Of interest, the indications that specific types of childhood trauma are associated with specific findings in the structure of the brain, like in our cortical thickness study, may open avenues for further elucidating not only the trajectories and vulnerability for ACE/CSA , but possibly also potential approaches to modify these trajectories in a more personalised way. (48).

2.4 Considerations and limitations

There are several potential limitations for the empirical studies in this thesis. First, although we were aware that gender influences brain development and gene environment interactions, such as the reaction to trauma, we could not address this topic because our participants were predominantly female. We elaborated on this aspect in our discussion of the results of the CT study (see 1c.) (3). Second, the CSA-related PTSD group was significantly older and more advanced in pubertal development than the control group. This could have influenced the results. However, the differences partly remained when we controlled for age and pubertal development. Third, full-scale IQ measures differed significantly between the CSA-related PTSD group and controls. As PTSD has been found to depress IQ values, the CSA-related PTSD group might originally have been more equal to the control group with respect to intellectual ability (31;49;50). Fourth, we did not control for social-economic status (SES). SES is of relevance since certain SES factors such as poverty have been found to influence neuro-cognitive and brain functioning. In the recent review by Killion and Weyandt on structural imaging in maltreatment related PTSD populations across the lifespan, only half of the studies took SES into account. In our own review on studies in minors, seven of the 26 studies with a group comparison did not mention SES. Brito and Noble reviewed 21 studies concerning the relationship between SES and structural brain development and conclude that the underlying causal pathways between environmental disadvantage and developmental outcomes are not yet clear (51). Several factors like age, sex, education, poverty, life events and brain development (even in adults) seem to interact differentially. For example, the study by Luby et al. showed that the relationship between income and hippocampal volume in childhood was mediated by caregiving support / hostility and stressful life events (52). Rigorous assessment is advocated, combining careful social science with the most advanced neuroscientific approaches. Fifth, although often substantially motivated, it took a long time to include sufficient numbers of participants in the trauma group. This was possibly related to the severity of the traumatic experiences and the turmoil CSA often generates in families. As a result, the post-hoc analysis in the VBM study, had to be conducted in small groups because of PDS-data missing in many individuals, which subsequently changed the effect. Finally, timing and frequency of trauma are relevant when studying childhood

trauma. However, as in our study several of the perpetrators of the CSA were family members, it was not possible to reliably assess these aspects retrospectively.

Functional MRI (f-MRI) studies were not included in this thesis. So far, f-MRI studies in minors with CSA seem to indicate involvement of the hippocampus, frontal regions, visual cortex, cerebellum, ACC and total cerebral and intracranial volume (53;54). F-MRI studies in traumatised adults have shown altered activity in the limbic circuit: amygdala, ACC, ventromedial and lateral PFC, hippocampus, linking brain function to emotional-cognitive processes (14;55-57). Reviews show that functional MRI data from traumatised children and adolescents are even less available than structural studies and findings have usually not been replicated (53). Combining structural and functional MRI in studies more often, might help to better understand the relation between CSA and neurodevelopmental trajectories.

2.5 Directions for future neuroimaging research in adolescents with CSA

Recent reviews show that the literature about psychotraumatology in general has grown impressively the last two decades (58), while the neurobiological research in traumatised minors is still limited. Differences in findings between juvenile and adult populations are not yet understood. The following suggestions for future research can be made. First of all, to allow more meaningful comparison of CSA studies, groups must be well defined, using strict inclusion criteria and standardized assessments. Importantly, specifying trauma type and characteristics, might enable more comprehensive comparison of results with other pediatric as well as adult populations with or without PTSD and could play a role in elucidating different trauma-specific neurobiological pathways from childhood adverse experiences to pathology in adulthood. Trauma-specific neurobiological research might contribute to finding trauma-specific therapeutic and preventative interventions (56;59). Confounders like SES, age, IQ, gender, comorbidity, psychopharmacotherapy and puberty development are important to control for. Second, when planning studies in traumatised individuals, substantial effort must be put in preparing the inclusion of adequate numbers of participants. Although participants in our studies were highly motivated, we ended up with (too) small groups in the longitudinal part of the study due to attrition. Third, the dynamics of brain development calls for longitudinal studies where traumatised groups with and without pathology (PTSD) and specific types of trauma are compared with healthy, non-traumatised controls, with follow-up from childhood into adulthood. Global collaboration projects like the Enhancing NeuroImaging Genetics through Meta-analyses (ENIGMA) initiative where "ideas, algorithms, data and information on research studies and methods" are shared and data pooled, might provide such opportunities. One of the ENIGMA working groups targets PTSD and has included cohorts of minors, including the EPISCA sample, to eventually pool these data in minors, but also to identify possible developmental trajectories. Fourth, detailed mapping of the normal development of different brain (sub-)regions and circuitry, may help to interpret neuroimaging findings obtained from traumatised populations at different moments in childhood, adolescence and (young) adulthood.

A potential clinically relevant aspect of neuroimaging research in adolescents could be the identification of **biomarkers** that predict treatment response or guide selection of treatment. Research in traumatised adults suggests that structural and functional neuroimaging measures could indeed be potential biomarkers for treatment effect (43). Thomaes et al. showed in their review on trauma treatment effects that pharmacotherapy improved structural abnormalities (i.e., increased hippocampus volume) in both adult trauma and child abuse related PTSD. Adult trauma PTSD patients showed decreased amygdala and increased dorsolateral prefrontal activations post-treatment (43). A recent review about biomarkers of treatment effect in adults with PTSD included 20 studies, of which five structural neuroimaging studies, and provides preliminary evidence that specific structural and functional neural systems (typically involved in emotional information processing), glucocorticoid sensitivity and metabolism (part of the HPA-axis and the response to

stress), heart rate (involved with fear habituation), gene methylation, and certain genotypes (associated with serotonin and glucocorticoids) predicted positive response to PTSD treatment (60). Interestingly, these pre-treatment biomarkers are associated with processes included in PTSD treatment, such as those focusing on fear learning and extinction, cognitive restructuring, information processing, emotional processing, and interoceptive monitoring. Identifying pre-treatment biomarkers predicting treatment response may offer insight into the psychobiological mechanisms of psychological treatment and improve treatment. Clearly, these biomarker studies should be extended to juvenile populations.

Epigenetic research shows that the interaction of environmental factors, especially adverse life events, with genetic predisposition underlies the risk for developing psychiatric disease (45;61). The regulation of the stress hormone system with glucocorticoids (GCs) and glucocorticoid receptors (GRs) plays a crucial role here (62). An example is the potential role of the **FKBP5** protein. FKBP5 is a strongly stress responsive part of the GR-complex for which gene & early adversity interactions are reported (63). Epigenetic mechanisms influence the development of many pathways implicated in neuronal function, synaptic plasticity and DNA-methylation. FKBP5 genotypes are associated with alterations in brain structure and function that affect behaviour, particularly in brain regions associated with emotional processing, learning, memory and inhibition (64). It is hypothesised that increased FKBP5 expression following GR activation delays the negative feedback phase of the HPA-axis, resulting in prolonged cortisol response to stress and trauma. Specifically the disruption of regulatory homeostasis of FKBP5 following stress might cause long-lasting changes in the brain circuits involved in emotion regulation, eventually leading to psychopathology. FKBP5 is mentioned in relation to stress resilience as a potential therapeutic target to treat PTSD and major depressive disorder (MDD) (65).

Part of the work of this thesis can be placed in the framework of the **Research Domain Criteria (RDoC) initiative**. Despite major advances in methods and findings in the central nervous system (CNS) research, neuroscience to date has made no great progress to advance the prevention and cure of mental illness. The NIMH therefore launched the Research Domain Criteria initiative (66). RDoC is an effort to promote the development of an interdisciplinary science of psychopathology that consists of dimensional constructs integrating psychology and biology, especially genetics and neuroscience. The goal is to elaborate a set of psychological constructs linked to behavioural dimensions for which strong evidence exists of neurobiological circuits that implement these functions and relate to functioning (impairment), independent of diagnostic categories (67). Core aspects within this construct are development and environment (68;69). Childhood and brain development play a crucial role in the first aspect and adversity in the second, with both cutting through diagnostic classification, the central element of RDoC (70). The research of this thesis, starting with CSA as an inclusion criterion and concentrating on development, might contribute to the goal of RDoC.

Another approach to identify underlying constructs was suggested by Caspi and Moffit, who based on results from their Dunedin Multidisciplinary Health and Development Study, focus on the common factors in different psychiatric diagnoses, looking at dimensionality, persistence, co-occurrence and sequential comorbidity: the General Psychopathology or **p-Factor** (71). ACE are known to be related to many psychiatric as well as somatic disorders (72;73) and are likely to be an important environmental element contributing to the p-Factor. The p-factor approach was employed in some other studies in the EPISCA project on neural correlates of attachment (74-77). These studies found unresolved-disorganised attachment to be associated with smaller left hippocampal volume and higher hippocampal functional connectivity, as well as with atypical amygdala resting-state functional connectivity, independent of diagnosis and independent of a general psychopathology factor.

Prevention is of course the holy grail, in particular in youth. More recently, it has been advocated by McCrory et al. that neurocognitive processes can be monitored by functional MRI (for example via amygdala reactivity) in a preventative manner, before the presentation of psychiatric disorder, and might give indications for specific interventions that promote resilience (78;79). Based on new neuroimaging results, McCrory et al. present a **vulnerability model** (79), in which altered neurocognitive processes associated with childhood maltreatment, including threat processing, reward processing, emotion regulation and executive control, give rise to brain changes that in interaction with environmental and genetic risk and protective factors, create vulnerability or resilience for psychiatric symptomatology.

Clearly, more research in larger studies with a longitudinal design and ideally combining multiple state-of-the art modalities and approaches is needed. Similarly, it is crucial to emphasize that the potential implications of the findings in this thesis and in other projects do not speak for themselves. Given the impact of ACE, these findings need a translation for clinicians, the public, and the policymakers in order to eventually better help the many children, adolescents and adults that experienced ACE (80).

Reference List

(1) Cukor J, Wyka K, Jayasinghe N, Difede J. The nature and course of subthreshold PTSD. J.Anxiety.Disord. 24[8], 918-923. 2010.

(2) Huang H, Zhang J, Jiang H, Wakana S, Poetscher L, Miller MI, van Zijl PC, Hillis AE, Wytik R, Mori S. DTI tractography based parcellation of white matter: application to the mid-sagittal morphology of corpus callosum. Neuroimage. 26[1], 195-205. 5-15-2005.

(3) Killion BE, Weyandt LL. Brain structure in childhood maltreatment-related PTSD across the lifespan: A systematic review. Appl.Neuropsychol.Child , 1-15. 10-23-2018.

(4) Heyn SA, Keding TJ, Ross MC, Cisler JM, Mumford JA, Herringa RJ. Abnormal Prefrontal Development in Pediatric Posttraumatic Stress Disorder: A Longitudinal Structural and Functional Magnetic Resonance Imaging Study. Biol.Psychiatry Cogn Neurosci.Neuroimaging 4[2], 171-179. 2019.

(5) Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, Rutter M, Sonuga-Barke EJ. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. J.Child Psychol.Psychiatry 50[8], 943-951. 2009.

(6) Yang P, Wu MT, Hsu CC, Ker JH. Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: a functional MRI study. Neurosci.Lett. 370[1], 13-18. 11-3-2004.

(7) Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. Mol.Psychiatry 21[5], 642-649. 2016.

(8) Labonte B, Suderman M, Maussion G, Navaro L, Yerko V, Mahar I, Bureau A, Mechawar N, Szyf M, Meaney MJ, Turecki G. Genome-wide epigenetic regulation by early-life trauma. Arch.Gen.Psychiatry 69[7], 722-731. 2012.

(9) Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 18[8], 729-736. 2008.

(10) O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res. 232[1], 1-33. 4-30-2015.

(11) Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev.Psychopathol. 13[3], 419-449. 2001.

(12) Teicher MH. Scars that won't heal: the neurobiology of child abuse. Sci.Am. 286[3], 68-75. 2002.

(13) Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: clinical implications. Biol.Psychiatry 48[8], 778-790. 10-15-2000.

(14) McCrory E, De Brito SA, Viding E. Research review: the neurobiology and genetics of maltreatment and adversity. J.Child Psychol.Psychiatry 51[10], 1079-1095. 2010.

(15) Bremner JD, Vermetten E. Stress and development: behavioral and biological consequences. Dev.Psychopathol. 13[3], 473-489. 2001.

(16) van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM. Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biol.Psychiatry 68[9], 832-838. 11-1-2010.

(17) Aghajani M, Veer IM, van Hoof MJ, Rombouts SA, van der Wee NJ, Vermeiren RR. Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. Hum.Brain Mapp. 37[3], 1120-1135. 2016.

(18) Ahmed F, Spottiswoode BS, Carey PD, Stein DJ, Seedat S. Relationship between neurocognition and regional brain volumes in traumatized adolescents with and without posttraumatic stress disorder. Neuropsychobiology 66[3], 174-184. 2012.

(19) Busso DS, McLaughlin KA, Brueck S, Peverill M, Gold AL, Sheridan MA. Child Abuse, Neural Structure, and Adolescent Psychopathology: A Longitudinal Study. J.Am.Acad.Child Adolesc.Psychiatry 56[4], 321-328. 2017.

(20) Gold AL, Sheridan MA, Peverill M, Busso DS, Lambert HK, Alves S, Pine DS, McLaughlin KA. Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. J.Child Psychol.Psychiatry 57[10], 1154-1164. 2016.

(21) Hodel AS, Hunt RH, Cowell RA, Van Den Heuvel SE, Gunnar MR, Thomas KM. Duration of early adversity and structural brain development in post-institutionalized adolescents. Neuroimage. 105, 112-119. 1-15-2015.

(22) Kelly PA, Viding E, Wallace GL, Schaer M, De Brito SA, Robustelli B, McCrory EJ. Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? Biol.Psychiatry 74[11], 845-852. 12-1-2013.

(23) Kelly PA, Viding E, Puetz VB, Palmer AL, Samuel S, McCrory EJ. The sexually dimorphic impact of maltreatment on cortical thickness, surface area and gyrification. J.Neural Transm.(Vienna.) 123[9], 1069-1083. 2016.

(24) Klabunde M, Weems CF, Raman M, Carrion VG. The moderating effects of sex on insula subdivision structure in youth with posttraumatic stress symptoms. Depress.Anxiety. 34[1], 51-58. 2017.

(25) Lim L, Hart H, Mehta M, Worker A, Simmons A, Mirza K, Rubia K. Grey matter volume and thickness abnormalities in young people with a history of childhood abuse. Psychol.Med. 48[6], 1034-1046. 2018.

(26) McLaughlin KA, Sheridan MA, Winter W, Fox NA, Zeanah CH, Nelson CA. Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. Biol.Psychiatry 76[8], 629-638. 10-15-2014.

(27) Whittle S, Dennison M, Vijayakumar N, Simmons JG, Yucel M, Lubman DI, Pantelis C, Allen NB. Childhood maltreatment and psychopathology affect brain development during adolescence. J.Am.Acad.Child Adolesc.Psychiatry 52[9], 940-952. 2013.

(28) Kuhn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol.Psychiatry 73[1], 70-74. 1-1-2013.

(29) Landre L, Destrieux C, Baudry M, Barantin L, Cottier JP, Martineau J, Hommet C, Isingrini M, Belzung C, Gaillard P, Camus V, El HW. Preserved subcortical volumes and cortical thickness in women with sexual abuse-related PTSD. Psychiatry Res. 183[3], 181-186. 9-30-2010.

(30) Herting MM, Maxwell EC, Irvine C, Nagel BJ. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb.Cortex 22[9], 1979-1992. 2012.

(31) De Bellis MD, Keshavan MS. Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. Neurosci.Biobehav.Rev. 27[1-2], 103-117. 2003.

(32) Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat.Rev.Neurosci. 8[4], 287-299. 2007.

(33) Badaruddin DH, Andrews GL, Bolte S, Schilmoeller KJ, Schilmoeller G, Paul LK, Brown WS. Social and behavioral problems of children with agenesis of the corpus callosum. Child Psychiatry Hum.Dev. 38[4], 287-302. 2007.

(34) Innocenti GM, Ansermet F, Parnas J. Schizophrenia, neurodevelopment and corpus callosum. Mol.Psychiatry 8[3], 261-274. 2003.

(35) Frazier TW, Hardan AY. A meta-analysis of the corpus callosum in autism. Biol.Psychiatry 66[10], 935-941. 11-15-2009.

(36) Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention-deficit/hyperactivity disorder. Biol.Psychiatry 57[11], 1263-1272. 6-1-2005.

(37) Luders E, Thompson PM, Toga AW. The development of the corpus callosum in the healthy human brain. J.Neurosci. 30[33], 10985-10990. 8-18-2010.

(38) Galinowski A, Miranda R, Lemaitre H, Paillere Martinot ML, Artiges E, Vulser H, Goodman R, Penttila J, Struve M, Barbot A, Fadai T, Poustka L, Conrod P, Banaschewski T, Barker GJ, Bokde A, Bromberg U, Buchel C, Flor H, Gallinat J, Garavan H, Heinz A, Ittermann B, Kappel V, Lawrence C, Loth E, Mann K, Nees F, Paus T, Pausova Z, Poline JB, Rietschel M, Robbins TW, Smolka M, Schumann G, Martinot JL. Resilience and corpus callosum microstructure in adolescence. Psychol.Med. 45[11], 2285-2294. 2015.

(39) Tupler LA, De B. Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. Biol.Psychiatry 59[6], 523-529. 3-15-2006.

(40) Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M. Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 117[6], 2093-2100. 2006.

(41) Nardo D, Hogberg G, Looi JC, Larsson S, Hallstrom T, Pagani M. Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J.Psychiatr.Res. 44[7], 477-485. 2010.

(42) Ansell EB, Rando K, Tuit K, Guarnaccia J, Sinha R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol.Psychiatry 72[1], 57-64. 7-1-2012.

(43) Thomaes K, Dorrepaal E, Draijer N, Jansma EP, Veltman DJ, van Balkom AJ. Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. J.Psychiatr.Res. 50, 1-15. 2014.

(44) Turecki G, Ota VK, Belangero SI, Jackowski A, Kaufman J. Early life adversity, genomic plasticity, and psychopathology. Lancet Psychiatry 1[6], 461-466. 2014.

(45) Provencal N, Binder EB. The neurobiological effects of stress as contributors to psychiatric disorders: focus on epigenetics. Curr.Opin.Neurobiol. 30, 31-37. 2015.

(46) Dennison MJ. The importance of developmental mechanisms in understanding adolescent depression. Soc.Psychiatry Psychiatr.Epidemiol. 51[6], 791-793. 2016.

(47) McLaughlin KA, Lambert HK. Child Trauma Exposure and Psychopathology: Mechanisms of Risk and Resilience. Curr.Opin.Psychol. 14, 29-34. 2017.

(48) Shonkoff JP. Protecting brains, not simply stimulating minds. Science 333[6045], 982-983. 8-19-2011.

(49) Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl) 214[1], 55-70. 2011.

(50) Perez CM, Widom CS. Childhood victimization and long-term intellectual and academic outcomes. Child Abuse Negl. 18[8], 617-633. 1994.

(51) Brito NH, Noble KG. Socioeconomic status and structural brain development. Front Neurosci. 8, 276. 2014.

(52) Luby J, Belden A, Botteron K, Marrus N, Harms MP, Babb C, Nishino T, Barch D. The effects of poverty on childhood brain development: the mediating effect of caregiving and stressful life events. JAMA Pediatr. 167[12], 1135-1142. 2013.

(53) Milani AC, Hoffmann EV, Fossaluza V, Jackowski AP, Mello MF. Does pediatric post-traumatic stress disorder alter the brain? Systematic review and meta-analysis of structural and functional magnetic resonance imaging studies. Psychiatry Clin.Neurosci. 71[3], 154-169. 2017.

(54) Rinne-Albers MA, van der Wee NJ, Lamers-Winkelman F, Vermeiren RR. Neuroimaging in children, adolescents and young adults with psychological trauma. Eur.Child Adolesc.Psychiatry . 4-4-2013.

(55) Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, Domschke K, Hohoff C, Ohrmann P, Bauer J, Lindner C, Postert C, Konrad C, Arolt V, Heindel W, Suslow T, Kugel H. Limbic Scars: Long-Term Consequences of Childhood Maltreatment Revealed by Functional and Structural Magnetic Resonance Imaging. Biol.Psychiatry . 11-21-2011.

(56) Hayes JP, Vanelzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. Front Integr.Neurosci. 6, 89. 2012.

(57) Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. Nat.Rev.Neurosci. 17[10], 652-666. 9-19-2016.

(58) Olff M. Psychotraumatology on the move. Eur.J.Psychotraumatol. 9[1], 1439650. 2018.

(59) Hedges DW, Woon FLM. Structural magnetic resonance imaging findings in posttraumatic stress disorder and their response to treatment: A systematic review. Current Psychiatry Reviews 3[2], 85-93. 2007.

(60) Colvonen PJ, Glassman LH, Crocker LD, Buttner MM, Orff H, Schiehser DM, Norman SB, Afari N. Pretreatment biomarkers predicting PTSD psychotherapy outcomes: A systematic review. Neurosci.Biobehav.Rev. 75, 140-156. 2017.

(61) Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. Science 297[5582], 851-854. 8-2-2002.

(62) de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat.Rev.Neurosci. 6[6], 463-475. 2005.

(63) Matosin N, Halldorsdottir T, Binder EB. Understanding the Molecular Mechanisms Underpinning Gene by Environment Interactions in Psychiatric Disorders: The FKBP5 Model. Biol.Psychiatry 83[10], 821-830. 5-15-2018.

(64) Matosin N, Halldorsdottir T, Binder EB. Understanding the Molecular Mechanisms Underpinning Gene by Environment Interactions in Psychiatric Disorders: The FKBP5 Model. Biol.Psychiatry 83[10], 821-830. 5-15-2018.

(65) Sabbagh JJ, O'Leary JC, III, Blair LJ, Klengel T, Nordhues BA, Fontaine SN, Binder EB, Dickey CA. Age-associated epigenetic upregulation of the FKBP5 gene selectively impairs stress resiliency. PLoS.One. 9[9], e107241. 2014.

(66) Cuthbert BN, Kozak MJ. Constructing constructs for psychopathology: the NIMH research domain criteria. J.Abnorm.Psychol. 122[3], 928-937. 2013.

(67) Kozak MJ, Cuthbert BN. The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. Psychophysiology 53[3], 286-297. 2016.

(68) Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the research domain criteria (RDoC) framework. Biol.Psychiatry 76[5], 350-353. 9-1-2014.

Ref Type: Journal

69) Mittal VA, Wakschlag LS. Research domain criteria (RDoC) grows up: Strengthening neurodevelopment investigation within the RDoC framework. J.Affect.Disord. 216, 30-35. 2017.

(70) Garvey M, Avenevoli S, Anderson K. The National Institute of Mental Health Research Domain Criteria and Clinical Research in Child and Adolescent Psychiatry. J.Am.Acad.Child Adolesc.Psychiatry 55[2], 93-98. 2016.

(71) Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, Meier MH, Ramrakha S, Shalev I, Poulton R, Moffitt TE. The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? Clin.Psychol.Sci. 2[2], 119-137. 2014.

(72) Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur.Arch.Psychiatry Clin.Neurosci. 256[3], 174-186. 2006.

(73) Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am.J.Prev.Med. 14[4], 245-258. 1998.

(74) Riem MME, van Hoof MJ, Garrett AS, Rombouts SARB, van der Wee NJA, van IJzendoorn MH, Vermeiren RRJM. General psychopathology factor and unresolved-disorganized attachment uniquely correlated to white matter integrity using diffusion tensor imaging. Behav.Brain Res. 359, 1-8. 10-10-2018.

(75) van Hoof MJ, Riem MME, Garrett AS, van der Wee NJA, van IJzendoorn MH, Vermeiren RRJM. Unresolved-disorganized attachment adjusted for a general psychopathology factor associated with atypical amygdala resting-state functional connectivity. Eur.J.Psychotraumatol. 10[1], 1583525. 2019.

(76) van Hoof MJ, van Lang ND, Speekenbrink S, van IJzendoorn MH, Vermeiren RR. Adult Attachment Interview differentiates adolescents with Childhood Sexual Abuse from those with clinical depression and non-clinical controls. Attach.Hum.Dev. 17[4], 354-375. 2015.

(77) van Hoof MJ, van den Bulk BG, Rombouts SARB, Rinne-Albers MAW, van der Wee NJA, van IJzendoorn MH, Vermeiren RRJM. Emotional face processing in adolescents with childhood sexual abuse-related posttraumatic stress disorder, internalizing disorders and healthy controls. Psychiatry Res. 264, 52-59. 6-30-2017.

(78) McCrory EJ, Gerin MI, Viding E. Annual Research Review: Childhood maltreatment, latent vulnerability and the shift to preventative psychiatry - the contribution of functional brain imaging. J.Child Psychol.Psychiatry 58[4], 338-357. 2017.

(79) McCrory EJ, Puetz VB, Maguire EA, Mechelli A, Palmer A, Gerin MI, Kelly PA, Koutoufa I, Viding E. Autobiographical memory: a candidate latent vulnerability mechanism for psychiatric disorder following childhood maltreatment. Br.J.Psychiatry 211[4], 216-222. 2017.

(80) Shonkoff JP, Bales SN. Science does not speak for itself: translating child development research for the public and its policymakers. Child Dev. 82[1], 17-32. 2011.

Nederlandse samenvatting

Inleiding

Traumatische ervaringen in de jeugd komen veel voor. In Nederland worden ieder jaar tussen de 90.000 en 127.000 kinderen misbruikt of verwaarloosd (De Derde Nationale Prevalentiestudie Mishandeling van Kinderen en Jeugdigen, 2017; www.wodc.nl). Wereldwijd laat een onderzoek van de Wereld Gezondheidsorganisatie (WHO), met een iets bredere definitie van trauma, zien dat in zowel rijke als arme landen hoge aantallen worden gevonden (38,4% versus 39,1%) van ongeveer één op de drie kinderen. Behalve dat dit veel leed veroorzaakt direct na deze ervaringen, zoals angst, depressie, slaap- en leerproblemen of een posttraumatische stressstoornis (PTSS), zijn de gevolgen op langere termijn ernstig en veelvormig en omvatten een vergroot risico op niet alleen psychiatrische, maar ook lichamelijke stoornissen zoals hart- en vaatziekten, chronische longaandoeningen en diabetes.
Het menselijk brein ontwikkelt zich tot ver in het derde decennium en verloopt van een indrukwekkende toename van hersencellen, hun vertakkingen en verbindingen in de eerste fase tot differentiatie en terugsnoeien gedurende de adolescentie en vroege volwassenheid. Het proces van selectieve snoei gebeurt op grond van ervaringen en volgt globaal het principe “use it or lose it”, ofwel: wat wordt gebruikt blijft. Op deze manier past het zich ontwikkelende brein zich aan de omgeving aan en faciliteert maximale adaptatie en overleving. Dit proces van selectieve snoei of verlies van cellen, vertakkingen en synapsen wordt in ieder geval gedeeltelijk gecontroleerd door de neurotoxische effecten van stresshormonen zoals cortisol. Dit zou kunnen verklaren hoe en waarom traumatische ervaringen in de jeugd, als intens bedreigende en stressvolle ervaringen, een grote invloed uitoefenen op de structurele ontwikkelingstrajecten van het brein. Er is wel gesuggereerd dat pathologie in het latere leven, na het doormaken traumatische ervaringen in de jeugd, het resultaat zou kunnen zijn van een in oorsprong adaptief proces. Op je hoede zijn en hyperalert in een bedreigende situatie is een passende reactie, maar wanneer het gevaar is geweken kunnen dezelfde fenomenen een uiting zijn van een angststoornis of PTSS later in het leven.

Doel van dit proefschrift

Het doel van dit proefschrift is om meer zicht te krijgen op de structuur van het brein van getraumatiseerde jongeren om uiteindelijk beter te begrijpen hoe traumatische ervaringen in de jeugd kunnen leiden tot een toename van het risico op psychische en lichamelijke stoornissen op latere leeftijd. Hiertoe worden structurele beeldvormende technieken gebruikt om structurele karakteristieken van het brein te exploreren in een groep van adolescenten die seksueel misbruik hebben meegemaakt. De bevindingen van dit proefschrift zouden mogelijk kunnen bijdragen aan het ontwikkelen van optimale behandel- en preventieve strategieën.

Centrale onderzoeksvragen:

- Wat zijn de structurele karakteristieken van het adolescentenbrein geassocieerd met traumatische ervaringen in de jeugd, specifiek seksueel misbruik?

- Is er een relatie tussen structurele afwijkingen in het adolescentenbrein en traumasymptomatologie?

Literatuurstudie

Als eerste is een literatuuroverzicht gemaakt om de resultaten in kaart te brengen van eerder beeldvormend hersenonderzoek (neuroimaging) bij kinderen en jongeren met psychologisch traumatiserende ervaringen in de jeugd. Dit leverde 27 studies op, gepubliceerd tussen 1999 en 2013. Slechts twee studies kwamen van buiten de Verenigde Staten en de overige waren afkomstig van drie onderzoeksgroepen, van deBellis (Pittsburgh), Carrion (Stanford) en Teicher (Harvard). 24 studies presenteerden resultaten van structureel onderzoek, waarvan vier gebruik maakten van Diffusion Tensor Imaging (DTI) techniek die de witte stof in de hersenen onderzoekt en drie studies presenteerden functioneel onderzoek.

De groepen van getraumatiseerde individuen waren zeer divers, wat de resultaten waarschijnlijk heeft beïnvloed. Sommige studies onderzochten specifieke vormen van trauma, zoals seksueel misbruik, fysieke mishandeling, vroege verwaarlozing, meemaken van huiselijk geweld, opgroeien in een instelling of het getuige zijn van een aardbeving. Andere selecteerden deelnemers op grond van de gevolgen van de traumatische ervaring, zoals een PTSS of verschijnselen hiervan. Deze verschillen in groepen deelnemers maakt het vergelijken van studies lastig.

De meest robuuste bevinding van de literatuurstudie was bij de groep van getraumatiseerde kinderen en adolescenten een verminderde grootte van verschillende gedeelten van de hersenbalk, die beide hersenhelften verbindt, het corpus callosum (CC) en een vermindering van het totale hersenvolume. Een kleinere omvang van de hippocampus, die vaak wordt vermeld bij volwassenen met PTSS werd niet consistent aangetoond bij kinderen of adolescenten. Bevindingen in de prefrontale cortex (PFC) en amygdala waren beperkt en divers. Behandeleffectstudies werden niet gezien.

Vanwege het beperkt aantal studies, de beperkte groepsgrootte van vele studies, de variatie in inclusiecriteria en dat sommige studies van dezelfde onderzoekspopulatie afkomstig waren, kunnen slechts voorzichtig conclusies worden getrokken. Het aantal onderzoeken met behulp van hersenscans bij getraumatiseerde kinderen en adolescenten lag duidelijk achter bij het aantal met getraumatiseerde volwassenen en met vergelijkbaar onderzoek met hersenscans bij ADHD en autisme.

Empirisch onderzoek

Het empirisch onderzoek van dit proefschrift was onderdeel van het Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA) project. Het doel van het EPISCA-project is het onderzoeken van neuronale emotie-regulerende circuits in de hersenen bij adolescenten van 12-18 jaar met angst- of depressieve stoornissen of met seksueel trauma in de voorgeschiedenis (Childhood Sexual Abuse – CSA) in vergelijking met gezonde, niet getraumatiseerde controlepersonen van dezelfde leeftijd. Deelnemers ondergingen structurele en functionele Magnetic Resonance Imaging (MRI) hersenscans. Voor het onderzoek van dit proefschrift naar de impact van seksueel misbruik werd een specifieke groep jongeren geïncludeerd die gedurende hun leven meer dan eenmalig seksueel misbruik hadden ervaren door één of meer daders, binnen of buiten het gezin. De groep werd geworven bij het Psychotraumacentrum in Leiden (onderdeel van Rivierduinen) en het Kinder- & Jeugdtraumacentrum (KJTC) in Haarlem. Alle deelnemers van de seksueel misbruik groep hadden PTSS terwijl dit niet een inclusiecriterium was. De groep werd daarom benoemd als (Eng) CSA-related PTSD. Bij alle structurele scantechnieken werd gekeken naar een mogelijke relatie met klinische symptomen.

Grijze stof – Voxel Based Morphometry (VBM) – Limbisch systeem

Het doel van deze studie was om afwijkingen in de grijze stof te bestuderen bij adolescenten met CSA-related PTSD in vergelijking met de gezonde controlegroep en de relatie met ernst van de klinische symptomen. De grijze stof van de hersenen bestaat voornamelijk uit de cellichamen van de zenuwcellen of neuronen. Gebaseerd op het literatuuroverzicht en studies bij volwassenen werden als ROI's (Regions of Interest) gekozen: de hippocampus, amygdala, anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC) en superior temporal gyrus (STG). De adolescenten met CSA-related PTSD vertoonden een 14,8% groter volume van de dorsale ACC in vergelijking met de controlegroep. De ACC heeft een sleutelpositie in de emotieregulatie van het brein en is onderdeel van het limbische (emotieregulatie-) systeem van de hersenen. Vanwege geringe mulicollinariteit van leeftijd en puberteitsontwikkeling (gemeten met de Puberty Development Scale – PDS) werd een post-hoc analyse uitgevoerd waarin zowel leeftijd als PDS werden toegevoegd als covariaten. In deze post-hoc analyse vertoonde de ACC geen verschil tussen de groepen, maar werd een kleiner volume gevonden van de rechter amygdala, ook onderdeel van het limbisch systeem. Het resultaat van een kleiner volume van de grijze stof van limbische structuren wordt ook gezien in populaties van getraumatiseerde volwassenen. Trauma symptomatologie, gemeten met de Trauma Symptom Checklist for Children (TSCC) gaf geen correlatie met VBM.

Grijze stof – Cortical Thickness – Type trauma

Cortical Thickness wordt gezien als een aanvullende methodiek ten opzichte van VBM ter bestudering van de grijze stof in de hersenen. Gebaseerd op eerder onderzoek bij zowel pediatrische als volwassen populaties werden de volgende ROI's gekozen: ventromediale PFC (vmPFC), ACC, insula, en middel / superior temporal gyrus. Er werd geen groepseffect gevonden voor cortical thickness, suface area of volume. Deze resultaten worden ook gezien bij volwassen vrouwen met sexual abuse-related PTSD in tegenstelling tot studies met volwassenen met ander type trauma's, suggererend dat het negatieve resultaat specifiek gerelateerd zou kunnen zijn aan vrouwen die seksueel misbruik hebben ervaren, onafhankelijk van de leeftijd.

Witte stof – Diffusion Tensor Imaging (DTI) – Corpus callosum

Het doel van deze studie was het onderzoeken van de integriteit van de witte stof van de hersenen in jongeren met CSA-related PTSD en controlepersonen. De witte stof van de hersenen bestaat voornamelijk uit de lange uitlopers van de zenuwcellen die zorgen voor de onderlinge verbindingen tussen neuronen en daardoor circuits in de hersenen weergeven. De witte kleur wordt veroorzaakt door de witte omhulling van deze uitlopers, de myelineschede. Gebaseerd op onze literatuurstudie selecteerden we een ROI bestaande uit: bilaterale fasciculus uncinatus (UF), genu, splenium en body van het corpus callosum (CC), en het bilaterale cingulum.

Een ROI-based, tract-based spatial statistics (TBSS) analyse toonde aan dat, vergeleken met de controlegroep, de CSA-related PTSD groep had lagere fractional anisotropy (FA) waarden in de genu, midbody en splenium van het CC. We vonden een significante negatieve correlatie tussen scores op de anger-subschaal van de TSCC en FA-waarden in de linker body van het CC. Post-hoc analyses van de additionele diffusion-parameters in het CC toonden een significante toename van radial en mean diffusivity (resp. RD and MD) in de CSA-related PTSD group in vergelijking met controles. Omdat deze parameters demyelinisatie (minder ontwikkeling van de myelineschede) aanduiden en dysmyelinisatie (afwijkende ontwikkeling van de myelineschede), verbindt dit de afwijkingen van de integriteit van het CC met de mogelijke invloed van stresshormonen.

Topografisch onderzoek aan het CC toont aan dat los van frontale connecties, de body van het CC ook connecties heeft met subcorticale hersenkernen (nucleï). De afwijkingen in de midbody van het CC, aangetoond in onze studie zouden daardoor kunnen zijn gerelateerd aan verstoringen van de connectiviteit met subcorticale limbische nucleï, veroorzaakt door stoornissen in de emotieregulatie.

Dit proefschrift genereerde zeven belangrijke bevindingen:

Ten eerste, neuroimaging studies met getraumatiseerde kinderen en adolescenten zijn beperkt in aantal en heterogeen in opzet, met name wat betreft geselecteerde groepen en type trauma.

Ten tweede, de resultaten van structurele neuroimaging studies in getraumatiseerde minderjarigen verschillen van studies met getraumatiseerde volwassenen, vooral met betrekking tot de hippocampus en het corpus callosum.

Ten derde, parallel aan de inconsistente bevindingen betreffende reductie van hippocampus volume in getraumatiseerde minderjarigen, toonde onze VBM-studie geen verschil tussen groepen voor het hippocampus volume.

Ten vierde, VBM liet kleinere volumes zien van centrale delen van het limbisch systeem (ACC, amygdala) in de CSA-related PTSD groep in vergelijking met de controlegroep.

Ten vijfde, vrouwelijke adolescenten met seksueel misbruik-gerelateerde PTSS laten geen verschil zien in cortical thickness, overeenkomstig bevindingen in volwassenen.

Ten zesde, adolescenten met CSA-related PTSD laten minder integriteit zien van delen van het corpus callosum in vergelijking met gezonde, niet-getraumatiseerde controles.

Ten zevende, onze structurele neuroimaging (VBM, Cortical Thickness en DTI) studies lieten beperkte associaties zien met traumasymptomatologie, in overeenstemming met bevindingen in eerdere studies met minderjarigen

Potentiële klinische implicaties

De bevindingen van dit proefschrift hebben geen directe klinische implicaties. Echter, een beter begrip van de neurobiologische trajecten die traumatisering in de jeugd verbinden met pathologie later in het leven, kan helpen manieren te identificeren om de loop van deze trajecten in het nog plastische adolescentenbrein te beïnvloeden door preventie en behandeling. Studies van getraumatiseerde volwassenen hebben al aangetoond dat veranderingen in de hersenen, structureel zowel als functioneel, gerelateerd zijn aan behandeleffect.

Traumatische ervaringen vroeg in het leven kunnen leiden tot veranderingen in genexpressie door epigenetische mechanismen (gen & omgeving-interactie), zich uitend in veranderingen in stress-reactiviteit, hersenfunctie en gedrag. Deze kwetsbaarheid kan overgedragen worden op de volgende generatie en wetenschappelijk onderzoek suggereert dat ook therapie-effect kan worden doorgegeven aan de volgende generatie. Het belang van het vinden van de juiste behandelstrategieën om de consequenties van misbruik en geweld in de jeugd bij te sturen wordt hiermee vergroot.

De indicatie dat een specifiek type trauma geassocieerd is met specifieke afwijkingen in het brein, zoals in onze cortical thickness studie, zou wegen kunnen openen, niet alleen voor het verhelderen

van trajecten en kwetsbaarheid voor de gevolgen van vroeg trauma, maar ook potentiële manieren om te komen tot meer gepersonaliseerde vormen van therapie.
Neuroimaging onderzoek bij jeugdigen met traumatische ervaringen in de voorgeschiedenis sluit aan bij verschillende nieuwe ontwikkelingen in het wetenschappelijk onderzoek, waarbij meer gekeken wordt naar overkoepelende, interdisciplinaire processen en dimensionaliteit dan de eerder gebruikelijke gerichtheid op classificatie. Ontwikkeling en de invloed van de omgeving zijn hierin belangrijke thema's. Traumatische ervaringen en vooral die vroeg in het leven, blijken een centrale rol te spelen bij Gen & Omgeving interactie. Thema's die terugkomen in projecten als het Research Domain Criteria (RDoC) initiative van Het National Institute of Mental Health (NIMH) in de VS dat probeert nieuwe wegen te creëren voor de wetenschap. Ook staat hierin persoonlijk functioneren binnen een context meer op de voorgrond dan de stoornis.

Gezien de maatschappelijke impact van vroege traumatisering is de vertaling van wetenschappelijke bevindingen naar de praktijk van essentieel belang ten behoeve van een betere preventie en de behandeling van de vele kinderen, adolescenten en volwassenen met traumatische ervaringen in de jeugd.

Dankwoord

Aan de keukentafel heeft Thomas, mijn man, gepromoveerd op de neurobiologische gevolgen van trauma bij borderline patiënten, mij geïnspireerd tot dit onderzoek, waarvoor ik hem nog steeds dankbaar ben.

Wijlen Professor Flip Treffers dank ik voor het stimuleren van mijn onderzoeksplannen in de allereerste fase.

Professor Robert Vermeiren, mijn eerste promotor, realiseerde mijn onderzoeksplan in het EPISCA-project. Ik wil hem bijzonder bedanken voor alle mogelijkheden die hij me gegeven heeft op wetenschappelijk èn klinisch gebied binnen Curium-LUMC.

Professor Nic van der Wee heeft met zijn deskundigheid de inhoudelijke kern van dit proefschrift vormgeven en het proces professioneel begeleid, waarvoor mijn grote dank.

Professor Francien Lamers-Winkelman, vanaf het begin enthousiast, arrangeerde de samenwerking met haar Kinder- en Jeugdtraumacentrum (KJTC) en introduceerde me in het traumaveld. Ik ben haar zeer dankbaar voor de inspiratie in mijn werk die ik daar sindsdien aan ontleen.

Professor Serge Rombouts, neuro-radioloog, bedank ik voor zijn bijdrage aan het EPISCA-project als geheel, Professor Eveline Crone voor haar waardevolle inbreng bij de ontwikkeling van het EPISCA-project.

Van de onderzoekers bedank ik allereerst mijn geweldige co-auteurs Steven van der Werff, Nienke Pannekoek en Charlotte Boateng voor hun uitstekende analyses en bijdragen aan de artikelen, Natasja van Lang, geruime tijd hoofdonderzoeker van het EPISCA-project, voor haar constructieve en altijd vriendelijke begeleiding, Marie-José van Hoof voor de lange coöperatie en steun in barre tijden, Paul Meens en Bianca van den Bulk, voor de fijne samenwerking en met hen de onderzoeksassistenten en studenten voor het uitvoeren van de hersenscans, Carien Gelderblom voor haar hulp bij de inclusie binnen Rivierduinen, Margreet Visser en de andere psychotherapeuten van het KJTC voor hun enthousiaste ondersteuning bij de inclusie, Moji Aghajani en Eline Roelofs voor enkele mooie illustraties.

Mijn allergrootste dank gaat uit naar de deelnemers aan het onderzoek die bereid waren voor de wetenschap nog eens te vertellen wat ze hebben meegemaakt. Ook bedank ik de vrijwilligers die, heel gemotiveerd, als controlegroep het onderzoek doorliepen.

Collega's van Curium-LUMC, vrienden en familie wil ik bedanken voor hun interesse en steun tijdens het lange promotietraject en hun begrip als ik minder aanwezig was, fysiek of met aandacht, vanwege doorwerken in weekenden of late avonden.

Thomas wil ik ook bedanken voor zijn altijd aanwezige zorg en de uitjes, etentjes of reizen als echt even afleiding nodig was.

Alexander, Jean-Paul, Beatrice, opgegroeid tijdens de promotietrajecten van jullie ouders, jullie zijn mijn grootste inspiratiebron.

Curriculum Vitae

Mirjam Aleida Wilhelmina Albers is geboren 21 januari 1959 in De Haag. Ze volgt een jaar middelbaar onderwijs aan het Haags Montessori Lyceum en volbrengt het VWO aan het Eckart College in Eindhoven, waar ze in 1977 cum laude het VWO-diploma behaalt. Aansluitend studeert zij geneeskunde aan de Erasmus Universiteit in Rotterdam en haalt daar in 1980 het kandidaatsexamen. Ze vervolgt de studie in 1981 aan de Vrije Universiteit in Amsterdam die zij in 1986 afsluit met het artsexamen. Vervolgens werkt ze enkele maanden op de afdeling interne geneeskunde (hematologie, oncologie en algemene interne geneeskunde) van het Diaconessenziekenhuis (nu Maxima Medisch Centrum) in Eindhoven.

In december 1986 start zij bij Psychiatrisch Centrum Vogelenzang in Bennebroek waar ze in juni begint aan de psychiatrie-opleiding met als hoofdopleider dr. P. Bierenbroodspot. Het deelgebied kinder- en jeugdpsychiatrie wordt gevolgd in het Academisch Medisch Centrum (AMC) in Amsterdam van 1991 tot 1993 bij Prof. dr. J.A.R. Sanders-Woudstra en Prof. dr. W.B. Gunning. Daar is zij van 1992-1995 staflid, waarvan het laatste jaar waarnemend chef de clinique en doet patiëntenzorg op de dagkliniek en residentiële unit. Inmiddels als Mirjam Rinne-Albers is zij van 1995 tot 1999 werkzaam bij de RIAGG Zuid/Nieuw-West in Amsterdam en is daar o.a lid van het Speciaal Onderwijs team, autismeteam, incestteam en geeft consultatie aan schoolartsen, meidenhuizen van Amstelstad en het crisiscentrum voor islamitische meisjes.

In 1999 start zij bij Curium (nu Curium-LUMC) waar zij van 1999 tot 2009 werkzaam is als clustermanager patiëntenzorg van het ambulant cluster (polikliniek en dagbehandeling Oegstgeest en Gouda). Van maart 2009 tot 1 juli 2010 heeft zij deze functie voor het klinisch cluster (12 klinische units). In deze periode is zij behandelaar van verschillende (dag-)klinische en poliklinische teams. Na een, onder anderen door haar vormgegeven, reorganisatie is zij aansluitend tot 2020 programmaleider van het Zorgprogramma Ontwikkelingsstoornissen Adolescent en werkzaam op de dagkliniek en klinische unit voor adolescenten met een autismespectrum stoornis. Van 2003 tot 2012 is zij waarnemend directeur patiëntenzorg en van 2003-2009 plaatsvervangend opleider kinder- en jeugdpsychiatrie bij Curium-LUMC. Per 1 mei 2020 is zij geneesheer directeur van Curium-LUMC en vanaf 1 juli 2020 waarnemend opleider voor het aandachtsgebied kinder- en jeugdpsychiatrie binnen Curium-LUMC. Daarnaast is zij op dit moment werkzaam op de dagbehandeling voor adolescenten met een autisme spectrum stoornis.

Het eerste initiatief voor het onderzoek van deze dissertatie wordt genomen samen met de eerdere directeur van Curium Prof. dr. Ph.D.A. Teffers, de realisatie vindt plaats dankzij de huidige directeur, die in 2007 aantreedt, Prof. dr. R.R.J.M. Vermeiren, binnen het kader van het EPISCA-project: Emotional Pathways' Imaging Studies in Clinical Adolescents.

Mirjam Rinne-Albers bekleedde verschillende bestuurlijke functies: Tijdens de opleiding lid van het bestuur van de Subvereniging Assistenten Psychiatrie, waarvoor afgevaardigde in het Concilium Psychiatricum en het bestuur van de Sectie (nu Afdeling) Beleidspsychiatrie van de Nederlandse Vereniging voor Psychiatrie; vanaf het beëindigen van de opleiding lid van het bestuur van de Sectie (nu Afdeling) Beleidspsychiatrie op persoonlijke titel, van februari '97 tot april '98 in de functie van secretaris/penningmeester, vanaf april '98 tot zomer '99 als voorzitter; van 2000 tot 2005 lid van het bestuur van de Sectie (nu Afdeling) Kinder- en Jeugdpsychiatrie van de NVvP, vanaf januari 2003 als secretaris, vanuit dit laatste bestuur als afgevaardigde lid van de Commissie Beroepsuitoefening van de NVvP; van 2008 tot 2013 lid van de Raad voor de Beroepscode van de NVvP, gedurende deze periode is door de Raad de Beroepscode voor Psychiaters herzien en het Intern Tuchtreglement voor psychiaters opgesteld; van 2000-2004 lid van de Commissie Jeugdzorg van de Stichting Kinderpostzegels Nederland, voor de beoordeling van subsidieaanvragen, waarvan het laatste jaar als voorzitter.

Publications

Rinne-Albers M.A.W., Keemink M.A.J., Hermans P.J., van der Ploeg G.J. De reaktie van Nederlandse behandelaars op de suïcide van een patiënt. Tijdschrift voor Psychiatrie 1993/7, p. 484-489.

Rinne-Albers M.A.W. Beleidspsychiatrie of de opleiding tot playing captain. Tijdschrift voor Psychiatrie 2000/4, p. 283-287. (Thema issue Psychiatrie en Opleiding)

Rinne-Albers M.A.W. Angststoornissen. In: Praktijkboek Jeugdgezondheidszorg, 2003, p. V3.5-1 – V3.5-13. Amsterdam, Elsevier

Rijnders R.J.P., Rinne-Albers M.A.W., Siebelink B.M.: Vreemdelingenrecht en gevolgen voor het kinder- en jeugdpsychiatrisch handelen. Jeugdpsychiatrie & recht, red: Duits N., Bartels J.A.C. en Gunning W.B., van Gorcum, Assen. 2004, p. 309-312.

Rinne-Albers M.A.W., Angststoornissen bij kinderen en jeugdigen: vroege signalering door de jeugdgezondheidszorg kan veel leed besparen. Tijdschrift voor Jeugdgezondheidszorg, 36, nr. 5, oktober 2004, p. 92-96.

Treffers Ph.D.A. & Rinne M.A.W. SSRI's bij kinderen en adolescenten (1) Inleiding. Maandblad Geestelijke Volksgezondheid, 2005, 60, p. 247-259.

Treffers Ph.D.A. & Rinne M.A.W. SSRI's bij kinderen en adolescenten (2) Werkzaamheid. Maandblad Geestelijke Volksgezondheid, 2005, 60, p. 260-275.

Rinne M.A.W. & Treffers Ph.D.A. SSRI's bij kinderen en adolescenten (3) Problemen met klinische trials. Maandblad Geestelijke Volksgezondheid, 2005, 60, p. 276-288.

Rinne M.A.W. & Treffers Ph.D.A. SSRI's bij kinderen en adolesceneten (4) Interactie met rijping en ontwikkeling. Maandblad Geestelijke Volksgezondheid, 2005, 60, p. 299-310.

Rinne-Albers M.A.W. Traumatisering in de jeugd. In: Vliet I., Knoppert E., Kolling P. & Sleeboom I. (red) Vrouw & Leven; psychopathologie bij vrouwen in de diverse levensfasen. Bohn, Stafleu, van Loghum, 2006, p. 97-121.

Rinne-Albers M.A.W. & Treffers Ph.D.A., Posttraumatische stressstoornis. In: Kinder- en Jeugdpsychiatrie, behandeling en begeleiding. Verheij, F, Verhulst, F.C. & Ferdinand, R.F. (red.) 2007, van Gorcum, Assen, p. 273-282.

Treffers Ph.D.A. & Rinne-Albers M.A.W. Selectief Mutisme. In: Kinder- en Jeugdpsychiatrie, behandeling en begeleiding. Verheij, F, Verhulst, F.C. & Ferdinand, R.F. (red.) 2007, van Gorcum, Assen, p. 283-291.

Treffers Ph.D.A. & Rinne-Albers M.A.W. Obsessieve-compulsieve stoornis. In: Kinder- en Jeugdpsychiatrie, behandeling en begeleiding. Verheij F., Verhulst F.C. & Ferdinand R.F. (red.) 2007, van Gorcum, Assen, p. 292-302.

Treffers,Ph.D.A. Treffers & Rinne-Albers,M.A.W. Schoolweigering. In: Kinder- en Jeugdpsychiatrie, behandeling en begeleiding. Verheij F, Verhulst F.C. & Ferdinand R.F. (red.) 2007, van Gorcum, Assen, p. 303-311.

Rinne-Albers M. Boekbespreking van 'Als glas in lood. Integratieve behandeling van vluchtelingenkinderen en –gezinnen' Voor het Maandblad Geestelijke volksgezondheid. 2007, 10, p 907-909.

Ee E. van, Rijnders R.J.P & Rinne-Albers M.A.W. Alleenstaande minderjarige asielzoekers. In: Jeugdpsychiatrie en Recht. Duits N. & Bartels J.A.C. (red.) 2011, van Gorcum, Assen, p 81-86.

Rinne-Albers M.A.W., van der Wee N,J.A., Lamers-Winkelman F., Vermeiren R.R.J.M.: Neuroimaging in children, adolescents and young adults with psychological trauma. Child and Adolescent Psychiatry. 2013, 22, p. 745-755.

Rinne‑Albers M.A.W., Werff S. J. A., van der Hoof M., van Lang N.D., Lamers‑Winkelman, F., Rombouts, S.A., Vermeiren, R.R.J.M., van der Wee, N.J.A. Abnormalities of white matter integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study. Eur Child Adolesc Psychiatry, 2016, 25, p. 869–878
DOI 10.1007/s00787-015-0805-2

Rinne-Albers, M.A.W., Pannekoek, J.N., Hoof, M.J. van, Lang, N.D. van, Lamers-Winkelman, F., Rombouts, S.A., Wee, N.J. van der, Vermeiren, R.R.J.M. Anterior cingulate cortexgrey matter volume abnormalities in adolescents with PTSD after childhood sexual abuse. Eur. Neuropsychopharmacology, 2017, 27, p. 1163–1171
S0924-977X(17)30899-4 [pii];10.1016/j.euroneuro.2017.08.432 [doi]

Rinne-Albers M. A., Boateng C.P., van der Werff S.J., Lamers-Winkelman F., Rombouts S.A., Vermeiren R.R., van der Wee N.J. Preserved cortical thickness, surface area and volume in adolescents with PTSD after childhood sexual abuse. Scientific Reports, 2020, 10:3266 | https://doi.org/10.1038/s41598-020-60256-3

Posters

Rinne-Albers M.A.W., Keemink M.A.J., Hermans P.J. en van der Ploeg G.J. De reaktie van Nederlandse behandelaars op de suïcide van een patiënt.

This poster was awarded the Poster Prize 1993 on the Annual Congress of the Dutch Psychiatric Society.

Lectures

Beleidspsychiatrie in de kinder- en jeugdpsychiatrie, Najaarssymposium Sectie Beleidspsychiatrie and Sectie Kinder en Jeugdpsychiatrie NVvP, Duivendrecht, november 25, 1999.

Biologische gevolgen van vroege traumatisering, scientific lecture Curium, march 2001.

Littekens in het brein: biologische gevolgen van vroege traumatisering, Mentrum GGZ, Amsterdam, february 18, 2003.

Somatoforme stoornissen, in het bijzonder conversie. Postgraduate Boerhaave course for pediatricians 2003, Leiden, may 15, 2003.

Neurobiologische bevindingen bij kinderen en jeugdigen met PTSS. Pediatric department LUMC, Leiden, september 16, 2003.

Biochemische veranderingen in relatie met PTSS. Postgraduate Boerhaave course child and adolescent psychiatry, Leiden, november 13, 2003.

Littekens in het brein: biologische gevolgen van vroege traumatisering. Course 'Aard en behandeling van psychotrauma', Vereniging ter bevordering van ortho-agogische aktiviteiten, (O & A), november 13, 2004, Ede.

De identiteit van de kinder- en jeugdpsychiatrie. Boerhaave course Child and Adolescent Psychiatry, may 26, 2005

Psychomedicatie bij kinderen en jeugdigen: wanneer wel, wanneer niet? Symposium Bijzonderheden bij angststoornissen bij kinderen en de consequenties voor de behandeling, Najaarsconferentie Vereniging voor Gedragstherapie en Cognitieve Therapie. Veldhoven, november 11, 2005

Kinder- en jeugdpsychiatrische diagnostiek bij angststoornissen. Postgraduate Boerhaave course Child and Adolescent Psychiatry, february 23, 2006.

De gevolgen van trauma in de kindertijd en late gevolgen. Symposium Centrum 45 'Trauma: late gevolgen voor kinderen en volwassenen', october 12, 2011.

Neuroimaging en trauma (with Zantvoord, J.B.), Boerhaave symposium 'Hechting en Trauma', februari 9, 2012.

Neuroimaging in children, adolescents and young adults with psychological trauma, Symposium: Neurobiological studies in traumatized children and adolescents, ESTSS Congress: Trauma and its clinical pathways: PTSD and beyond. Bologna, Italy, june 6-9 2013.

Het Getraumatiseerde Brein, Boerhaave symposium Trauma, Utrecht, march 17, 2016

Neuroimaging in children, adolescents and young adults with psychological trauma, congress of the European Society for Child and Adolescent Psychiatry (ESCAP), Vienna, june 30 – July 4, 2019.

Gevolgen, behandeling, preventie van kindermishandeling en hun neurobiologische trajecten, workshop Subvereniging van Arts-assistenten Psychiatrie (SAP-dag) Leiden University Medical Center, Leiden, november 12, 2019.

Media

Interview on-line Tijdschrift Kindermishandeling: Krijgen mishandelde kinderen vervolgens ook de hulp die ze nodig hebben? Journalist Ditty Eimers. Publ : 1-10-2013
Link : http://tkmnieuws.nl/krijgen-mishandelde-kinderen-vervolgens-ook-de-hulp-die-ze-nodig-hebben/.

Interview for Scientific Supplement NRC : Kinderleed zet je niet meer uit je hoofd. Journalist: Nienke Beintema, d.d. october 26/27, 2013, p.7.

Interview for Weekend Supplement Kind, de Volkskrant in Week van de Kinderrechten: Hoogspanning. De invloed van leven onder stressvolle omstandigheden op de hersenontwikkeling en de mogelijkheid van correctieve ervaringen zoals therapie.
Journalist Jop de Vrieze. November 2014, p. 46-49.

Blog

Weinig neuroimagingonderzoek bij getraumatiseerde kinderen en adolescenten. Landelijk Kenniscentrum Kinder- en Jeugdpsychiatrie, Publ: 15-10-2013.
Link: http://blogs.kenniscentrum-kjp.nl/author/mirjam-rinne-albers/