Childhood sexual abuse and its effect on adolescent brain structure

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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.