Childhood sexual abuse and its effect on adolescent brain structure

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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).

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