Unresolved-disorganized attachment, psychopathology, and the adolescent brain

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Als tranen verdampen
Spin weemoed uit wol
Kras banen
Kerf vloeken in strepen
Brei truien van steen
Luidt klokken
Roep mensen bijeen
Schenk glazen vol woorden

Nan Romijn (1959)

When tears vanish
Spin melancholy from wool
Scratch lanes
Notch swearing in stripes
Knit sweaters from stone
Ring bells
Convene people
Pour glasses full of words

GENERAL INTRODUCTION

CHAPTER 1: GENERAL INTRODUCTION

The development of a child depends on the caregiving it receives, its neurobiological predisposition and the interaction between both. The concept of attachment in that context still needs a lot of clarification and operationalisation for use in clinical practice: e.g. how does intergenerational transmission of attachment come about, what happens in case of trauma, how does attachment relate to emotion regulation? Studying brain mechanisms in attachment could help conceptualize the concept further. Which brain mechanisms are essential in attachment? How plastic is the adolescent brain when it comes to the interplay between attachment, trauma and emotion regulation? How does attachment relate to brain volume and activity?

This thesis therefore focuses on attachment, trauma and emotion regulation and their interrelatedness by investigating: 1. behavioural and mental health correlates of attachment and emotion regulation (i.e. attention bias) in adolescence; 2. neural correlates of emotional face processing (as a proxy of emotion regulation) in adolescence; 3. differential neural correlates of attachment and psychopathology in adolescence. We studied a mixed sample of adolescents with childhood sexual abuse cq. childhood sexual abuse-related posttraumatic stress disorder) (CSA; CSA-related PTSD), anxiety and depressive disorders (in this thesis called clinical depression), and non-clinical controls.

Clarification of neurobiological mechanisms underlying attachment, trauma and emotion regulation may help to 1) understand atypical development and behaviour 2) identify the course of psychopathology and its neural plasticity, and 3) inform daily practice and future scientific research. Childhood sexual abuse (CSA) as well as clinical depression are serious conditions. They need timely, effective treatment, yet available treatment does not always turn out to be effective. Study of brain mechanisms pertinent to these conditions is therefore needed, because it may help to identify unique and overlapping factors in either condition. Identifying such factors may change theoretical concepts and practices following from them.

STRUCTURE OF THE GENERAL INTRODUCTION CHAPTER

Below we choose to first explain the concept of adolescence and puberty applicable to the study sample in general and diagnostic classifications prevalent in the study sample. In addition, we explain several underlying concepts to the topic of this thesis per aim. This explication is meant to be helpful in understanding all parts of the hybrid nature of this dissertation from different perspectives.

GENERALLY APPLICABLE CONCEPTS TO THE STUDY SAMPLE

ADOLESCENCE AND PUBERTY

The study of this thesis was conducted in adolescents, comprising diverse pubertal stages. Bodily changes induce metabolic, hormonal and neural imbalances of different sorts. During this developmental stage, adolescents are particularly open to new developmental challenges as well as vulnerable for problems with emotion regulation, parent-child interaction and development itself (Blakemore, 2012a; Casey, et al., 2010; Crone & Dahl, 2012; Obsuth, Hennighausen, Brumariu, & Lyons-Ruth, 2014). Many psychiatric disorders, e.g. depression and anxiety disorders, emerge during adolescence and interfere with typical maturational processes. Anxiety disorders often precede depression in adolescence (Paus, Keshavan, & Giedd, 2008). Adolescent depression in turn predicts other mental disorders in adulthood, e.g. anxiety disorders, substance-related disorders (Thapar et al., 2012).

DIAGNOSTIC CLASSIFICATIONS IN STUDY SAMPLE

We specifically mention diagnostics of posttraumatic stress disorder, depressive and anxiety disorders (named clinical depression in this thesis) in the context of global prevalence of mental disorders in adolescence (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). We refer to both the DSM-IV-TR (2000) and DSM-5 (2000/2013).

Posttraumatic Stress Disorder

The lifetime prevalence of PTSD in adolescents aged 13-18 years is 5% (Merikangas et al., 2010), with prevalence higher for girls than for boys (8% vs 2.3%) and increasing with age (Kessler et al., 2012). Rates over the past month are 3.9% (Merikangas et al., 2010). Type of event and intensity of exposure determine the degree to which one develops PTSD. PTSD in children and adolescents may present different from PTSD in adults (Van der Kolk, 2014). Therefore, criteria for PTSD include age-specific features for some symptoms (Cloitre et al., 2009). Adolescents are likely to engage in traumatic re-enactment, incorporating aspects of the trauma in daily life. They are also likely to exhibit impulsive and aggressive behaviours. Research of PTSD in this age group, in particular in repetitive trauma, is scarce. The American Academy of Child and Adolescent Psychiatry published the Practice Parameters for the Assessment and Treatment of Children and Adolescents with Posttraumatic Stress Disorder (2010).

Clinical Depression

Prevalence of depression and anxiety in adolescence is high. About 10% of adolescents ever develop a depression and about 20-24% any anxiety disorder (Kessler et

al., 2012). Depressive and anxiety disorders are known to frequently co-occur. Essau (2008) showed that about half of the adolescents with depression simultaneously had an anxiety disorder. Besides, depressive and anxiety disorders have much clinical overlap with regard to phenomenology and type of treatment., raising the question whether they are caused by common neural correlates (Van den Bulk, 2015). Comorbidity has been associated with higher severity (Kessler et al., 2012; 2014). In case of comorbidity global functioning worsens, academic problems and the risk for attempted suicide increase (Lewinsohn, Gotlib, & Seeley, 1995). As an adult, adolescents with depressive or anxiety disorders have a 2- to 3-fold increased risk for having a repeated depressive or anxious episode (Pine, Cohen, Gurley, Brook, & Ma, 1998). In this thesis we use the term clinical depression for adolescents who had depressive disorders and/or anxiety disorder with subclinical depression.

SPECIFIC CONCEPTS PER AIM

AIM 1: DETERMINING BEHAVIOURAL AND MENTAL HEALTH CORRELATES OF ATTACHMENT AND EMOTION REGULATION IN ADOLESCENCE

ATTACHMENT THEORY

Attachment theory as proposed by John Bowlby and Mary Ainsworth (1969/1982; 1973; 1980; 1988; Van Rosmalen, 2015) is rooted in the 19th-early 20th century theories on evolution by Charles Darwin, on psychoanalysis by Sigmund Freud and on security by William Blatz. The consequence of both World Wars of the 20th century, resulting in a lot of casualties and orphans, further feeded thinking about attachment and the impact of loss and trauma on human functioning. Attachment theory states that early interactions with attachment figures form the base of emotion regulation across the lifespan through inner working models of self and others (Bowlby, 1969/1982; 1988). Ainsworth's particular scientific contribution was her detailed observation that children from infancy onwards systematically use defensive strategies, when caregivers refuse or fail to sooth their fear or distress (the Strange Situation Procedure; Salter Ainsworth & Bell, 1970; Van Rosmalen, 2015). These infant defensive adaptations involve changes in both attention and affect expression. Main, Kaplan, & Cassidy (1985) made a move to the representational level through linguistic analysis of discourse about attachment experiences. They operationalized thinking about the relationship with caregivers in adulthood as attachment representation, to be measured with the Adult Attachment Interview (AAI). Beijersbergen (2008) validated the AAI for adolescents.

Lyons-Ruth called attachment "the psychological version of the immune system" (Lyons-Ruth, 2003b). She reasoned that the attachment system is a behavioural system that

is fit beforehand to combat and reduce stress, just as the immune system is the biological system to combat external pathogens. Under normal circumstances a well-functioning i.e. secure attachment relationship will buffer the child against extreme levels of fear. However, when the attachment system itself malfunctions, it may go awry, i.e. the child may become insecure or disorganized attached, just as the immune system may develop autoimmune disorders.

When attachment representation is secure, there is a good chance that emotion regulation is stable and psychopathology attenuated in its presentation. In case of adversity like loss and abuse, attachment representation may become unresolved-disorganized, Ud, i.e. the most serious insecure form of attachment (Hesse & Main, 2000; Main, Goldwyn, & Hesse, 2003). Being unresolved-disorganized may compromise healthy emotion regulation, leading to or increasing psychopathology (Harari, et al., 2009; Main & Hesse, 1990). In this thesis we therefore focus on unresolved-disorganized attachment representation and associated low coherence of mind.

CHILD PSYCHIATRY AND ATTACHMENT THEORY

Given the impact of adversities, like loss and abuse, on attachment, emotion regulation and psychopathology (e.g. Cassidy & Mohr, 2001; Liotti, 2004; Lyons-Ruth, Dutra, Schuder, & Bianchi, 2006), one would expect child psychiatrists to systematically consider the effects of adversities in childhood (adverse childhood experiences (ACEs); Anda et al., 2006; Felitti et al., 1998). However, though child and adolescent psychiatrists, using the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 1994/2000/2013) for categorical classification of illness, have fortunately started to inquire about adversities during the past decade, they have not explicitly included attachment representation, nor the systematic evaluation of the interaction between adversities and attachment into its diagnostic framework yet (Teicher & Samson, 2016; Van der Kolk, 2016). Instead of attachment representation, stemming from attachment theory, child psychiatry has used the DSM-based categorical diagnoses 'reactive attachment disorder' and 'disinhibited social engagement disorder' for children who experienced severe abuse or neglect before age 5 (Scheper, et al., 2016). However, these DSM-constructs have unfortunately "almost not" been informed by attachment theory (Van IJzendoorn & Bakermans-Kranenburg, 2003, p. 1).

The categorical DSM classifications have been composed, based on observable characteristics of affect and behaviour, presuming these classifications would have traceable underlying etiology. This has not turned out to be the case yet, initiating research into the existence of a General Psychopathology Factor (GPF, see for an explanation under aim 3; Caspi et al., 2014; Lahey, et al., 2012). Therefore, we intend to show in this thesis

that it is needed to identify complementary or underlying dimensional constructs, such as attachment representation and a GPF. Differentiation of neural correlates of attachment representation from those of a GPF, controlled for each other, could further increase insight in specific brain mechanisms. In light of the discussion on the usefulness of psychiatric classification versus dimensional psychiatric symptom diagnostics, we explicitly used both approaches in our study (Kecmanovic, 2012; Musalek & Scheibenbogen, 2008).

In contrast to DSM-based categorical classification of illness in child and adolescent psychiatry, attachment research has a longstanding tradition of investigating the sequelae of loss and abuse across different developmental domains (Bowlby, 1969/1982; Hesse, 2008; 2016; Main, Kaplan, & Cassidy, 1985; Roisman, Fraley, & Belsky, 2007). These sequelae may manifest in several domains, e.g. affective, behavioural and disorganizing aspects of emotion regulation, psychiatric illness and somatic disease and may also impact intergenerational transmission of attachment and the psychosocial environment (e.g. Fraley, Roisman, & Haltigan, 2013; Hesse, 2016; Hsiao, Koren-Karie, Bailey, & Moran, 2014; Zajac, & Kobak, 2009). Behavioural and affective sequelae of loss and abuse are partially captured by the DSM and additionally within the concept of attachment representation, e.g. when using the AAI. In addition, disorganizing sequelae of loss and abuse can be solely captured using the AAI. The underlying concepts of attachment and emotion regulation have not made it into the DSM yet, owing to difficulty operationalizing these concepts into clinically valid and useful criteria or measuring them reliably.

The available diagnostic classification systems, DSM-5 (APA, 2013) and ICD-11 (International Classification of Diseases; World Health Organization, 2018) have not yet integrated the attachment-based behavioural, affective, somatic, disorganizing and psychosocial sequelae of loss and abuse as identified by Main, Hesse and colleagues (e.g. Hesse, 2016; Main, Goldwyn, & Hesse, 2003; Hesse & Main, 2000). There is a discussion whether the DSM is able to integrate all relevant concepts to psychiatric illness such as attachment and emotion regulation at all. It is therefore argued that the Research Domain Criteria should be leading in (child and adolescent) mental health research (RDoC; http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml#toc_background). Recently, neurobiological factors of attachment are increasingly being investigated, fitting RDoC social domain/affiliation and attachment construct criteria (e.g. Riem, Bakermans-Kranenburg, Van IJzendoorn, Out, & Rombouts, 2012). Maybe RDoC will ultimately function as a way to integrate concepts like attachment and emotion regulation with dimensional and categorical criteria for psychiatric illness (e.g. Sharp et al., 2016).

In this era of call for dimensional neurobiological and environmental factors to guide psychiatric diagnostics and treatment "from neurons to neighbourhoods" (Brüne et al., 2012; Jaffee, Caspi, Moffitt, Polo-Tomás, & Taylor, 2007; 2013; 2015; Shonkhoff & Phillips, 2000), it should be studied how to integrate findings from attachment research

into (child and adolescent) psychiatric practice. In order to do so, research should focus on investigating 1) brain mechanisms underlying trauma, attachment and emotion regulation and their interaction (this thesis); 2) differentiation of attachment representation in relation to psychiatric disorders (this thesis in relation to adolescence) and expand this to all age groups and their transgenerational transmission; 3) application of neurobiological findings into clinical practice.

CHILDHOOD SEXUAL ABUSE - CSA

The third National Incidence Study (NIS-3 code; Sedlak, 2001; see Appendix A in Stoltenborgh, Van IJzendoorn, Euser, & Bakermans-Kranenburg, 2011) operationalized CSA as "any form of child abuse in which an adult or older adolescent uses a child for sexual stimulation" (see committee of the American Psychological Association Board of Professional Affairs, 2013, p. 30). One in ten youth, mainly female, reports CSA (Stoltenborgh et al., 2011). CSA has a serious impact on mental health. CSA has a high incidence among adolescents and is often accompanied by PTSD (Bicanič, 2014). It can be accompanied by depressive, anxious, dissociative, externalizing and/or posttraumatic stress symptoms (Fergusson, McLeod, & Horwood, 2013; Gospodarevskaya, 2013; Kim-Spoon, Cicchetti, & Rogosch, 2013). Specifically in female adolescents, depressive and anxiety disorders and CSA-related PTSD coincide (Bicanič, 2014; Christiansen, & Hansen, 2015). CSA has a substantial risk for lifelong psychosocial and somatic problems (Anda et al., 2006; McCrory, De Brito, & Viding, 2012; Teicher & Samson, 2013), through direct consequences of the abuse and indirect, immunological and epigenetic changes (e.g. Caspi et al., 2002; McGowan et al., 2009). The likelihood of transgenerational transmission of sexual abuse and (psycho)pathology increases simultaneously (McCloskey, & Bailey, 2000; Putnam, 2003). Given that CSA has a detrimental impact on one's life, it is important to identify underlying or complementary generic factors of the sequelae of CSA, such as attachment representations.

CSA often goes along with multiple other forms of emotional and/or physical abuse and neglect (e.g. Gospodarevskaya, 2013). As mentioned above, sequelae of CSA can comprise not only posttraumatic stress symptoms, but a myriad of simultaneous affective and behavioural symptoms and relational problems, increasing comorbidity (Bicanič, de Jongh, & ten Broeke, 2015; Stöfsel & Mooren, 2015). Herman already 25 years ago suggested to call this co-morbid constellation complex post-traumatic stress disorder (complex PTSD; Herman, 1992), in adults as well as in children (Cloitre et al., 2009; D'Andrea, Ford, Stolbach, Spinazolla, & Van der Kolk, 2012; Dorrepaal et al., 2012; Jonkman, Verlinden, Bolle, Boer, & Lindauer, 2013). Among clinicians in the trauma field the term complex PTSD has been used since for a clinical presentation with multiple psychiatric, emotion

regulation, self-organization, and relational problems as a consequence of (multiple) trauma or abuse (Ford & Courtois, 2014; Marinova & Maercker, 2016). Meanwhile, complex PTSD has become a diagnosis in the ICD-11 (Cloitre et al., 2013; Cloitre, Garvert, Weiss, Carlson, & Bryant, 2014; Cloitre, 2015; Ford, 2015; Perkonigg et al. 2016; Stolbach et al. 2013). In the DSM-5 however (APA, 2013), complex PTSD has not yet been recognized as a separate diagnosis. The DSM only refers to PTSD complicated by dissociation as "PTSD with prominent dissociative symptoms". Better description of the diagnosis complex PTSD and underlying neurobiological mechanisms seems warranted to resolve the diagnostic debate (Armour, 2015). Use of a GPF could be instrumental in doing so.

We suppose that not the type of trauma (such as CSA) per se, but that sequelae such as incoherence of mind and unresolved-disorganized attachment representation, (simultaneous) psychiatric illness, and somatic consequences are the factors ultimately determining the impact of trauma intra-individually, while contextual factors probably play a moderating role. This thesis focuses in particular on coherence of mind and unresolved-disorganized attachment representation as a distinct complementary or underlying vulnerability factor for trauma sequelae in adolescent groups of CSA-related PTSD and clinical depression. Literature on the subject is however scarce and inconsistent (Bakermans-Kranenburg, & Van IJzendoorn, 2009; Fearon, Bakermans-Kranenburg, Van IJzendoorn, Lapsley, & Roisman, 2010; Groh, Roisman, Van IJzendoorn, Bakermans-Kranenburg, & Fearon, 2012). Therefore further research differentiating psychiatric symptomatology from attachment representation dimensions is needed (Chapters 2, 4-6).

TRAUMA, DISSOCIATION, AND (UNRESOLVED-)DISORGANIZED ATTACHMENT

Liotti (2004) postulated that "trauma, dissociation and disorganized attachment are three strands of a single braid". Unresolved-disorganized attachment, i.e. disorganization and disorientation in relation to loss or trauma as indices in the AAI, are referred to as unresolved loss or trauma within the AAI terminology (Hesse, 2016). They are inherently accompanied by low coherence of mind. These terms cover phenomena that could also be regarded as dissociation. Bryant (2007) described several aspects of conceptualization of dissociation and suggested dissociative experiences can present itself as different phenomena. Dissociation was already described in the nineteenth century when Janet (1889; Van der Kolk, 1989; 1994; 2014) postulated that intense emotional reactions to trauma would lead to e.g. visceral and visual memories, dissociated from consciousness (i.e. dissociation), that kept one fixated on the trauma. Since then, trauma researchers and clinicians have mainly focused on dissociation in relation to trauma (e.g. Frewen & Lanius, 2014; Lanius, 2015; Van der Hart, Nijenhuis, & Steele, 2005), not attachment.

Brown (2006) described different types of dissociation as having different psychological mechanisms, e.g. detachment, vs compartmentalization. Detachment refers to an altered state of consciousness characterized by a sense of separation from aspects of everyday experience, e.g. depersonalization, emotional numbing, while compartmentalization refers to e.g. unexplained neurological symptoms, hypnotic phenomena, multiple identities, and amnesia due to retrieval deficit. Lanius (2015) described dissociative experiences based on aspects of time, thought, body and emotion. Unresolved-disorganized attachment seems to have conceptual overlap with dissociation as well as trauma and therefore may be a factor that also should be taken into account.

As to measurement of trauma, dissociation and unresolved-disorganized attachment in our study, the EPISCA sample was assessed using the Anxiety Disorders Interview Schedule, child and parent version (ADIS C/P) (Silverman & Albano, 1996), also including items on PTSD and dissociation. In Chapter 2 we studied behavioural and mental correlates of attachment (unresolved-disorganized attachment, i.e. unresolved loss or trauma, coherence of mind scales) and posttraumatic stress symptoms, dissociative and depressive symptoms in relation to each other (table 2, Chapter 2) in adolescents with CSA(-related PTSD) or with clinical depression compared to controls (aim 1). In Chapter 3 we covaried attention bias and emotional face processing group comparisons for posttraumatic, dissociative and depressive symptoms. In Chapters 4-6 we studied unresolved-disorganized attachment (Ud) and a general psychopathology factor (GPF; Caspi et al., 2014; Lahey et al., 2012; Zald & Lahey, 2017) in relation to brain correlates, using posttraumatic and dissociative symptoms among others from the Trauma Symptoms Checklist for Children (TSCC; Briere, 1996) respectively Adolescent Dissociative Experiences Scale (A-DES; Armstrong, Putnam, Carlson, Libero, & Smith, 1997) to create a GPF (see under aim 3).

ATTENTION BIAS AS A PROXY FOR EMOTION REGULATION

From an attachment perspective

Attachment is the relational outcome of internal working models of social cognition (Damasio, 1996) and emotion regulation, especially in case of stress, which has neurobiological underpinnings that still have to be elucidated. The quality of the attachment relationship determines whether or not the child feels the freedom to turn attention away from threat and security issues toward exploration, learning and play (Salter Ainsworth & Bell, 1970). Thus, attachment (in)security has consequences for the regulation of fearful arousal, e.g. whether threat is avoided or being paid attention to (i.e. attention bias; Atkinson et al., 2009; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007;

Belsky & Fearon, 2002a; 2002b; Fearon & Belsky, 2004; Jacobsen, & Hofmann, 1997).

Therefore, one of the important issues mentioned in attachment research are facial expressions of emotions during parent-child interaction (Brüne et al., 2012; Cassidy, Jones, & Shaver, 2013; De Wolff & Van IJzendoorn, 1997). Darwin already took an evolutionary perspective and focused on the biology of emotion, i.e. the physiology of emotion and the anatomy of facial expression (Ekman, 2009; Darwin, 1998). As measurement of reactions to emotional faces in natural situations is very difficult for technical reasons, it therefore has not been researched much yet. An alternative used in neuroimaging research is to measure 1) emotion recognition, e.g. reaction time and intensity scores to different emotional faces (e.g. angry, sad, fearful, happy, neutral), which makes it possible to determine attention bias, i.e. focus on negative emotions (aim 1 of this thesis); and 2) brain activity in reaction to viewing emotional faces (aim 2 of this thesis). Emotion recognition is likely to evolve over the lifespan, though little is known about how it does in each developmental period. In this thesis adolescents are exposed to an fMRI emotional faces task to determine attention bias and emotional face processing (Chapter 3).

From an emotion regulation perspective

Emotion regulation is defined as the goal-directed monitoring, evaluation and modifying of emotional reactions (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015; Thompson, 1994). This can involve immediate implicit, unconscious, automatic processes and explicit, conscious strategies to modify emotional responses. For the latter, multiple, higher-order processes including executive functions are needed to recognise the emotional significance of stimuli and need for regulation and to select and implement an appropriate strategy (Sheppes, Suri, & Gross, 2015). For health as well as psychopathology, it is of interest to understand how emotions are regulated at behavioural and neural levels.

Disturbed emotion regulation (Fergusson, McLeod, & Horwood, 2013) can be captured by negative attention bias, defined as the tendency to direct attention to negative emotions expressed by others (Bar-Haim, et al., 2007; Pollak & Kistler, 2002; Masten et al., 2008). In observational studies the speed of the motor response is registered to determine the reaction time when looking at emotional faces. Furthermore, it was shown that emotional face processing in CSA as compared to non-abused children and adolescents is distinct (e.g. Pollak & Kistler, 2002; Masten et al., 2008; Monk et al., 2006; Pine et al., 2005). Some studies however, reported attention bias away from threat (Masten et al., 2008; Monk et al., 2006), while other studies reported attention bias towards threat (Pollak & Kistler, 2002). In observational studies it is not clear which neural mechanisms precede the motor response. Therefore, attention bias (aim 1) and emotional face processing neuroimaging studies (aim 2) may help to study emotion regulation (Chapter 3).

AIM 2: DETERMINING NEURAL CORRELATES OF EMOTIONAL FACE PROCESSING IN ADOLESCENCE AS A PROXY FOR EMOTION REGULATION

NEUROIMAGING EMOTIONAL FACE PROCESSING

Neuroimaging methods are widely used to examine neural mechanisms involved in the processing of emotional information. The number of emotional face processing studies has substantially increased during the past ten years (e.g. Okon-Singer, Hendler, Pessoa, & Shackman, 2015). Over the last years, several studies have focused on maltreatment-related PTSD (Cisler, Steele, Smitherman, Lenow, & Kilts, 2013; Crozier, Wang, Huettel, & De Bellis, 2014; Fusar-Poli et al., 2009; Lenow, Steele, Smitherman, Kilts, & Cisler, 2014) or sexual assault (Cisler et al., 2015; Garrett et al., 2012; Wolf, & Herringa, 2016). Up until now, most emotional face processing studies included adults only, not adolescents. Also, these studies included only few participants with sexual abuse experiences, while sexual assault was usually defined, if defined at all, as a one-time assault or rape. Common results were hyper-activation of either amygdala, hippocampus, insula, dACC and/or PFC and/or hypo-activation of the dlPFC when viewing fearful or neutral faces in the PTSD group compared to controls (Cisler et al., 2013; Crozier et al., 2014; Fusar-Poli et al., 2009; Lenow et al., 2014) or in the sexual assault group compared to controls (Cisler et al., 2015; Garrett et al., 2012; Wolf, & Herringa, 2016).

Findings in emotional face processing imaging are derived using various paradigms in task fMRI studies, e.g. pictures, scripts of autobiographical memory, words, or faces. These emotional stimuli are used to induce a positive (happy) or negative (sad) emotion. Depending on the included age group and chosen perspective (e.g. PTSD, maltreatment and type of maltreatment) different brain areas were found to be involved with emotional face processing, usually including amygdala, (dorsal) anterior cingulate cortex, hippocampus, insula and/or prefrontal cortex. In ***adults with PTSD compared to trauma-exposed adults*** reduced amygdala and ventral striatum activity were found when viewing happy faces, associated with emotional numbing (Felmingham et al., 2014). Amygdala response to negative stimuli following a terrorist attack predicted ***PTSD onset in adolescents*** (McLaughlin et al., 2014). In ***maltreated adolescents*** dysfunction and less resilience in attentional networks was found in fearful versus calm or scrambled face targets. Posterior cingulate activations positively correlated with PTSD symptoms. While viewing fearful faces maltreated female and male adolescents showed differential activation of brain areas (Crozier et al., 2014). An fMRI study in ***adolescents with PTSD due to interpersonal violence, among others sexual assault***, showed greater activation than controls in amygdala/hippocampus, medial PFC, insula and ventrolateral PFC, and less activation in dlPFC when viewing angry, happy and neutral faces, especially during the early phase of the block. Post-hoc analyses showed significant Group x Phase interactions in the right amygdala and left hippocampus (Garrett

et al., 2012). In order to simultaneously study behavioural and neural correlates of emotion regulation in adolescence, we performed an fMRI study on attention bias and emotional face processing in clinical adolescent groups with CSA-related PTSD or clinical depression, compared to non-clinical adolescents (Chapter 3).

AIM 3: DIFFERENTIATING ATTACHMENT FROM PSYCHOPATHOLOGY NEURAL CORRELATES

NEUROIMAGING AND ATTACHMENT

In contrast to emotion regulation and emotional face processing, the relation of ***attachment*** with brain volume and functioning has been focus of only few neuroimaging studies, some Voxel-Based Morphometry (VBM) and Resting State Functional Connectivity (RSFC) (Benetti et al., 2010; Kok et al., 2015; Lyons-Ruth, Pechtel, Yoon, Anderson, & Teicher, 2016; Moutsiana et al., 2014; 2015; Narita et al., 2010; 2012) and some functional Magnetic Resonance Imaging (fMRI) studies in adults using various paradigms (e.g. Buchheim, Georg, Erk, Kächele, & Walter, 2006a; Buchheim et al., 2006b; 2008; Vrtička, Andersson, Grandjean, Sander, & Veuilleumier, 2008; Vrtička, Bondolfi, Sander, & Vuilleumier, 2012; Vrtička & Vuilleumier, 2012). No studies were performed examining the relationship between attachment and white matter integrity (WMI) of the brain using Diffusion Tensor Imaging (DTI). Only very few imaging studies used the AAI to measure attachment representation (e.g. Riem, Bakermans-Kranenburg, Van IJzendoorn, Out, & Rombouts, 2012; Riem, Alink, Out, Van IJzendoorn, Bakermans-Kranenburg, 2015). However, these two studies used inferred parental experience scales of the AAI to outline the abuse as an event and not unresolved loss or trauma scales, i.e. unresolved-disorganized attachment representation, as we focus on in this thesis. Besides, none of the previous studies were performed in adolescents. Therefore, we performed a combined structural-RSFC study of the amygdala and hippocampus volume in adolescents using the AAI category Ud, controlled for a GPF (Chapter 4), as well as an RSFC study of the amygdala and dACC in adolescents using Ud and GPF controlled for each other (Chapter 6). In addition, we examined WMI of white matter tracts of the adolescent brain for Ud and a GPF, controlled for each other (Chapter 5). We present the studies in the order they were performed, as this best illustrates our progress in methodology and interpretation of results.

NEUROIMAGING AND THE GENERAL PSYCHOPATHOLOGY FACTOR

To estimate the effects of psychopathology separate from Ud we decided to use a GPF in part of our studies (Chapters 4-6). The GPF represents lesser-to-greater severity

of psychopathology. It is associated with negative emotionality (Tackett et al., 2013), compromised brain integrity (Caspi et al., 2014), lower IQ, higher negative affectivity, and lower effortful control in 1954 children from a birth cohort, aged 6 to 8 years (Neumann et al., 2016). In addition, the GPF has been shown to have a significant Single Nucleotide Polymorphism (SNP) heritability of 38% (Neumann et al., 2016) and was identified as having a connectome wide functional signature of transdiagnostic risk for mental illness (Elliott, Romer, Knodt, & Hariri, 2018). Besides, use of the GPF in girls and in young adolescents was shown to be valid (Lahey et al., 2015 respectively Patalay et al., 2015).

THESIS OUTLINE

Focus and aims of the present thesis

The focus of this thesis are the concepts of attachment, trauma and emotion regulation and their interrelatedness. The general three aims of the current thesis are to investigate: 1. behavioural correlates of attachment and emotion regulation (i.e. attention bias) in adolescence; 2. neural correlates of emotional face processing (as a proxy of emotion regulation) in adolescence; 3. differential neural correlates of attachment and psychopathology in adolescence. attachment and emotion regulation and their relationship with the adolescent brain. The studies presented in Chapters 2-6 are based on a sample of mainly female participants, described under EPISCA sample. Figure 1 presents a graphic representation of the topics of the current dissertation as described below.

EPISCA sample

The sample studied in this thesis was part of a slightly larger recruited pool of participants in the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents). This thesis comprises the first measurement only and is thus cross-sectional in nature. In total, 82 right-handed adolescents (aged 12–20) participated in the EPISCA study, a longitudinal outpatient MRI study in which adolescents with CSA(-related PTSD) (*N=21*), anxiety/depressive disorders (*N=28*) or healthy (*N=28*) were followed over a period of six months. They were recruited through outpatient clinics in the Leiden region in the Netherlands, two specialized in psychotrauma, and through local advertisements (controls). Both adolescents and their parents were assessed with a semi-structured diagnostic interview (ADIS-C/P, Silverman & Albano, 1996), and parents filled out the Child Behaviour Checklist, CBCL, Achenbach, 1991a. Besides, adolescents filled out the following questionnaires: Youth Self

Report (YSR; Achenbach, 1991b), Children's Depression Inventory (CDI; Kovačs, 1985), Trauma Symptom Checklist for Children (TSCC; Briere, 1996), Adolescent Dissociative Experiences Scale (A-DES; Armstrong, et al., 1997), Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000; Oldehinkel, 2000), Sentence Completion Test for Children and Youth (ZALC; Westenberg, 2002), Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988), Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski, Kraaij, & Spinhoven, 2002). Adolescents were additionally interviewed for attachment representation using the AAI (Main, Kaplan, & Cassidy, 1985). The adolescents with CSA-related PTSD and anxiety/depression (referred to as clinical depression) underwent an individual diagnostic assessment and an MRI scanning protocol before the start of their regular psychotherapy, and three and six months later. The controls were examined over similar periods for more detail see Van den Bulk et al., 2013; appendices EPISCA study design).

Adolescents were generally included if they met the following inclusion criteria: aged between 12 and 20 years, estimated full scale IQ $\geq$ 80 as measured by Dutch versions of the Wechsler Intelligence Scales for Children (WISC-III; Wechsler, 1991) or Adults (WAIS-III; Wechsler, 1997), 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, lead tattoos, irremovable piercings, claustrophobia or possible pregnancy). Additional inclusion criteria for adolescents with CSA were having experienced sexual abuse during their lifetime more than once by one or more perpetrators in- or outside the family, and being referred for treatment at the participating psychotrauma centre. Additional inclusion criteria for adolescents with anxiety and/or depressive disorders were: being referred for outpatient treatment, having a clinical diagnosis of DSM-IV depressive and/or anxiety disorders and no history of CSA (see Aghajani et al., 2013; Pannekoek et al., 2014a, 2014b). Exclusion criteria for all participants were: (1) a primary DSM-IV diagnosis of Attention Deficit and Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, 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 the scanning; and (3) current substance abuse. Controls were included if they had no clinical scores on validated mood and behavioural questionnaires or past or current DSM-IV classification, no history of traumatic experiences and no current psychotherapeutic intervention of any kind. Controls were recruited through local advertisement.

To objectify any abuse or neglect as well as risk for functional impairment and morbidity (Karam et al., 2014), 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 (see for more detail Van Hoof et al., 2015). To assess the GPF in

our sample we used parent and self-report measurements for behavioural and emotional problems in children and adolescents: YSR (Achenbach, 1991b), CBCL (Achenbach, 1991a), RCADS (Chorpita, et al., 2000), TSCC (Briere, 1996), CDI (Kovačs, 1992), and the A-DES (Armstrong, et al., 1997). Using these (sub)scales, Principal Component Analysis was performed. The Kaiser-Meyer-Olkin statistic showed sampling adequacy (KMO=.92). There were two components with eigenvalues larger than 1 (eigenvalue component 1 = 9.24, eigenvalue component 2 = 1.40). The scree plot showed an inflection justifying the extraction of one component explaining 61.63%, see Chapters 4-6 for an overview of the loadings. We calculated individual factor scores in order to estimate the GPF (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). We used the regression method to calculate factor score coefficients, which were multiplied with the (sub)scale scores to obtain factor scores. These factor scores represent individual standardized scores on the GPF, based on their scores on the constituent scales. All calculations were performed in SPSS with Principal Component Analysis. We provided mean psychopathology scores across the psychopathology groups in supplemental materials.

At each measurement all participants were trained to lie still in a mock scanner, which simulated the environment and sounds of an actual MRI scanner. In-between scanning, participants were asked to report subjective stress levels on a visual analogue scale (VAS) ranging from 0–100. Between measurements, there was a significant decline in subjective stress level ($F_{(2,34)} = 8.4$, $p = 0.005$), but between subsamples at first measurement, there were no significant differences. Stimulus presentation and the timing of all stimuli and response events were acquired using E-Prime software. Head motion was restricted by a pillow and foam inserts that surrounded the head. All anatomical scans were reviewed and cleared by a radiologist.

From the original sample of 82 adolescents, overall, three participants were excluded due to technical problems, i.e. failed voice and video recording of the AAI (one CSA), unintelligible recording (one control), incorrect interview technique (one control). Two participants (one control and one adolescent with anxiety/depressive disorder) were excluded because they refused the AAI because of the interview itself. Depending on which scan sample was used, some adolescents were excluded due to excessive head movement (>4 mm), technical problems during scanning, anomalous findings reported by the radiologist or subclinical scores on some questionnaires.

All CSA adolescents fulfilled the DSM-IV criteria for PTSD, according to the ADIS, however one adolescent missed a point on the interference score, which was clinically rendered non-significant and therefore included as having CSA-related PTSD. SSRI's were used by four adolescents with CSA and two with anxiety/depressive disorder. Estimated full scale IQ scores were acquired with the use of six subtests of either the Wechsler Intelligence scale for Children-III (WISC-III; Wechsler, 1991) or the Wechsler Adult Intelligence Scale

(WAIS; Wechsler, 1997): picture completion, similarities, picture arrangement, arithmetic, block design and comprehension. All participants scored in the average range. The sex distribution was unequal with 86% females.

Written informed assent and consent was obtained from all adolescents and their parents. Participants received a financial compensation including travel expenses. The medical ethics committee of the Leiden University Medical Centre approved the study (nr. P 08.175).

Chapters outline

Attachment representations and psychiatric symptoms in diagnostic groups – Chapter 2

The aim of this study is to investigate whether attachment representation differentiates adolescents with CSA from those with clinical depression and non-clinical controls beyond psychiatric symptomatology. The following three hypotheses are examined. 1. Adolescents with CSA will more often have an insecure or unresolved-disorganized attachment representation than adolescents with clinical depression and non-clinical controls; 2. Unresolved status and low coherence of mind will correlate with more severe clinical symptomatology in both clinical adolescent groups; 3. The unresolved status and coherence of mind will differentiate the CSA group from the clinical depression group and non-clinical controls beyond psychiatric symptomatology; 4. Coherence of mind and unresolved status differentiate those with either sexual and/or physical abuse from absence of these types of abuse, beyond psychiatric symptomatology. We will use both categorical and continuous AAI measures to explore whether dimensional scale scores of the AAI may better predict clinical functioning of the interviewee than the categorical attachment classifications.

Attention bias and fMRI emotional face processing- Chapter 3

The aim of this fMRI study is to investigate neural correlates of emotional face processing in adolescents with CSA-related PTSD, adolescents with clinical depression and non-clinical controls. We focus on dimensional symptoms of posttraumatic stress, dissociation and depression, given the overlap in both clinical groups. We hypothesize adolescents with CSA to have a negative attention bias away from threat, i.e., interpreting negative and neutral faces more negatively and more slowly compared to clinically depressed adolescents and non-clinical controls. In addition, we hypothesize the adolescents with CSA to show more activation in the limbic brain areas (like the amygdala) and less activation in the prefrontal brain areas (like the dlPFC) when interpreting emotional faces as fearful, happy or neutral compared to adolescents with clinical depression and non-clinical controls (Garrett et al., 2012; Masten et al., 2008). Finally, we hypothesize that

severity of posttraumatic stress, dissociation and depressive symptoms in adolescents with CSA or clinical depression will correlate with increased activation of amygdala and insula and decreased activation of dlPFC as compared to non-clinical controls.

AAI-Structural-RSFC hippocampus and amygdala - Chapter 4

The aim of this AAI-VBM-RSFC study is to investigate whether Ud is associated with amygdala and/or hippocampal volume in a sample of adolescents with either CSA-related PTSD, anxiety and/or depressive disorders or no mental health problems. We will use categorical as well as dimensional AAI variables, to best predict clinical functioning of the interviewee. We hypothesize that Ud will correlate with brain structure and volume of amygdala and hippocampus, controlled for a GPF.

AAI-DTI corpus callosum- Chapter 5

The aim of this AAI-DTI study is to investigate whether unresolved-disorganized attachment and a GPF differentially relate to white matter integrity, more specifically white matter tracts, of the brain in a sample of adolescents with either CSA-related PTSD, anxiety/depressive disorders or without mental health problems. We will use categorical as well as dimensional AAI variables to best predict clinical functioning. We use the AAI to assess trans-diagnostic risk factors. First, we hypothesize that a GPF and Ud are differentially related to white matter integrity of white matter tracts. Secondly, we hypothesize that after adjusting for a GFP, Ud is associated with a reduction in WMI in regions previously associated with childhood adversity, that is the cingulum, corpus callosum, and the superior longitudinal fasciculus (Daniels, Lamke, Gaebler, Walter, & Scheel, 2013).

AAI-RSFC amygdala and dACC – Chapter 6

The aim of this AAI-RSFC study of the amygdala and dorsal anterior cingulate cortex (dACC) is to evaluate whether there are differences in functional connectivity of the amygdala respectively dACC with the medial frontal cortex with regard to Ud and a GPF, controlled for each other, in a sample of adolescents with either CSA-related PTSD, anxiety/depressive disorders or without mental health problems. We will use categorical as well as dimensional AAI variables.

Studies using DIAGNOSTIC GROUP (CSA-related PTSD vs clinical depression vs non-clinical controls)	Chapter
Relationship with attachment representation and psychopathology (posttraumatic, dissociative and depressive symptoms)	2
Relationship of attention bias and emotional face processing with brain functioning	3
Studies using ENTIRE SAMPLE (CSA-related PTSD, anxiety/depressive disorders, non-clinical participants), Ud and GPF	**Chapter**
Relationship with structure/ gray matter volume of hippocampus and amygdala and resting state functional connectivity	4
Relationship with white matter integrity of white matter tracts and corpus callosum	5
Relationship with resting state functional connectivity of amygdala and dACC	6

Figure 1. Overview of chapters and their connections: associations of attachment, trauma, emotion regulation and the brain. The top two studies use diagnostic categories: one study has looked at attachment and psychopathology in diagnostic categories, the other study has looked at emotion regulation and psychopathology in diagnostic categories, specifically attention bias and emotional face processing. The lower three studies use unresolved-disorganized attachment (Ud) and a General Psychopathology Factor (GPF) in the entire sample; In the boxes on the righthand side the numbers represent the chapters involved with the study. In Chapter 2 we examine whether attachment representation differentiates adolescents with childhood sexual abuse (CSA) from those with clinical depression (anxiety and/or depressive disorders) and non-clinical controls beyond psychiatric symptomatology. In Chapter 3 an fMRI study about the role of attentional bias and emotional face processing in adolescents with childhood sexual abuse related posttraumatic stress disorder (CSA-related PTSD), those with clinical depression and non-clinical controls, covarying for psychiatric symptoms, is presented; also the influence of psychiatric symptoms on emotional face processing is explored. In Chapter 4 we explore correlates of Ud with brain gray matter volume of the amygdala and hippocampus and functional connectivity of the hippocampus, covarying for a GPF. In Chapter 5 we explore correlates of both Ud and a GPF with white matter integrity, in particular white matter tracts, covarying both factors for each other. In Chapter 6 we focus on functional brain connectivity of the amygdala and dorsal anterior cingulate cortex (dACC) in a 'task-free' setting, the resting state of the brain, covarying Ud for a GPF and vice versa.