Unresolved-disorganized attachment, psychopathology, and the adolescent brain

Hoof, M.J. van

UNRESOLVED-DISORGANIZED ATTACHMENT, PSYCHOPATHOLOGY, AND THE ADOLESCENT BRAIN

Marie-José van Hoof

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"How wonderful it is that nobody need wait a single moment
before starting to improve the world!"

Anne Frank (1929, Frankfurt am Main-1945, Bergen Belsen)

To Sjef and Netty van Hoof-Peters
May their memory be for a blessing

CONTENTS

SECTION II: ATTACHMENT, PSYCHOPATHOLOGY AND NEUROIMAGING

Scientific research consists in seeing what everyone else has seen,
but thinking what no one else has thought

Albert Szent-Györgyi von Nagyrápolt (1893, Budapest - 1986, Woods Hole)

PROLOGUE

PROLOGUE

When working as a resident in paediatrics I met a girl admitted to the hospital because of not being able to stand or walk (astasia-abasia in medical terms), while the function of her legs and brain regarding standing and walking was intact and no organic cause was found. While I was running after all sorts of somatic investigations, she turned out to have been sexually abused within the family. What she presented with was a severe conversion disorder that only gradually could be lifted after she disclosed her experiences.

In 1996, I got the opportunity to study the brain in a functional magnetic resonance imaging study (fMRI) in patients with psychotic disorders at New York State Psychiatric Institute/Columbia University. After a few months it turned out that the planned research could not be continued to be conducted due to non-availability of the fMRI scanner. Instead I participated amongst others in a study measuring the volume of hippocampi and amygdalae of patient groups, and a study on Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). The study on cortisol in posttraumatic stress disorder (PTSD) I initially had wanted to conduct died an untimely death without sponsor.

In 2001, when about to finish my residency in psychiatry, I noticed a training gap concerning trauma and PTSD in the curriculum, for which I wanted to cover up at Sinai Centre in Amsterdam. However, my attendance at the regular residency training program was required and trauma judged to be non-essential for psychiatric practice despite a longstanding Dutch tradition to study psychotrauma (Vermetten & Olff, 2013).

During my childpsychiatric training that followed, I once had to assess a child whose behavior was severely disorganized and in which case a serious suspicion of Childhood Sexual Abuse (CSA) was raised. However, trauma was not assessed and the clinic had an eleven-step protocol, that prevented anyone from reporting this suspicion out of fear to be sued or to be proven wrong, leaving the child to its fate, the professionals standing by in bloodshed. My cheeks still flush from shame at the very thought. This girl, adding concern and evidence to the one described before, has ignited my advocacy activities for the sake of childabuse and neglect.

In 2004, I happened to read the book “Destructive Emotions” by Daniel Goleman describing the dialogues between His Highness the 14th Dalai Lama of Tibet and Western scientists on the topic, exchanging knowledge on emotions from Buddhist and Western psychology. Paul Ekman showed results of his study of facial expression of emotions and Richard Davidson showed e.g. that brain function altered according to experience, facial emotions and meditative state of mind. In these years Frans de Waal published one book after another about emotions in chimps and bonobos and how these resembled and sometimes differed from human emotions. Damasio’s books were the literary and philosophical

framework against which all new findings were resonating. It became clear to me that the interplay between cognition, emotion and the brain in development intrigued me.

At that time, I started working with children and adolescents admitted to a residential mental health institute. They puzzled me through the presentation of their symptoms: a lot of destructive emotions and equal behaviour. At the same time parent-child relationships were poor and most had had a lot of Adverse Childhood Experiences (ACE). As a child and adolescent psychiatrist, I had to diagnose according to the Diagnostic Statistical Manual of Mental Disorders (DSM). As an orthopedagoge I wondered about the role of parent-child interaction and attachment problems. As a medical doctor, educated that trauma apparently did not belong to the psychiatric field, I noticed their severely traumatized histories and behaviour. Now which aspect had to prevail? Psychiatric diagnosis, attachment or trauma? And how were these aspects associated?

GGZ Kinderen en Jeugd Rivierduinen, Curium-LUMC and the Department of Child and Family Studies at the Faculty of Social Sciences of Leiden University gave me the opportunity to research these questions, which resulted in this PhD thesis. It describes a brave sample of adolescents that had the guts to participate in a scientific study. They endured interviews and questionnaires assessing psychiatric symptoms, attachment representation, and MRI scanning for emotion recognition. They did so out of idealism, curiosity, lack of pocketmoney or hope to move science forward despite their own troubles and tribulations. This baseline study on attachment, psychopathology and emotion regulation in association with the brain, part of a longitudinal neuro-imaging study, will be presented below.

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.

SECTION I:
ATTACHMENT AND EMOTION REGULATION

Miracles don't happen, you make them

Reuven Feuerstein

(1921, Botosani – 2014, Jerusalem)

2

Adult Attachment Interview differentiates adolescents with Childhood Sexual Abuse from those with clinical depression and non-clinical controls

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ABSTRACT

Although attachment representation is considered to be disturbed in traumatized adolescents, it is not known whether this is specific for trauma, as comparative studies with other clinical groups are lacking. Therefore, attachment representation was studied by means of the Adult Attachment Interview in adolescents with Childhood Sexual Abuse (CSA) (*N* = 21), clinical depression (*N* = 28) and non-clinical controls (*N* = 28). Coherence of mind and unresolved loss or trauma, as well as the disorganized attachment classification differentiated the CSA group from the clinical depression group and controls, over and above age, IQ, and psychiatric symptomatology. In the current era of sustained criticism on criteria-based classification, this may well carry substantial clinical relevance. If attachment is a general risk or vulnerability factor underlying specific psychopathology, this may guide diagnostic assessment as well as treatment.

INTRODUCTION

Adolescents who experienced trauma in their lives are suggested to have a different attachment representation than their peers who did not (e.g. Cassidy & Mohr, 2001; Liotti, 2004; Lyons-Ruth, Dutra, Schuder, & Bianchi, 2006). Attachment representation refers to the way one conceives and narrates the relationship with his or her parents or caretakers. It is suggested that traumatized adolescents are characterized by high rates of insecure and unresolved-disorganized attachment representations due to the impact of trauma on their lives (e.g. Lyons-Ruth et al., 2006). For instance, they may idealize or deny the importance of the relationship with their caretakers (dismissive attachment representation), they may be preoccupied with anger and fear (preoccupied attachment representation), they might be unresolved for loss of attachment figures or traumatic experiences (unresolved attachment representation), or they express all of these signs of insecure and unresolved-disorganized attachment at the same time (Hesse, 2008; Neufeld Bailey, Moran, & Pederson, 2007). In all of these instances the coherence of the narrative, called coherence of mind, is moderate to very low.

Surprisingly few studies have investigated attachment representations in clinical groups of adolescents with and without a history of trauma (for a meta-analysis see Bakermans-Kranenburg & Van IJzendoorn, 2009). Studying attachment representations in specific clinical groups could add to a better understanding and (differential) diagnosis of their symptomatology. This is especially the case for adolescents who experienced Childhood Sexual Abuse (CSA), as they are likely to have severe anxiety and depressive symptoms, besides post-traumatic stress and dissociative symptoms (e.g. Cicchetti & Toth, 1995; Cloitre et al., 2009; Pollak & Kistler, 2002). Thus, adolescents with clinical depression, who exhibit a mix of depressive and anxious symptoms, are of particular interest as a comparison group for adolescents with CSA, because of partially overlapping symptomatology. The aim of

this paper is to determine whether attachment representations differentiate adolescents with CSA from clinically depressed adolescents and matched controls beyond psychiatric symptom assessment.

CSA is defined 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), using the third National Incidence Study (NIS-3) operationalized definitions of CSA Specific Form of Maltreatment (NIS-3 code; Sedlak, 2001; see Appendix A in Stoltenborgh, Van IJzendoorn, Euser, & Bakermans-Kranenburg, 2011). As self-reported CSA prevalence worldwide is found to be one in 10 youths (Stoltenborgh et al., 2011), it can be considered a serious global mental health problem. Sustained, repeated and cumulative traumas, as often occur in CSA, can go along with a myriad of depressive, anxious, dissociative, externalizing and post-traumatic stress symptoms (Fergusson, McLeod, & Horwood, 2013; Gospodarevskaya, 2013; Kim- Spoon, Cicchetti, & Rogosch, 2013). From the nature of CSA, adolescents who experienced this adversity are at 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, epigenetic changes (Caspi et al., 2002; McGowan et al., 2009). This increases the likelihood of transgenerational transmission of sexual abuse and (psycho) pathology (McCloskey & Bailey, 2000; Putnam, 2003). Given this detrimental impact of CSA on one's life, it is important to identify underlying general pathogenic factors, such as incoherent or unresolved (Ud) attachment representations, that might provide clues for better diagnostics and treatment. We expect unresolved loss or trauma to be a stronger indicator of CSA than lack of coherence as the latter might also be observed in narratives about adverse past or current attachment experiences without specific losses or trauma.

Abuse and neglect have also been associated with contradictory attachment strategies within the same narrative (the "cannot classify" attachment classification, CC; Hesse, 2008; Neufeld Bailey et al., 2007) and with pervasive fear throughout attachment narratives of the Adult Attachment Interview (AAI, the so-called E3 classification; Main, Kaplan, & Cassidy, 1985; Turton, McGauley, Marin-Avellan, & Hughes, 2001). These classifications have been associated with diverse psychiatric disorders in adults such as PTSD (Harari et al., 2009), borderline personality disorder (Agrawal, Gunderson, Holmes, & Lyons-Ruth, 2004; Barone, Fossati, & Guiducci, 2011; Lyons-Ruth, Brumariu, Bureau, Hennighausen, & Holmes, 2014; Lyons-Ruth, Bureau, Holmes, Easterbrooks, & Brooks, 2013), and anti-social personality disorder (Levinson & Fonagy, 2004; Van IJzendoorn et al., 1997). In all of these instances the coherence of the narrative, called coherence of mind, is low. Because Ud, CC and E3 classifications may all be caused by underlying loss and/or trauma experiences in the Main, Goldwyn, and Hesse (2003) coding system, we will examine their associations with trauma in adolescents who suffer from sexual abuse experiences or struggle with clinical depression, and with typically developing peers.

We are aware of alternative or complementary classification systems to describe attachment representations of traumatized individuals. For example, Lyons-Ruth and colleagues (e.g. Lyons-Ruth, 2003b; Lyons-Ruth, Melnick, Patrick, & Hobson, 2007; Lyons-Ruth & Spielman, 2004) developed the hostile/helpless (HH) category to explain why some non- traumatized mothers have disorganized children. Mothers who were not judged unresolved nevertheless manifested a pervasive sense of hostility or helplessness throughout the AAI transcript. This appeared to be based on childhood experiences of lack of attunement in parent–child interactions, role-reversal (Vulliez-Coady, Obsuth, Torreiro-Casal, Ellertsdottir, & Lyons-Ruth, 2013), and emotional neglect (Milot et al., 2014). Also, childhood loss and trauma were found to be differentially associated with maternal unresolved and hostile-helpless states of mind (Lyons-Ruth, Yellin, Melnick, & Atwood, 2003). How both coding systems (Lyons-Ruth, Bronfman, & Parsons, 1999; Main et al., 2003) are interrelated was studied in low risk, poor and maltreating mothers (Frigerio, Costantino, Ceppi, & Barone, 2013). The authors found HH profiles not to overlap with Ud, CC and E3 categories. In the current study we focus on the more frequently used and well-validated Main et al. (2003) coding system to facilitate comparison with previous (clinical) studies on attachment (Bakermans-Kranenburg & Van IJzendoorn, 2009). It should also be noted that the AAI does not assess (reactive) attachment disorders as defined by the DSM-IV or DSM-5 (for the differences, see Van IJzendoorn & Bakermans-Kranenburg, 2003; Zeanah & Smyke, 2008).

For several reasons, there is need to study attachment issues in adolescence, in particular in clinical samples. First, puberty is known to be accompanied by emotion regulation and parent–child interaction problems, which might exacerbate emerging clinical issues (Blakemore, 2012; Obsuth, Hennighausen, Brumariu, & Lyons-Ruth, 2014). Secondly, several psychiatric disorders, like clinical depression, become only clearly visible in adolescence (Paus, Keshavan, & Giedd, 2008). Thirdly, CSA has a high incidence in adolescence (Bicanič, 2014) and is often accompanied by PTSD. Thus, especially in female adolescents, depressive and anxiety disorders and CSA-related PTSD coincide (Bersani et al., 2014; Bicanič, 2014; Christiansen & Hansen, 2015), making it vital to disentangle disorder-specific from general psychiatric symptoms. In contrast to the extensive literature on attachment in the general population, the small number of studies on the association of attachment with specific psychiatric disorders is surprising (e.g. Allen, 2008; Dozier, Chase Stovall-McClough, & Albus, 2008; Duchesne & Ratelle, 2014; Nelson, Westerlund, Martin McDermott, Zeanah, & Fox, 2013; Wallis & Steele, 2001; Waters, Merrick, Treboux, Crowell, & Albersheim, 2000). The few clinical studies have focused on infants, institutionalized children or adult samples (e.g. Bentovim, Cox, Bingley Miller, & Pizzey, 2009; Fonagy et al., 1996; MacKinnon, 2012; Strathearn, 2011; Zeanah & Smyke, 2008), but only rarely on adolescent groups (Allen, 2008; Lionetti, Pastore, & Barone, 2015; Wallis & Steele, 2001; Zegers, Schuengel, Van IJzendoorn, & Janssens, 2006, 2008). We therefore decided

to contribute to the small set of attachment studies in clinically disturbed adolescents with an outpatient adolescent group.

In summary, our aim is to investigate whether attachment representations differentiate adolescents with CSA from those with clinical depression and from controls and whether information from AAIs complements the symptomatology derived from conventional psychiatric assessments for depression and post-traumatic stress. The following three hypotheses are examined.

(1). Adolescents with CSA will more often show an insecure and especially an unresolved-disorganized attachment representation than adolescents with clinical depression and non-clinical controls.
(2). Unresolved status and low coherence of mind will be associated with more severe clinical symptomatology in both clinical adolescent groups.
(3). Unresolved status and coherence of mind will differentiate the CSA group from the clinical depression group and controls beyond psychiatric symptomatology.

METHODS

Participants

AAI and clinical data were collected for two outpatient groups of adolescents and one control group: N = 21 CSA adolescents, N = 28 adolescents with DSM-IV anxiety or depressive disorders, further referred to as clinical depression (DEP) and N = 28 matched non-clinical controls (CNTR). The adolescents from all three groups were part of the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents), a longitudinal study in which adolescents were followed over a six-month period. The CSA and DEP groups underwent a 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 (see for more detail Van den Bulk et al., 2013). The current study reports on the AAI and clinical characteristics of the three groups using data of the first measurement only. The imaging data will be published in separate reports.

Related to the neuroimaging protocol all participants 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). The CSA group was recruited in two psychotrauma centres of child and adolescent psychiatric institutes in the Leiden region in the Netherlands. Inclusion criteria for the CSA group were having

experienced sexual abuse during their lifetime more than once by one or more perpetrators in- or outside the family, and being referred for treatment at the psychotrauma centre. The inclusion criteria for the DEP group 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 both clinical groups 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. The controls were recruited through local advertisement, with the following inclusion criteria: 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.

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. Most adolescents with CSA (87%) reported during the AAI serious and/or longstanding physical sexual contact including repeated or group rape, in 63.6% by a person other than an attachment figure. In addition, 36.4% of the CSA group also experienced physical abuse, 22.7% by a person other than an attachment figure, 9.1% by an attachment figure, in one case by both. Sexual abuse was reported to the police in 60.9%, child welfare was involved in 56.5% of the cases, while 17.4% had a child protection measure (family custody). None of the participating control and DEP adolescents had experienced CSA, but they did mention physical and emotional abuse, bullying, and other incidents. No controls were involved with police, child welfare or child protection, while 23% of the DEP group had child welfare involvement.

From the original sample of 82 adolescents, three participants were excluded due to technical problems, i.e. failed voice and video recording (one CSA), unintelligible recording (one control), incorrect interview technique (one control). Two participants (one control and one DEP) were excluded because they refused the AAI because of the interview itself. Of the $N = 77$ in this sample, 86% were girls. All CSA adolescents fulfilled the DSM-IV criteria for PTSD, according to the ADIS, however one adolescent missed a point on the interference score to fully qualify for PTSD. SSRI's were used by four of the CSA group and two of the DEP group.

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.

Procedure

After adolescents and their parents had given assent and consent to participate in the EPISCA study they filled out questionnaires, usually at home, and were tested for IQ and interviewed for DSM-IV classification and attachment representation at the clinic in separate appointments.

Measures

We used the following measures: the AAI (attachment representations), the ADIS C/P (DSM-IV classifications), WISC/WAIS (intelligence), TSCC, A-DES, CDI (clinical symptoms of trauma, dissociation respectively depression), PDS (puberty development), and ZALC (socio-emotional development).

AAI: Adult Attachment Interview (Main et al., 1985) is an hour-long semi-structured interview (Hesse, 2008), validated for adolescents (Beijersbergen, Bakermans-Kranenburg, Van IJzendoorn, & Juffer, 2008; Beijersbergen, Juffer, Bakermans-Kranenburg, & Van IJzendoorn, 2012) and with additional trauma probes (Madigan, Vaillancourt, McKibbon, & Benoit, 2012). The AAI asks how the interviewee thinks about the relationship with parents or other primary caregivers in his or her youth, how these experiences have influenced him or her, how the actual relationship with parents or other primary caregivers is and whether there were any experiences of illness, separation, fear, trauma or loss. The interviewee is asked to give specific examples supporting each evaluation. The coherence of the narrative matters, not its autobiographical content.

After transcription and coding of the AAI according to the manual of Main et al. (2003) by a certified coder, an attachment representation classification can be given according to the DEFU system: dismissive (Ds), preoccupied (E), secure-autonomous (F), unresolved-disorganized (Ud). Ds, E and F classifications are organized forms of attachment (Hesse, 2008; Main, 2000), while Ud represents disorganized forms of attachment. In organized attachment representations there is one coherent mental strategy with regard to attachment figures, either secure-autonomous (F) or insecure (Ds or E). In disorganized attachment representation different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory (Hesse & Main, 2000). In insecure-dismissive attachment representations (Ds) the narrative is coloured by idealization, denial and lack of memory, resulting in moderate to low coherence of the narrative. In insecure-preoccupied representations (E) the narrative is coloured by vague and passive speech or speech showing signs of preoccupied anger or fear, also resulting in moderate to low coherence of narrative. A high to moderate coherence of the narrative is seen in secure-autonomous (F) attachment interviews in which the interviewee can give ample evidence for general evaluative statements made regarding attachment relationships and attachment experiences whether good or bad.

In case of unresolved loss or trauma, the attachment representation is labelled

unresolved-disorganized (Ud). This classification can be given in addition to a Ds, E or F classification. A fifth category, cannot classify (CC), has been suggested by Hesse (1999) and is used when the interviewee presents contrasting attachment strategies for attachment figures in the course of the interview resulting in very low coherence of narrative. The CC classification can be given in combination with any DEFU classification and renders the final classification disorganized. Besides the five categories Ds, F, E, U, and CC, we used the dichotomous variables F-nonF and Ud-nonUd. Derived from the DEF system, the contrast between F-nonF is considered a forced two-way classification in which unresolved state of mind is not taken into account. This implies that subjects with a secure and at the same time unresolved state of mind are considered secure, just like subjects who were classified as secure-autonomous without the additional classification as unresolved. The contrast between Ud-nonUd is used to characterize the presence or absence of unresolved-disorganized attachment representations (U or CC). Coherence of mind and Unresolved for loss or trauma (Ulosstrauma) are two dimensional scales of the AAI which are assigned scores rated between 1 and 9 by the judge coding the AAI. Lowest score for Coherence means there is little or no coherence of mind, highest score for Ulosstrauma means there is high impact of loss or trauma. A $\log_{10}$ transformation was performed to lift the positive skew for Ulosstrauma. To avoid multiple testing in a relatively small sample we decided a priori to focus in our analyses on these two central AAI scales that cover most of the variance between the classifications in clinical samples.

Because of the recruitment procedure the dominant factor in the U classification and scale score was trauma, and in only one case was loss rated higher than trauma which resulted in a U classification based on loss but accompanied with traumatic experiences as well. In our relatively small sample it was therefore impossible to separate Uloss and Utrauma. We refrained from a cumulative loss and trauma experiences score, because we were aware of the measurement problems inherent in reconstructing past (loss or trauma) experiences especially in case of high co-morbidity. This is why we decided to stick to the AAI representational variables not suffering from the retrospective bias (Van IJzendoorn, 1995b).

The AAI is found to have remarkably good test-retest, discriminant reliability as well as predictive validity (Aikins, Howes, & Hamilton, 2009; Bakermans-Kranenburg & Van IJzendoorn, 1993, 2009; Benoit & Parker, 1994; Crowell et al., 1996; Sagi et al., 1994; Steele, Steele, & Fonagy, 1996; Van IJzendoorn, 1995a; Waters, Merrick, Treboux, Crowell, & Albersheim, 2000). In this study, the AAI was administered by MJvH and CIG, verbatim transcribed according to protocol, and coded by GK (trained by Diane and Dave Pederson), and SdH (trained by Diane and Dave Pederson, and June Sroufe). Both reached intercoder reliability standards in the AAI classification system. Ten cases were also coded by MJBK. Interrater agreement in this sample was 80% for F-nonF, 90% for Ud-nonUd and 70% for four-way classification (DEFU). Kappas for coding F-nonF (.59) and Ud-nonUd (.62) were

both statistically significant and reasonable to satisfactory.

ADIS: The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS C/P) (Silverman, Saavedra, & Pina, 2001; Dutch version by Siebelink & Treffers, 2001a, 2001b) are semi-structured interviews designed specifically for DSM-IV classification of anxiety and other related disorders such as depression and PTSD in children and adolescents. Based on results obtained from the interviews with the children and parents separately, the interviewer provides definite classifications. The ADIS is used in many studies to describe the participants' DSM-IV classifications in clinical and maltreated adolescents (e.g. Brown, DiNardo, Lehman, & Campbell, 2001). With regard to the psychometric qualities, Silverman and colleagues (2001) reported excellent validity and reliability. In this study, the ADIS was applied to all participants by certified trained clinicians and researchers.

WISC-III-NL and WAIS-III: Short versions of the Wechsler Intelligence Scale for Dutch Children aged 6–16 years, WISC-III-NL (Wechsler, 1991) and adolescents aged 16 and above and adults, the Wechsler Adult Intelligence Scale, WAIS-III (Wechsler, 1997) were used. They consisted of six subtests: picture completion, similarities, picture arrangement, arithmetic, block design, and comprehension. In earlier studies, these subtests were found to give a valid and reliable IQ estimate (reliability coefficient > .90; e.g. Crawford, Mychalkiw, Johnson, & Moore, 1996; Kaufman, Kaufman, Balgopal, & McLean, 1996).

TSCC: The Trauma Symptom Checklist for Children (Briere, 1996) is a 54-item self-report for children and adolescents aged 8–17, which measures trauma-related symptoms. There are separate profile sheets for boys and girls. On a 4-point scale (never to almost all of the time), the adolescent indicates how often a thought, feeling or behaviour occurs. The items are grouped into six clinical scales on anxiety, depression, post-traumatic stress, sexual concerns, dissociation, and anger. The total score is summed from the frequency of all items, with scores ranging from 0 to 162. The total score reflects post-traumatic symptomatology (Wekerle et al., 2001). The standardization of TSCC was based on 3008 school children from different parts of the USA. Good psychometric qualities have repeatedly been confirmed in other studies on trauma in adolescents (Nilsson, Wadsby, & Svedin, 2008). In the present study, only the TSCC total score was used (Cronbach's alpha coefficient .96).

A-DES: The Adolescent Dissociative Experiences Scale (Armstrong, Putnam, Carlson, Libero, & Smith, 1997) is a self-report for adolescents aged 11–18 measuring possible dissociation. The self-report consists of 30 questions reflecting experiences and coping skills rather than symptoms and disabilities. It consists of four different scales: (1) dissociative amnesia; (2) absorption and imaginative involvement; (3) passive influence; and (4) depersonalisation and derealisation, items reflecting dissociated identity and dissociated relatedness. All items are scores from 0 (never the case) to 10 (always the case). The total score is the mean of all item scores (range 0–10). A mean score of ≥ 4.0 suggests pathological dissociation, while a mean score of 3 suggests high risk for dissociative disorder (Armstrong

et al., 1997). Smith and Carlson (1996) and Armstrong and colleagues (1997) found that the A-DES had good validity and reliability. In this study the mean total score on the A-DES was used, and had a Cronbach's alpha coefficient of .95. A log10 transformation was performed to lift the positive skew.

CDI: The Children's Depression Inventory (Kovačs, 1985) is a 27-item, self-rated, depression symptoms-oriented scale suitable for youths aged 7 to 17. The CDI is sensitive to changes in depressive symptoms over time and is a useful index of the severity of the depression. There are five subscales that measure different components of depression: (1) anhedonia; (2) negative self-esteem; (3) ineffectiveness; (4) interpersonal problems; and (5) negative mood. Each item offers respondents three alternatives scored 0 (absence of symptom), 1 (mild symptom), or 2 (clearly present symptom) and accordingly raw scores range from 0 to 54. Several studies (e.g. Matthey & Petrovski, 2002) recommended 13 as a cut-off score for clinical populations and 19 as the thresh- old for community samples in the United States, while 16 has been recommended as a cut-off for Dutch samples (e.g. Roelofs et al., 2010). The CDI has good psychometric properties of validity and reliability (Kovačs, 1992), though discriminant validity has been subject to discussion (e.g. Timbremont, Braet, & Dreessen, 2004). In this study the total CDI score is used and has a Cronbach's alpha coefficient of .93.

PDS: The Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988) measures the actual level of physical development during puberty. It is a 5-item self-report that measures items like body growth, body hair, and skin changes for both sexes. For boys there are items on beard growth and voice changes. For girls there are items on breast growth and menstrual bleeding. Items can be answered on a 5-point scale with a total score range of 0–20. Internal consistency is adequate for both sexes, consistent across samples, while the predictive validity of the PDS is satisfactory (Robertson et al., 1992). The PDS was filled out by 87% of participants in this study.

ZALC: The Sentence Completion Test for Children and Youth (Westenberg, 2002) measures the socio-emotional level of development. It is an 80 item questionnaire containing incomplete sentences that have to be completed by the child or youngster. It is based on the Washington University Sentence Completion Test (WUSCT), a test developed by Loevinger (Loevinger, 1976; Westenberg, Jonckheer, Treffers, & Drewes, 1998), who views psychosocial development as changes in impulse control, conscious preoccupations, character development and interpersonal orientation. There is evidence for good reliability and discriminant validity (Drewes & Westenberg, 2001). The ZALC was filled out by 91% of participants in this study.

Analysis

Preliminary descriptive analyses were performed and distribution of data was checked. A MANOVA for diagnostic group differences regarding IQ and age was performed,

as well as crosstabs for differences in PDS and ZALC categories with Pearson's χ^2 and Cramer's *V* reported. Bootstraps (1000 samples) were performed in order to acquire robust standard errors in the relatively small study group. Fisher's exact test (2-sided) was reported in case of bootstrap. A MANOVA was performed on total scale scores of the psychiatric symptoms measures TSCC, A-DES and CDI. Subsequent MANCOVA's were performed with age and IQ as covariates, because groups differed significantly in this respect. Post- hoc LSD tests (alpha 0.05) were performed to examine univariate effects. Effect sizes (partial η2) were reported; interpretation of these effect sizes is debatable, rule of thumb might be: .02 ~ small, .13 ~ medium .26 ~ large.

To test the first hypothesis group differences in attachment representations were examined, using categorical and dimensional AAI variables. For the categorical approach the five-way classification DEFCCU was used, unless explicitly stated otherwise. We used adjusted residuals to determine over- or under-representation of attachment classifications. Also the dichotomies F-nonF and Ud-nonUd were used. For the dimensional approach we used two continuous state of mind scales of the AAI, Coherence and Ulosstrauma, as dependent variables, group as independent variable with age and IQ as covariates in a MANCOVA.

To test the second hypothesis, Pearson correlation was used to examine the associations between the AAI Coherence and Ulosstrauma scale scores and the psychiatric symptoms measures TSCC, A-DES and CDI total scale scores.

To examine the third hypothesis, we tested whether the AAI could distinguish diagnostic groups beyond psychiatric symptom profile using dimensional attachment scales (Ulosstrauma and Coherence). We performed MANCOVA's on groups with Ulosstrauma and Coherence as dependent variables and TSCC, A-DES and CDI as covariates.

RESULTS

Sample characteristics

The groups differed with respect to age ($F_{(2,74)} = 4.68$, $p < .01$, partial $\eta^2 = .11$) and IQ ($F_{(2,74)} = 4.49$, $p < .01$, partial $\eta^2 = .11$), with CSA and DEP groups being significantly older than the controls (both $p < .05$), and the CSA group having a significantly lower IQ than both the DEP and controls (both $p < .05$). As expected based on group differences for age, the PDS showed that the CSA and DEP groups were most often in the late- or post-pubertal phase, while the controls were most often in the mid- or late-pubertal phase (Pearson's $\chi^2_{(8)} = 22.14$, exact $p = .00$, Cramer's $V = .41$). Surprisingly, socio-emotional development as measured with the ZALC was equal across groups (Pearson's $\chi^2_{(12)} = 10.36$, exact $p = .64$, Cramer's $V = .27$), with most adolescents (44/70) being rated as conformists. Despite the older age of the clinical groups, they were not more often self-aware or responsible than controls, but in contrast functioning at the same socio-emotional developmental level.

Psychiatric symptoms profile

On the psychiatric symptoms measures, a MANCOVA with age and IQ as covariates showed a significant effect for group with rather large effect sizes ($F_{(10, 120)} = 7.48$, $p < .00$, partial $\eta^2 = .38$). As expected, the two clinical groups differed from the controls on all three scale scores, but not among each other (TSCC and CDI both at $p < .00$; A-DES CNTR vs. DEP group at $p = .04$ and CNTR vs. CSA group at $p = .00$; TSCC $F_{(2,65)} = 12.02$, $p < .00$, partial $\eta^2 = .28$; A-DES $F_{(2,65)} = 4.73$, $p = .01$, partial $\eta^2 = .13$; CDI $F_{(2,65)} = 23.40$, $p < .00$, partial $\eta^2 = .43$; see Table 1).

AAI profile

Regarding the most fine-grained DEFCCU attachment classifications cross-tabulation with group resulted in a Fisher's Exact Test of 18.39, $p = .00$. Inspection of the adjusted standardized residuals showed that the CC classification differentiated the CSA group (adjusted residual 3.2) from both the DEP (adjusted residual −1.5) and the CNTR groups (adjusted residual −1.5). As can be seen in Table 1, most of the adolescents in the CSA group had insecure attachments (16/21: 76%), and the same was true for about half of the adolescents in the two other groups. The percentage with dismissing classification was similar in the three groups (CSA 43% (9/21), DEP 39% (11/28), 46% (13/28)). None of the adolescents had a preoccupied (E) classification. Unresolved-disorganized representations including CC were significantly more present in the CSA group (9/21: 43%; adjusted residual 2.9) than in the DEP group (6/28: 21%; adjusted residual 0.1) and controls (1/28: 4%; adjusted residual −2.8). In addition, the dimensional AAI scale scores Ulosstrauma and Coherence differentiated the three groups, with age and IQ included as covariates ($F_{(10,120)} = 7.48$, $p < .00$, partial $\eta^2 = .38$). Post hoc LSD analysis showed that the CSA group had a significantly higher score than the controls and DEP group on the Ulosstrauma scale ($F_{(2,65)} = 13.81$, $p < .00$, partial $\eta^2 = .31$), and a significantly lower score than the controls and DEP group on the Coherence scale ($F_{(2,65)} = 6.60$, $p = .00$, partial $\eta^2 = .17$; see Table 1).

Table 1. Sample characteristics with psychiatric symptoms and attachment variables ($N = 77$).

	CSA ($N = 21$)		DEP ($N = 28$)		CNTR ($N = 28$)					
	N	%	*N*	%	*N*	%				
Sample characteristics										
Females	18	86	24	86	24	86				
Number meeting PTSD criteria[1]	20		-		-					
Number of stable SSRI use[2]	4		1		-					
Number in PDS categories[A]	19		22		28					
Pre-pubertal	1	1.5	0	0	0	0				
Early- pubertal	0	0	1	1.5	0	0				
Mid-pubertal	0	0	0	0	8	11.9				
Late- pubertal	7	10.4	12	17.9	12	17.9				
Post-pubertal	10	14.9	11	16.4	5	7.5				
Number in ZALC categories[B]	18		21		25					
Impulsive or self-protective	3	4.3	5	7.1	3	4.3				
Conformist	12	16.9	11	15.6	21	29.9				
Self-aware or responsible	5	7.1	6	8.6	4	5.7				
	Mean	*SD*	Mean	*SD*	Mean	*SD*	η_p^2	$F_{(2,70)}$	*p*	Significant group differences
Age in months***	199	24	192	16	181	20	.01	4.68	.05	CSA>DEP>CNTR
Full scale IQ***	99	8.6	104	9.5	106	7.9	.01	4.49	.05	CSA<DEP<CNTR

(*continued*)

Table 1. (*Continued*).

	CSA (*N* = 21)		DEP (*N* = 28)		CNTR (*N* = 28)					
	N	%	*N*	%	*N*	%				
Psychiatric symptom scores	Mean[3]	SD	Mean[4]	SD	Mean[5]	SD	η_p^2	$F_{(2,68)}$	*p*	Significant group differences
TSCC score	45.74	22.92	41.90	22.85	16.26	12.50	.28	12.02	.00	CSA, DEP >CNTR***
A-DES score	1.65	.42	1.46	.44	1.20	.46	.13	4.73	.01	CSA***, DEP*** > CNTR
CDI score	15.15	6.89	17.75	8.89	4.17	3.36	.43	23.40	.00	CSA, DEP > CNTR***
Attachment characteristics[6]	Mean[3]	SD	Mean[4]	SD	Mean[5]	SD	η^2	$F_{(2,68)}$	*p*	Significant group differences
Unresolved loss or trauma	.51	.31	.27	.29	.06	.17	.31	13.81	.00	CSA, DEP>CNTR*
Coherence of mind	2.47	1.6	4.29	1.9	4.71	2.3	.17	6.60	.00	CSA>CNTR**
	N	%	*N*	%	*N*	%				
F:nonF[7]	5:16	24:76	13:15	46:54	14:14	50:50				
Ud:nonUd[8]	9:12	43:57	6:22	21:79	1:27	4:96				
Ds	9	43	11	39	13	46				
U[9]	6(3)	21(14)	4	18	-	-				
CC[10]	6(3)	21(14)	1	4	1	4				

Abbreviations used: Childhood Sexual Abuse (CSA), clinical depression (DEP), non-clinical controls (CNTR), post-traumatic stress disorder (PTSD), Anxiety Disorders Interview Schedule for Child/Parent (ADIS-C/P), Pubertal Development Scale (PDS), Sentence Completion Test Curium (ZALC), standard deviation (*SD*), Selective Serotonine Reuptake Inhibitor (SSRI), F:non-F (secure versus insecure attachment classification), Ud:non-Ud (unresolved-disorganized versus organized attachment classification), dismissive attachment classification (Ds), unresolved for loss or trauma (U), Cannot Classify attachment classification (CC). *$p < .05$; **$p < .01$; ***$p < .00$; [1]All adolescents (but one missing one interference point on the ADIS) with CSA had PTSD as primary classification. [2]Stable SSRI use (fluoxetine) was permitted. [3] $N = 18$; [4] $N = 24$; [5] $N = 26$; [6] DEFCCU five-way classification with bootstrap Fisher's Exact Test value 18.385, exact *p* (2-sided) = .00 at $N = 77$. [7] non-F included Ds. E was not present in this sample. [8]Ud included both U and CC; in some cases both have been classified. Non-Ud included F and Ds. [9] 3 of 6 U were in combination with CC. U without CC have been added between brackets. [10] 3 of 6 CC were in combination with U. CC without U have been added between brackets. Adjusted residuals in the CSA group < −2.5 for F and > 2.5 for CC. [A] Ten were missing (3 CSA; 4 DEP and 3 CNTR); [B] Seven were missing (1 CSA and 6 DEP).

Associations between AAI scales and psychiatric symptoms

The Ulosstrauma and Coherence variables correlated negatively with each other (r = -.35; p < .01), meaning that higher Ulosstrauma scores were associated with a lower Coherence score. The Ulosstrauma scale score correlated positively with total scores on the TSCC (Pearson's r = .34, p < .00) and CDI (Pearson's r = .27, p < .05), but not with the total A-DES score. In contrast, there were no significant associations between the Coherence scores and the total TSCC, A-DES and CDI scores. The scores on TSCC, A-DES and CDI correlated positively and significantly with each other (Pearson's r = .56–.76, all ps < .01, see Table 2).

AAI scales differentiate CSA from both clinical depression and controls

When examining group differences for Ulosstrauma and Coherence, while controlling for age, IQ and psychiatric symptoms measured by TSCC, A-DES, and CDI, a significant main effect of group was found ($F_{(4, 120)}$ = 5.70, p < .00, partial η^2 = .17; Coherence $F_{(2,60)}$ = 6.45, p = .00, partial η^2 = .18; Ulosstrauma $F_{(2,60)}$ = 10.63, p < .00, partial η^2 = .26). Post-hoc LSD analyses indicated that the CSA group had a significantly higher score on the Ulosstrauma scale (p < .02) and a significantly lower score on the Coherence scale (p < .01) compared to both DEP group and controls. DEP group and controls had equal Coherence scale scores (p = .21).

Table 2. Pearson correlations (r) between the two AAI scales "Coherence of Mind" and "Unresolved" and clinical characteristics[1] (N = 68).

	Unresolved for loss or trauma	Coherence of mind	TSCC	A-DES	CDI
Unresolved for loss or trauma		-.35**	.34**	.21[2]	.27*
Coherence of mind			-.09	-.17	-.09
TSCC				.63***	.76***
A-DES					.56***
CDI					

Abbreviations used: Trauma Symptom Checklist (TSCC), Adolescent version Dissociative Experiences Scale (A-DES), Child Depression Inventory (CDI). *Significant at p < .05, **p < .01, ***p < .00, [2](p = .09). [1]Because questionnaires were not filled out by three CSA adolescents (TSCC, A-DES, CDI), and by four (A-DES), three (TSCC) and one (CDI) depressed adolescents, the analyses were performed on N = 68. Note: Because less than 20% of the items in TSCC, ADES and CDI were missing, expectation maximization as regression method was used to calculate the scale scores.

DISCUSSION

In the current study we tested whether attachment representation as measured with the AAI can distinguish a CSA group from a clinically depressed and a non-clinical control group when taking psychiatric symptoms into account. First, we found that the CSA group was most disorganized according to the AAI classifications, compared to both the clinical depression and control groups. This was due to the overrepresentation of unresolved trauma and "Cannot Classify" classifications (U/CC). Secondly, unresolved status but not coherence of mind correlated with severity of clinical symptomatology. Third, the CSA group had the highest score of being unresolved and the lowest coherence of mind score, compared to the clinical depression group and the controls. Co-varying IQ, age and psychiatric symptoms, only coherence of mind uniquely differentiated the CSA group from both the clinical depression group and controls. The unresolved loss or trauma scale differentiated both clinical groups from the controls, whereas coherence of mind differentiated CSA from the clinical depression and control groups.

It should be noted that the current sample showed rather elevated levels of psychiatric symptomatology, with serious problems requiring intensive outpatient treatment. For example, all adolescents but one in the CSA group had PTSD according to the ADIS and scores for post-traumatic stress, dissociative and depressive symptoms were rather high in both clinical groups. In addition, we found a very high percentage of serious and/ or longstanding physical sexual contact including repeated or group rape and implicit emotional abuse and neglect in the CSA group, and a high percentage of physical abuse, losses, bullying and other traumatic incidents in both clinical groups. All of these results together imply that a substantial percentage of adolescents with CSA seeking professional help suffer from complex PTSD (Herman, 1992; Jonkman, Verlinden, Bolle, Boer, & Lindauer, 2013; Karam et al., 2014) or "PTSD with prominent dissociative symptoms" (DSM-5; American Psychiatric Association [APA], 2013). The severity of the experiences and symptoms might be one of the reasons why their unresolved status and low coherence of mind, classified as unresolved-disorganized attachment representations (with an over-representation of CC classifications), characterize them even beyond regular psychiatric symptomatology.

The current study extends our knowledge by suggesting that adolescents with CSA can be characterized by a higher frequency of unresolved-disorganized attachment representations in contrast to clinically depressed adolescents as well as to typically developing adolescents who showed an overrepresentation of dismissive attachment representations. Our finding is in line with results found in traumatized adults (Cassidy & Mohr, 2001; Liotti, 2004; Lyons-Ruth et al., 2006), and in an at-risk sample of adolescent mothers with complex trauma symptoms, who showed elevated levels of unresolved attachments (Neufeld Bailey et al., 2007). Because of the cross-sectional nature of our study,

it is not clear whether adolescents with CSA have unresolved-disorganized attachment representations as a consequence of CSA or whether they were more vulnerable for CSA due to an already present insecure or unresolved-disorganized attachment representation (Harari et al., 2009; Liotti, 2004). This remains to be investigated in longitudinal studies.

Attachment was examined using categorical as well as dimensional variables of the AAI. We used both strategies because the conventional coding system (Main et al., 2003) yields categorical classifications as well as continuous scales, and because including dimensional scales may imply more statistical power to identify theoretically anticipated correlates of insecure states of mind than the classifications. It should be noted that if we would have only relied on the continuous scales the strong association between the CC classification and CSA would have escaped our attention. If we would only have concentrated on the classifications we might not have observed the special role of coherence of mind in separating CSA from both the clinical depression group and the controls whereas the unresolved scale was not able to differentiate the CSA from the depression group, when we co-varied IQ, age, and psychiatric symptoms. The current debate about continuous versus categorical AAI measures seems most pertinent to typically developing adolescents with low levels of loss or trauma experiences and concomitant U and CC classifications (see for the debate: Roisman, Fraley, & Booth- LaForce, 2014; Van IJzendoorn & Bakermans-Kranenburg, 2014).

With regard to the association between representational attachment scales for coherence and unresolved on the one hand and psychiatric symptoms on the other hand, we only found that being unresolved correlated with self-reported post-traumatic and depressive symptoms, but not dissociative symptoms. There was no association between coherence of mind and psychiatric symptoms. Though the A-DES is shown to have good reliability and validity (Armstrong et al., 1997), like the adult version (Bernstein & Putnam, 1986; Van IJzendoorn & Schuengel, 1996), dissociative symptoms may be easier to recognize for an interviewer or observer than for the dissociative adolescent herself. Furthermore, retrospect reporting may become distorted (Merckelbach & Muris, 2001). For these reasons self-reported incidence of dissociation may be different from observed incidence and more than one informant in a multi-informant approach may be preferable to self-report only (Van IJzendoorn & Schuengel, 1996). Coherence of mind is an evaluative judgment on the narrative of the AAI and is independent of self-knowledge and conscious self-reports of the individual. Therefore it may be no surprise that coherence of mind and presence of psychiatric symptoms do not have strong associations.

Finally, by broadening insights in the interrelatedness of trauma, dissociation and disorganized attachment representation, this study adds evidence to theories addressing ways in which individuals (fail to) cope with traumatic experiences (Cassidy & Mohr, 2001; Hesse, 2008; Liotti, 2004; Lyons-Ruth et al., 1999, 2006). These authors mentioned lapses in behavioural and attentional strategies in traumatized young adults having disorganized

attachment representations, and we indeed found disorganized attachments of the most severe kind (i.e. CC) in particular in the CSA group, which was also characterized as showing lowest levels of coherence of mind. Liotti (2004) developed the diathesis-stress model of trauma, dissociation and disorganized attachment as "three strands of a single braid" implying inherent vulnerability. Maybe pre-existent lack of coherence of the auto-biographical narrative due to highly insensitive parenting might have prepared the way for elevated disorganization in the face of sexual abuse. Of course this speculative interpretation should be tested in a longitudinal study.

With regard to implications for child and adolescent clinical practice, our findings suggest that attachment coherence and unresolved loss or trauma are potentially important concepts to be taken into account in child psychiatric diagnostic assessment and treatment of specific groups such as individuals suffering from CSA or clinical depression (Kim, Blashfield, Tyrer, Hwang, & Lee, 2014; Tarren-Sweeney, 2014; Tyrer, 2014). For general clinical application of the AAI, Steele and Steele (2008) already described several possibilities. One of them is that the AAI effectively engages the adolescent in reflection on the relationship with his or her parents, losses and traumatic experiences. In doing so, the AAI creates a bond between the adolescent and clinician, which makes it easier for the adolescent to trust the clinician and engage in therapy, which is important for those traumatized or depressed (e.g. Sheftall, Mathias, Furr, & Dougherty, 2013). For diagnosis and treatment of CSA victims, our findings emphasize the importance of not only looking at signs of unresolved trauma, but also at more general indications of an incoherent autobiographical narrative. Of course these implications are speculative and a follow-up study is needed to test the prognostic value of our findings and to study the usefulness of attachment representations in clinical practice.

We recognize several limitations in this study. First, caution is needed concerning the generalizability of our results: (a) Due to participation in a time-consuming, multi-disciplinary neuroimaging study, recruitment was restricted by many inclusion and exclusion criteria and therefore our sample was fairly small in size (N = 77). (b) The ethnicity and gender of our sample was restricted. We mainly recruited female Caucasian participants, only a few boys or adolescents from other ethnic groups (Bicanič, 2014; Van IJzendoorn & Sagi-Schwartz, 2008). Secondly, as we conducted a cross-sectional study, conclusions about cause and time aspects of the phenomena studied cannot be drawn. To be able to add further evidence to the discussion on interrelatedness of trauma, dissociation and disorganized attachment representation (Herman, 1992; Liotti, 2004) and to disentangle the long term impact of attachment and trauma on personality development (e.g. Fransson, Granqvist, Bohlin, & Hagekull, 2013; Pascuzzo, Cyr, & Moss, 2013), further longitudinal research is needed. Thirdly, we restricted our coding of the AAI to the established classifications and scales, although in clinical groups such as ours, with severe trauma and symptomatology, complementary coding such as HH would have been a fruitful addition.

In conclusion, our study is the first to present attachment representations and psychiatric symptom profiles of adolescents with CSA compared to clinically depressed adolescents and controls. We used categorical classifications as well as dimensional scales of the AAI, besides psychiatric diagnostic classifications and clinical dimensional measures of trauma, dissociation, and depression. The study is the first to show that there is not only clinical (Steele & Steele, 2008), but also scientific evidence that the AAI diagnostically differentiates a CSA group from clinical depression and control groups.

3

Emotional face processing in adolescents with childhood sexual abuse-related posttraumatic stress disorder, internalizing disorders and healthy controls

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ABSTRACT

Childhood Sexual Abuse related posttraumatic stress disorder (CSA-related PTSD), and anxiety and depressive disorders (clinical depression) have profound though differential impact on adolescent emotion regulation, attention bias and emotional face processing. We hypothesized increased negative attention bias for emotional faces and altered brain functioning in CSA-related PTSD compared to internalizing disorders and healthy controls in a cross-sectional fMRI study using an emotional face processing task in 19 12-20-year-old adolescents with CSA-related PTSD, 26 with internalizing disorders and 26 healthy controls. Outcome measures were reaction times, subjective ratings of emotional faces, and brain activation patterns for whole brain and for regions of interest. Compared to both other groups adolescents with CSA-related PTSD showed significantly slower reaction times and the highest subjective rating of emotional faces. On whole brain and ROI level, no significant group differences were found. Self-reported depressive, posttraumatic or dissociative symptoms were not associated with differences in task-related brain activity. Results support the hypothesis of increased negative attention bias for fearful and neutral faces in CSA-related PTSD versus both other groups. The absence of neural differences might indicate a brain-behavior neuro-imaging gap to be closed by larger and IQ matched samples or more sensitive paradigms to elicit emotion processing.

INTRODUCTION

About one in ten children worldwide experience Childhood Sexual Abuse (CSA; Stoltenborgh et al., 2011), with all too often long lasting and devastating consequences. These include a variety of psychiatric disorders related to emotion dysregulation, that usually last into adulthood (Anda et al., 2006; Fergusson et al., 2013). In order to develop early interventions and personalize treatment to reduce the impact of CSA, better insight in the neural sequelae of CSA, especially in adolescence, is warranted. While there are several behavioral and neurobiological studies on sequelae of CSA (Fergusson et al., 2013), only few studies (e.g. Garrett et al., 2012) have looked into underlying brain mechanisms.

Since emotional abuse and neglect are common findings in CSA and psychiatric disorders and emotion regulation is all too often disturbed in adolescents with CSA, as well as in CSA-related psychiatric disorders like posttraumatic stress disorder (PTSD) and anxiety and depressive disorders, it is of interest to focus on this concept. Disturbed emotion regulation can be observed through negative attention bias, i.e. the tendency to direct attention to threats or negative emotions expressed by others (Bar-Haim et al., 2007; Masten et al., 2008; Pine et al., 2005; Romens and Pollak, 2012).

Until recently, attention bias in CSA-related PTSD has been pre-dominantly studied in observational studies, focusing for example on emotional reactivity, i.e. reaction time in

relation to viewing emotional faces. In these experiments, it was shown that emotional face processing is distinct in maltreated children, some of whom experienced CSA or depression, as compared to non-abused children and adolescents (e.g. Masten et al., 2008; Pine et al., 2005; Romens and Pollak, 2012). However, results were inconsistent: some studies reported attention bias away from threat, finding slower reaction times in the maltreated group (Pine et al., 2005), other studies reported attention bias towards threat, finding faster reaction times in the maltreated group (Masten et al., 2008). In addition to behavioral measurement of attention bias, fMRI allows study of neural mechanisms involved in the processing of emotional information. The question is whether CSA-related PTSD diagnosis compared to a diagnosis of depression or anxiety disorder is specifically associated with attentional bias and emotional face processing, as measured through emotional reactivity towards emotional faces and by identification of neural correlates. We therefore studied attentional bias and emotional face processing in adolescents with CSA- related PTSD and in adolescents with internalizing disorders and healthy control adolescents with functional MRI (fMRI), using a non-passive emotional faces task (Van den Bulk et al., 2013).

Emotional face processing fMRI studies in maltreatment-related PTSD in adolescents are relatively scarce (Cisler et al., 2013; Crozier et al., 2014; Fusar-Poli et al., 2009; Lenow et al., 2014). Some of the larger studies on adolescents with sexual assault have partially overlapping inclusion criteria with the CSA-related PTSD sample of this study (Cisler et al., 2015; Garrett et al., 2012; Wolf and Herringa, 2016). These studies showed hyper-activation of either amygdala, hippocampus, insula, dACC and/or PFC and/or hypo-activation of the dlPFC in the PTSD group compared to controls when viewing fearful or neutral faces. Assuming that traumatic stress influences the development of brain regions important for emotion processing, it is suggested (Garrett et al., 2012) that previous trauma or current PTSD symptoms prompted these brain regions to hyperactivate to trauma-related stimuli. An alternative explanation proposed was that adolescents with PTSD are hypersensitive to threat, even before having experienced trauma (Garrett et al., 2012).

In adolescents with depression and/or anxiety disorders, MRI studies on attentional bias and emotional face processing demonstrated attentional bias to threat and fearful faces, but not to neutral faces (e.g. Hall et al., 2014; Hommer et al., 2014; Krain Roy et al., 2008; Waters et al., 2014). Trait anxiety was positively associated with attention bias for angry faces (Telzer et al., 2008). The common denominator for emotional face processing in depression and/or anxiety disorders was hyperactivation of the amygdala in relation to fearful faces (Hall et al., 2014; Swartz et al., 2014a, 2014b), deactivation of the rACC (Hall et al., 2014; Price et al., 2014; Swartz et al., 2014a), insula (Hall et al., 2014; Henje Blom et al., 2015) and superior temporal gyrus (STG; Hall et al., 2014). In order to determine whether diagnostic group is associated with attentional bias and emotional face processing, we directly compare a CSA-related PTSD and an internalizing disorders group on the same fMRI task, simultaneously measuring dimensional psychiatric symptoms.

The aim of this study is to investigate neural correlates of emotional face processing in adolescents with CSA-related PTSD versus adolescents with internalizing disorders and healthy controls. We focused on symptoms of posttraumatic stress, dissociation and depression, given the overlap in symptomatology between both clinical groups. We expected discrepancies in attention bias and emotional face processing between the included groups based on differential degrees of emotional maltreatment or neglect and experienced threat, leading to differential reactions to threat, when measuring reactivity to emotional faces and identifying neural correlates. In line with the literature (Bar-Haim et al., 2007; Cisler et al., 2013, 2015; Crozier et al., 2014; Garrett et al., 2012; Lenow et al., 2014; Masten et al., 2008; Pine et al., 2005; Romens and Pollak, 2012; Wolf and Herringa, 2016) we had three hypotheses. Firstly, we hypothesized adolescents with CSA-related PTSD to have a negative attention bias, showing in slower reaction times in response to fearful and neutral faces compared to adolescents with internalizing disorders (only fearful faces) and healthy controls (Garrett et al., 2012). We based this hypothesis on the expectation that CSA-related PTSD lead to difficulty to disengage from threat (Cisler & Koster, 2010), as induced by fearful faces as well as neutral faces, which are interpreted as ambiguous and therefore threatening (Masten et al., 2008; Pine et al., 2005). Secondly, we hypothesized the adolescents with CSA-related PTSD to show more activation in the thalamus and limbic brain areas (like the amygdala, hippocampus, mid-cingulate, and insula) and less activation in the prefrontal brain areas (like the dlPFC) when interpreting emotional faces compared to adolescents with internalizing disorders (less activation in the ACC and (para)hippocampal regions; Price et al., 2014; Swartz et al., 2014a) and healthy controls (Garrett et al., 2012; Hall et al., 2014). Thirdly, we hypothesized that severity of self-reported posttraumatic stress and dissociation symptoms in adolescents with CSA-related PTSD or internalizing disorders would correlate with increased activation of amygdala and decreased activation of dlPFC (Brown and Morey, 2012; Garrett et al., 2012; Hall et al., 2014; Hart and Rubia, 2012; McClure et al., 2007; Patel et al., 2012; Shin and Liberzon, 2010).

METHODS

Participants

From the original sample of 83 participants, 12 participants (CSA N=3, DEP N=4, CNTR N=5) were excluded from the analyses due to: technical problems during scanning (DEP N=3, CNTR N=1), excessive head movement (> 3 mm, CSA N=3, CNTR N=2), unforeseen clinical features (CNTR N=1) or anomalous findings reported by the radiologist (DEP N=1, CNTR N=1). This resulted in a final sample of 19 CSA adolescents (all had CSA-related PTSD), 26 adolescents with internalizing disorders (DEP) and 26 healthy controls (CNTR) from the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents) (Van den Bulk et al., 2013). Attachment and clinical characteristics of the three groups were

reported separately (Van Hoof et al., 2015).

All participants met the following inclusion criteria: aged 12–20 years, estimated full scale IQ ≥80 as measured by Dutch versions of the Wechsler Intelligence Scales for Children (WISC-III-NL; 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 contra-indications for MRI testing (e.g. braces, metal implants, lead tattoos, irremovable piercings, claustrophobia or possible pregnancy). The CSA group was recruited in two psychotrauma centers of child and adolescent psychiatric institutes, using the third National Incidence Study (NIS-3) operationalized definitions of CSA Specific Form of Maltreatment (NIS-3 code; Sedlak, 2001; see Appendix A in Stoltenborgh et al. (2011)). In order to be sure to get a homogeneous group of participants with substantial experiences and to avoid the discussion about whether sexual assault should be considered childhood sexual abuse, an additional inclusion criterion for the CSA group was having experienced sexual abuse during their lifetime more than once by one or more perpetrators in- or outside the family. Additional inclusion criteria for the internalizing disorders group were: being referred for outpatient treatment, a clinical diagnosis of DSM-IV depressive and/or anxiety disorders and no history of CSA. Exclusion criteria for both clinical groups 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. The healthy control adolescents were recruited through local advertisement, with the following additional inclusion criteria: no clinical scores, meaning scores below cut-off points for clinical presentation of symptoms, on validated mood and behavioral questionnaires or past or current Anxiety Disorders Interview Schedule (ADIS C/P) DSM-IV classification, no history of traumatic experiences on ADIS C/P and Adult Attachment Interview and no current psychotherapeutic intervention of any kind.

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.

Clinical assessment

In addition to standard child psychiatric assessment by a child and adolescent psychiatrist, the child and parent versions of the ADIS-C/P (Lyneham, Abbott, & Rapee, 2007; Silverman et al., 2001) were used to obtain a DSM-IV-based classification of anxiety and depressive disorders including PTSD, which determined diagnostic group. The participants with a secondary classification of non-CSA-related PTSD on the ADIS besides a primary diagnosis of an internalizing disorder, were included in the internalizing disorders group.

Estimated full scale IQ was acquired with six subtests of the WISC-III-NL (Wechsler, 1991) and the WAIS-III (Wechsler, 1997). After inclusion, three self-reports were used to assess the severity of posttraumatic stress, dissociation and depression; i.e. the Trauma Symptoms Checklist for Children (TSCC; Briere, 1996), the Adolescent Dissociative Experiences Scale (A-DES; Armstrong et al., 1997; Smith and Carlson, 1996) and the Children's Depression Inventory (CDI; Kovačs, 1992; Timbremont et al., 2004). Total scores of the TSCC and CDI and a $\log^{10}$ transformation of the total score of the A-DES, performed to lift the positive skew, were subsequently used in the analyses.

Sample characteristics

See Table 1.

Task paradigm

All adolescents performed an adapted version of the face processing task originally developed by McClure et al. (2007) and Monk et al. (2003, 2006) and has been described in detail previously (Van den Bulk et al., 2013, 2014). In short, the task consisted of three constrained state conditions (state questions: 'how afraid are you?', 'how happy are you?' and 'how wide is the nose?') and one unconstrained (passive viewing) state condition. After state presentation, participants viewed 21 emotional faces (7 fearful, 7 neutral and 7 happy facial expressions) per attention state, which they had to rate on a four-point rating scale referring to the presented state (1. not at all, 2. a little, 3. quite and 4. very). During the task, reaction times and subjective scoring of the different emotional faces (fearful, happy or neutral) were recorded for behavioral analyses.

All trials had the same structure: first participants were presented with one of the state questions for 4000 milliseconds which was followed by a centrally located fixation cross with a jittered interval between 500 and 6000 milliseconds. Thereafter, one of the pictures was shown for 3000 milliseconds again followed by a centrally located fixation cross (Fig. 1). When the participant did not respond within 3000 milliseconds the task proceeded to the next trial. The trials during which participants did not respond were recorded as missing trials (1,88% of all trials across all participants), and were not included in the behavioral and fMRI analyses. There were 21 trials per condition (one of the state questions×one of the emotions) and 252 trials in total. We used a mixed design in which trials were event related within blocks (state questions). We are aware of the ongoing debate whether "neutral" faces exist, or whether the term "ambiguous" faces should be used (e.g. Tahmasebi et al., 2012), but for consistency with our previous paper we use the term 'neutral' faces.

Table 1
Sample characteristics and psychiatric symptom scores.

Sample characteristics	CSA (n=19)		DEP (n=26)		CNTR (n=26)		χ^2	*df*	*p*	
Females/Males	17/2		22/4		23/3		0.28	2	0.01	
Number of stable SSRI use	2		1		–					
Number meeting PTSD criteria	19[a]		–		–					
	Mean	SD	Mean	SD	Mean	SD	η^2	$F_{(2,70)}$	*p*	Significant group differences
Age in years	16.62	1.78	15.98	1.45	15.25	1.64	0.11	4.03	0.02	CSA > DEP > CNTR
Full scale IQ	99.89	9.10	105.12	8.66	106.58	7.77	0.10	3.60	0.03	CSA < DEP < CNTR
Psychiatric symptom scores	Mean[b]	SD	Mean[c]	SD	Mean	SD	η^2	$F_{(2,68)}$	*p*	Significant group differences
TSCC score	45.74	22.92	41.90	22.85	16.26	12.50	0.31	13.23	0.00	CSA, DEP > CNTR*
A-DES score	1.65	0.42	1.46	0.44	1.20	0.46	0.18	6.37	0.03	CSA*, DEP** > CNTR
CDI score	15.15	6.89	17.75	8.89	4.17	3.36	0.49	27.85	0.00	CSA, DEP > CNTR*

Abbreviations used: Childhood Sexual Abuse (CSA), Clinical Depression (DEP), Healthy controls (CNTR), Trauma Symptom Checklist (TSCC), Adolescent Dissociative Experiences Scale (A-DES), Child Depression Inventory (CDI), Intelligence Quotient (IQ), Selective Serotonine Reuptake Inhibitor (SSRI), Standard Deviation (SD), η^2=effect size; Post-traumatic Stress Disorder (PTSD), MANOVA analyses used both demeaned age in years and demeaned IQ.

[a] According to ADIS 18 met full PTSD criteria and one failed the interference criterium only slightly.

[b] n=18.

[c] n=24.

* Significant at $p < 0.05$.

** Significant at $p < 0.01$.

Fig. 1. Overview of task design. Participants were presented with an attention condition, followed by a centrally located fixation cross. Thereafter, they saw one of the emotional faces, again followed by a centrally located fixation cross, after which another emotional face was shown. Participants had to rate each emotional face on a four-point rating scale ranging from "not at all" to "very," based on the presented attention condition (5).

fMRI data acquisition

Data were acquired using a 3.0 T Philips Achieva (Philips, Best, The Netherlands) scanner at the Leiden University Medical Centre. Stimuli were presented onto a screen located at the head of the scanner bore and viewed by participants by means of a mirror mounted to the head coil assembly. First, a localizer was obtained for each participant. Subsequently, T2*-weighted Echo-Planar Images (EPI) (TR=2200 ms, TE=30 ms, flip angle=80°, 80×80 matrix, FOV=220, 38 slices of thickness 2.72 mm) were obtained during three functional runs of 192 volumes each. Each run had two additional volumes, which were discarded to allow for equilibration of T1 saturation effects. Also, a sagittal 3-dimensional gradient-echo T1-weighted image was acquired for registration purposes with the following scan parameters: TR=9.8 ms; TE=4.6 ms; flip angle 8°; 140 sagittal slices; no slice gap; FOV=192×152 matrix; FOV=224×177×168 mm, 140 sagittal slices; no slice gap; 1.16×1.16×1.20 mm voxels.

We used a mock-scanner to familiarize all participants with the MRI scanner. Participants were placed in the mock-scanner and they received information about the scanning procedure. In addition, we presented the scanner sounds on a laptop so that participants knew what to expect while in the MRI scanner.

Imaging data analysis

We used SPM8 (Wellcome Department of Cognitive Neurology, London) to analyze the acquired data. Data was preprocessed using the following steps: 1. realignment of functional time series to compensate for small head movements and differences in slice timing acquisition, 2. registration and normalization of functional volumes (from EPI to individual structural T1 and thereafter to the T1 template), 3. spatially smoothing the functional volumes with an 8 mm, full-width at half- maximum isotropic Gaussian kernel. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions and resampled the volumes to three mm cubic voxels. The MNI (Montreal Neurological Institute) 305 stereotaxic space

templates (Cocosco, Kollokian, Kwan, & Evans, 1997) were used for visualization and all results are reported in this template, which is an approximation of Talairach space (Talairach and Tournoux, 1988).

Individual subjects' data were analyzed using the general linear model in SPM8. The fMRI time series were modeled by a series of events convolved with a canonical hemodynamic response function (HRF). The state questions were modeled separately as 4000 millisecond events and were added as covariates of no interest. The picture presentation of each emotional face was modeled as a 3000 millisecond duration event. In the model, the picture presentation was further divided in twelve separate function trials (four state questions by three expressed emotions). The modeled events were used as regressors in a general linear model along with a basis set of cosine functions that high- pass filtered the data. The least squares parameter estimates of the height of the best-fitting canonical HRF for each condition were used in pair wise contrasts (e.g. all faces vs. fixation). The resulting contrast images, computed on a subject-by-subject basis, were submitted to group analyses. At the group level, contrasts between conditions were computed by performing full factorial models on these images, treating subjects as a random effect. Task-related responses were considered significant if they consisted of at least 10 contiguous voxels at a corrected threshold of $p < 0.05$ (FDR corrected).

We used the MarsBaR toolbox for use with SPM8 (http://marsbar.sourceforge.net/; 44) to perform region of interest (ROI) analyses to further investigate patterns of activation. Based on the current literature about CSA, PTSD, major depression and anxiety disorders we used a priori and anatomically defined ROIs: (all left and right) dorsolateral PFC (DLPFC), amygdala, insula, thalamus, mid cingulum, hippocampus. The templates for the anatomically defined ROIs were derived from the MarsBaR toolbox (AAL-templates).

Data analyses

For the behavioral and fMRI analyses we used the same analysis frame work presented before (Van den Bulk et al., 2013, 2014). We compared groups regarding total scores on the TSCC, A-DES and CDI using MANCOVA (with simple bootstrapping). To analyze the effects of emotional faces on subjective scoring, we performed separate repeated measure ANCOVA's for each state question (three in total). We used a group (3 levels)×emotion (3 levels) design per state question. The three state questions were analyzed separately because values of the scores represent different interpretations for each state. For reaction time, a 3 (groups)×3 (state questions)×3 (emotions) repeated measure ANCOVA was performed. Because of the significant differences in age and IQ, we included demeaned age and IQ as covariates in all analyses. For all analyses, Greenhouse-Geisser correction (GG-corr.) was applied in case sphericity was not assumed and we used Bonferroni correction for post-hoc comparisons. Behavioral data were checked for outliers (by using boxplots and z-scores), but no consistent outliers were detected (z-score > 3.29).

The results of the ROI analyses were submitted to repeated measure ANCOVA's in SPSS. For each set of regions, we used a 3 (group)×2 (hemisphere)×4 (state question)×3 (emotion) repeated measure ANCOVA. We included hemisphere as a factor in the repeated measure ANCOVA's to limit the number of statistical analyses. We included demeaned age and estimated IQ level as covariates. Again, Greenhouse-Geisser correction (GG-corr.) was applied in case sphericity was not assumed and post hoc comparisons within a repeated measure ANCOVA were Bonferroni corrected for multiple comparisons. ROI data were also checked for outliers, but no consistent outliers were detected.

RESULTS

Behavioral data

- *Co-morbidity*

Of the participants with CSA-related PTSD in this sample 11/19 (57.1%) had a comorbid anxiety disorder, 7/19 (38.1%) had a comorbid depressive disorder and 7/19 (38.1%) had both comorbid anxiety and depressive disorders according to the ADIS. Of the participants in the internalizing disorders group in this sample, 8/26 (30.8%) individuals had PTSD comorbidity according to the ADIS. In the internalizing disorders group 5/26 (20%) had only anxiety disorder, 1/26 (4%) individuals only had a depressive disorder and 13/26 (50%) individuals had a combination of anxiety and depressive disorders.

- *Self-reported symptomatology*

A significant effect for clinical group (partial η^2=0.28, $F_{(6, 116)}$=7.33, $p < 0.001$) was found for trauma (TSCC) ($F_{(2,68)}$=13.23, $p < 0.001$, partial η^2=0.31), dissociation (A-DES) ($F_{(2,68)}$=6.37, p=0.03, partial η^2=0.18), and depression scores (CDI) ($F_{(2,68)}$=27.85, $p < 0.001$, partial η^2=0.49). Post-hoc comparisons showed significant higher levels of self-reported symptomatology in the CSA and DEP groups than in the CNTR group (TSCC and CDI both at $p < 0.001$; A-DES CNTR-DEP group at p=0.04 and CNTR-CSA group at p=0.004), but demonstrated no significant differences in self-reported symptomatology between both clinical groups (see Table 1).

- *Subjective rating of emotional faces*

The ANCOVA for the state induced by the question 'how wide is the nose?' resulted in a main effect of emotion ($F_{(2,132)}$=393.54, $p < 0.001$, partial η^2=0.86), in which subjective scoring for nose width was higher for happy faces compared to both fearful and neutral faces (both *p's* < 0.001). Also, scores were higher for fearful faces than for neutral faces (p< 0.001). There were no significant main or interaction effects with group.

The ANCOVA for the state induced by the question 'how afraid are you?' showed a main effect for group ($F_{(2,66)}$=5.29, $p < 0.01$, partial η^2=0.14), a main effect for emotion

($F_{(2,132)}$=57.72, p <0.001, partial η^2=0.47, GG-corrected), and a group × emotion interaction ($F_{(4,132)}$=3.88, p < 0.01, partial η^2=0.11, GG-corrected). Overall, CSA and DEP adolescents reported being more afraid of fearful faces than CNTR adolescents (p < 0.01 and p < 0.05 respectively). In addition, CSA adolescents reported being more afraid of neutral faces compared to CNTR adolescents (p < 0.05), and the DEP group (margin- ally significant, p=0.06). There were no significant group differences for happy faces (all p's > 0.42).

The ANCOVA for the state induced by the question 'how happy are you?' resulted in a main effect of group ($F_{(2,66)}$=4.72, p < 0.05, partial η^2=0.13), a main effect of emotion ($F_{(2,132)}$=121.89, p < 0.001, partial η^2=0.65, GG-corrected) and an emotion×group interaction effect ($F_{(4,132)}$=2.82, p < 0.05, GG-corrected, partial η^2=0.08). Overall, CSA and DEP adolescents reported being less happy when viewing fearful faces than healthy control group adolescents (p < 0.05 and p < 0.005 respectively).

- *Reaction times*

The ANCOVA resulted in a main effect for group ($F_{(2,66)}$=4.75, p < 0.05, partial η^2=0.13), a main effect of emotion ($F_{(2,132)}$=5.47, p < 0.01, partial η^2=0.08) and an interaction effect of state×emotion ($F_{(4,264)}$=10.17, p < 0.001, partial η^2=0.13). Reaction times were higher for the CSA group than for the DEP group (p < 0.01), but not for the CNTR group (p <

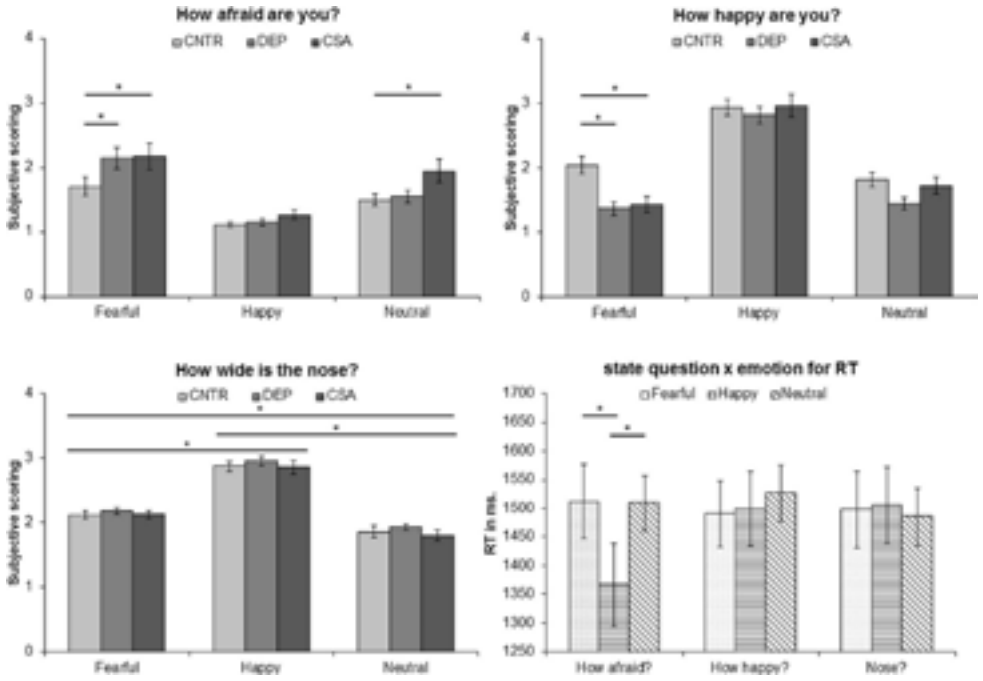

Fig. 2. Subjective scoring of emotional faces within the state 'how wide is the nose?' (A.), 'how afraid are you?' (B.) and 'how happy are you?' (C.) and mean reaction times in milliseconds per group (D.) *p < 0.05.

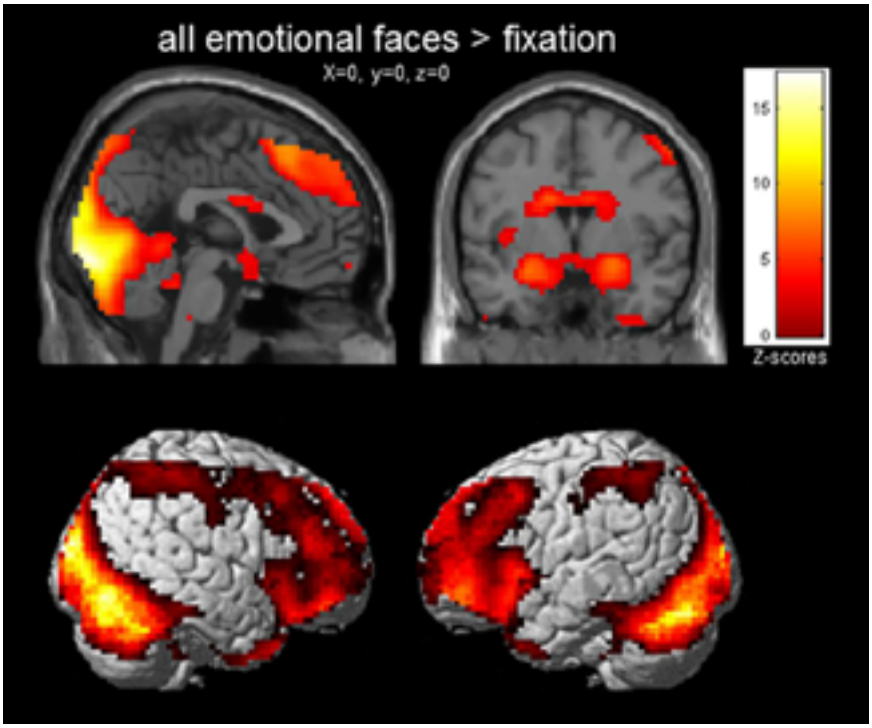

Fig. 3. Whole brain contrast showing task effects for the contrast all faces > fixation. The contrast was derived from a full factorial model with one factor for group (3 levels; total N=71) and demeaned age and estimated total IQ as covariates. Thresholding: FDR corrected, $p < 0.05$ with at least 10 contiguous voxels

0.20). Also there was no significant difference between the DEP and CNTR group ($p < 0.50$). Overall, participants reacted slower to fearful and neutral faces than to happy faces (both *p's* < 0.05). There was no significant difference between fearful and neutral faces ($p < 0.50$) Furthermore, reaction times within the state 'how afraid are you?', were higher for fearful and neutral faces than for happy faces (both *p's* < 0.001), while there was no difference between fearful and neutral faces ($p < 0.50$) (Fig. 2).

Whole brain analyses

To examine whether the task activated the expected brain regions, we performed whole brain analyses for the complete sample (N=71). As can be seen in Fig. 3, the analyses of all faces > fixation resulted in robust activation in brain regions related to emotional faces processing, including the bilateral amygdala, bilateral insula, bilateral thalamus and bilateral PFC. The whole brain contrasts for each emotion (fearful faces > fixation, happy faces > fixation, neutral faces > fixation) and the contrasts to test the differential effects of emotion processing (fearful face > neutral faces, happy faces > neutral faces, fearful faces

> happy faces and happy faces > fearful faces) across all participants are presented in Supplemental Table 1 and Supplemental Figure 1.

Because we were primarily interested in group differences, we performed direct comparisons between the three groups on whole brain level for all previously mentioned contrasts with the use of full factorial model ANOVA's. These analyses did not result in significant differential activation between the three groups.

Region of Interest analyses

We performed 3 (groups)×2 (hemispheres)×4 (state question)×3 (emotion) repeated measure analyses for each set of ROIs (DLPFC, amygdala, insula, thalamus, mid cingulum and hippocampus).

The results showed a significant hemisphere×state×emotion×group interaction effect for the hippocampus ($F_{(12,396)}$=2.11, $p < 0.05$, partial η^2=0.06). Post hoc comparisons showed more right hippocampus activation compared to left hippocampus activation in the CSA group (fearful faces within 'how happy are you?' and fearful, happy and neutral faces 'how wide is the nose?', all p's <0.05) and the internalizing disorders group (happy faces within 'how afraid are you?' and neutral faces within 'how wide is the nose?', both p's < 0.05). Also, for the healthy controls there was more left hippocampus activation for fearful compared to neutral faces within the state question 'how happy are you?' ($p < 0.05$). Finally, for the adolescents with internalizing disorders there was more left hippocampus activation for happy compared to neutral faces within the state question 'how wide is the nose?' (p=0.005).

For mid cingulate cortex, there was a significant hemisphere×state×group interaction ($F_{(6,198)}$=2.27, $p < 0.05$, partial η^2=0.06). Post- hoc comparisons showed more deactivation in left mid cingulate compared to right mid cingulate for the healthy controls ('how afraid are you?' $p < 0.05$; 'how wide is the nose?' $p < 0.005$), the adolescents with CSA-related PTSD ('how afraid are you?' $p < 0.01$; 'how wide is the nose?' $p < 0.01$) and the adolescents with internalizing disorders ('how wide is the nose?' $p < 0.05$). In addition, there was more right than left deactivation of the mid cingulate for passive viewing within the CSA group. Other regions showed no significant main or interaction effects for group. There were, however, some main and interaction effects for hemisphere, state and emotion (see Appendix).

When excluding the participants with stable SSRI use (N=1 DEP, N=2 CSA), the results of the ROI analyses were comparable and no additional significant main or interaction effects for group were found.

Correlation analyses

To examine whether there is a relation between brain activation and self-report measurements, we performed correlation analyses for the complete sample of *N*=71 and for all three groups separately in SPSS using demeaned age and IQ as covariates. We included the ROI results for bilateral amygdala and bilateral DLPFC activation and self-reported total scores on the TSCC, A-DES and CDI. There were no significant correlations between any of these variables.

DISCUSSION

In this article we examined the neural mechanisms of emotional face processing in adolescents with CSA-related PTSD versus internalizing disorders and healthy controls. In accordance with our first hypothesis, the CSA-related PTSD group reacted slower to all emotional faces across all questions than the internalizing disorders group. There was no significant difference in reaction time between the two clinical groups and the healthy controls. Also, all participants reacted slower to fearful and neutral faces compared to happy faces within the state question 'How afraid are you?'. Besides, both clinical groups reported higher levels of subjective fear in response to fearful faces than healthy controls and the CSA-related PTSD group reported higher levels of subjective fear to neutral faces than the internalizing disorders group and the healthy controls. Within the state question 'How happy are you?' the CSA-related PTSD group and the internalizing disorders group reported being less happy when viewing fearful faces than the healthy controls. Contrary to our second and third hypotheses, no significant differences between groups were found on whole brain and on ROI level, and no correlations between levels of self-reported posttraumatic stress, dissociation and depression and brain activation.

In line with our first hypothesis we found a negative attention bias in the CSA-related PTSD group: reaction times to emotional faces were slower compared to the internalizing disorders group and the healthy control group. Further, adolescents with CSA-related PTSD experienced higher subjective fear to fearful and neutral faces than healthy controls, while adolescents with internalizing disorders only had higher subjective fear scores compared to healthy controls when viewing fearful faces. These findings suggest that adolescents with CSA-related PTSD are more reactive to neutral emotional faces than adolescents with internalizing disorders and more reactive to fearful and neutral faces compared to healthy controls. However, in line with the literature and the definition we used (Cisler and Koster, 2010; Pine et al., 2005), we interpret this finding as a negative attention bias, due to a need from previous adverse experiences to carefully examine a possible threat even in neutral stimuli. As neutral faces are ambiguous, this may heighten their threat level. Attention bias to the threat will require more time to react and elicit higher subjective fear doing so,

as was the case in the CSA-related PTSD group and partly in the internalizing disorders group (for fearful faces only). We assume attention bias is the result of a combination of automatic and strategic emotional face processing in this case, involving heightened threat detection and difficulty to disengage (Cisler and Koster, 2010). Our finding of negative attention bias is consistent with studies in maltreated children and adolescents using a non-morphed emotional faces task like we did, which showed that maltreated youth process threat-related information more slowly than controls (Pine et al., 2005). Other studies (e.g. Masten et al., 2008; Romens and Pollak, 2012) used a heterogeneous sample that may use different attention bias components and strategies, a different paradigm (e.g. visual probe, visual discrimination and identification, or morphed facial emotion identification task), or a different presentation of emotional cues and questions posed, which all may account for inconsistency in attention bias between studies.

Contrary to our second hypothesis, whole-brain analyses nor ROIs revealed group differences. The interaction effects did not survive correction for multiple comparisons. Therefore, we refrain from interpreting these interaction effects as whole-brain or ROI group differences. Nevertheless, the paradigm used in this study has been shown to be valid and functional in measuring emotional face processing in youth (Van den Bulk et al., 2013, 2014; Masten et al., 2008). Though the task was shown to activate adequately, no significant differential amygdala activation was found between groups, contrary to previous findings in passively viewing fear and disgust (Nooner et al., 2013).

Contrary to our third hypothesis and the study by Garrett et al. (2012), no significant relation was found between levels of self-reported posttraumatic stress, dissociation or depression symptoms and ROI activation. Garrett's lab found a significant positive correlation between the severity of PTSD symptoms as measured by the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA; Nader et al., 1996) and activation of the mPFC when viewing fearful faces. Although TSCC (Nooner et al., 2013) and CDI (Pagliaccio et al., 2013) have been associated with brain activation in other studies, these self-reports cannot easily be compared to the CAPS-CA interview (Anderson, Bush, & Berry, 1986; Nader et al., 1996). The absence of significant relations between self-reported symptomatology and brain activation might furthermore be explained by the fact that the CSA-related PTSD and internalizing disorders groups appeared to not significantly differ in dimensionally assessed psychiatric symptomatology after they were included based on conventional inclusion criteria for diagnostic group. However, the clinical groups did differ significantly from the healthy control group. It is therefore surprising that no differences between diagnostic groups were found on whole brain or ROI level.

Several factors may explain the absence of group differences on the neural level in the current study. First, group sizes were rather small, given the heterogeneous nature of the conditions under investigation. Power was further decreased because we had to control for two covariates (age and IQ). Second, the CSA-related PTSD group was not

compared to a non-CSA-related PTSD group but to an internalizing disorders group, which partly appeared to have PTSD for other reasons than CSA. This group was too small to split. Given the overlap in clinical symptoms, this may have impacted the results. Third, the task may not be sensitive enough to detect group differences on the neural level. The original face attention paradigm developed by Monk, McClure and colleagues (McClure et al., 2007; Monk et al., 2003) was used in children with generalized anxiety disorder and controls. The adapted version of the task we used differed from the original paradigm. Anger as emotion was not displayed and therefore the question 'how hostile is the face?' was left out. This changes the perspective taken by the participant compared to the original task and may account for differences in the possibility to detect group differences of neural correlates. Also, the adaptations made to the original task might have prevented us from finding activation differences between the internal emotion focused state questions (e.g. 'how afraid are you?') and the external focused state question ('how wide is the nose?'). Fourth, the task was not tailored to content specificity of the clinical groups. As a recent meta-analysis suggests, greater attention bias toward disorder-congruent relative to disorder-incongruent threat stimuli might make a difference (Pergamin-Hight et al., 2015). Fifth, attention bias variability, i.e. attention fluctuations alternating toward and away from threat, rather than attention bias might have revealed group differences, as recently suggested by Naim et al. (2015). An alternative, but more unlikely explanation may be that internalizing disorders and CSA-related PTSD in adolescents do not substantially differ on the neural level, and that with regard to psychiatric symptomatology they have more in common than usually has been hypothesized (Van Hoof et al., 2015).

CONCLUSIONS

This is the first study that compared CSA-related PTSD adolescents with both adolescents with internalizing disorders and healthy controls, extensively measuring behavioral and neural correlates of emotional face processing at the same time. Our results support the hypothesis of increased negative attention bias towards fearful and neutral faces in adolescents with CSA-related PTSD versus internalizing disorders and healthy controls. It is however remarkable that no neural differences were found between all three groups. Clinical applications of knowledge about attention bias and emotional face processing are interesting future options for diagnostics and treatment of adolescents with CSA-related PTSD or internalizing disorders, e.g. Attention Bias Modification Treatment (Hakamata et al., 2010) or attention control training (Badura-Brack et al., 2015). It may well be that the slower reaction time to fearful and neutral emotional faces in adolescents with CSA- related PTSD interferes with their daily social functioning and prevents them from seeking and accepting help. In that case other strategies are needed first to engage them coming into psychotherapy.

FINANCIAL DISCLOSURES

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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APPENDIX A. SUPPORTING INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.04. 006.

SUPPLEMENTAL MATERIAL

Appendix

In addition to the hemisphere x state x emotion x group interaction described in the main text, the ROI analyses for DLPFC resulted in a main effect of state ($F_{(3,186)}$=6.26, p<.001, partial η^2=.09) and a state x hemisphere interaction effect ($F_{(3,186)}$=25.29, p<.001, partial η^2=.29). Post-hoc comparisons showed more left DLPFC activation for passive viewing (p<.001) and more right DLPFC activation for the state question 'how wide is the nose?' (p<.001). Furthermore, within left DLPFC there was more activation for the state questions 'how happy are you?' (p=.001) and 'how wide is the nose?' (p<.001) compared to passive viewing. Also, there was more left DLPFC activation for 'how wide is the nose?' compared to 'how afraid are you?'.

For amygdala the results showed a main effect of emotion ($F_{(2,132)}$=6.57, p<.005, partial η^2=.09), in which there was more amygdala activation in response to fearful faces compared to neutral faces (both p's<.01).

For insula the results showed a main effect of hemisphere ($F_{(1,66)}$=10.01, p<.005, partial η^2=.13), a hemisphere x emotion interaction effect ($F_{(2,144)}$=3.21, p<.05, partial η^2=.05) and a hemisphere x state x emotion interaction effect (($F_{(6,396)}$=3.34, p<.005, partial η^2=.05). There was more deactivation of right insula compared to the left insula when processing: (1) fearful faces within the state question 'how afraid are you?' (p<.05), (2) happy faces within the state question 'how happy are you?' (p<.001) and fearful and happy faces during passive viewing (p<.05 and p<.001 respectively).

The ANOVA for mid cingulate cortex resulted in a main effect of hemisphere ($F_{(2,66)}$=13.90, p<.001, partial η^2=.17) and a hemisphere x state interaction effect ($F_{(3,198)}$=11.34, p<.001, partial η^2=.15). Overall, there was more deactivation for left mid cingulum for the state questions 'how afraid are you?' (p<.001), 'how happy are you?' (p<.05) and 'how wide is the nose?' (p<.001). There was no significant hemisphere difference for passive viewing (p>.15).

Finally, the analysis for thalamus resulted in a main effect of state ($F_{(3,198)}$=5.13, p<.005, partial η^2=.07), a hemisphere x emotion interaction effect ($F_{(2,132)}$=4.00, p<.05, partial η^2=.06) and a hemisphere x state x emotion interaction effect ($F_{(6,396)}$=2.60 p<.05, partial η^2=.04). Posthoc comparisons showed more thalamus activation for fearful (left p<.01; right p<.05), happy (left p<.05) and neutral (left p<.005; right p=.005) face processing during the state question 'how happy are your?' compared to passive viewing. In addition, there was more right thalamus activation during the processing of neutral faces within the state question 'how wide is the nose?' compared to passive viewing (p<.05).

Supplemental Table 1. Whole brain activation patterns for the contrasts (N=71): A. all faces > fixation, B. fearful faces > fixation, C. happy faces > fixation, D. neutral faces > fixation, E. fearful faces > neutral faces, F. happy faces > neutral faces, G. fearful faces > happy faces and H. happy faces > fearful faces. Regions represent significant peaks of activation at $p<0.05$, FDR-corrected, at least 10 contiguous voxels and coordinates are listed in MNI space. * = $p<0.05$ when corrected for multiple comparisons at cluster-level (FWE).

Contrast	Region	Side	z-score	K_E	x	y	z	
A.								
All faces > Fixation	Cuneus	R	Inf.	16733	18	-97	13	*
	Middle occipital gyrus	R	Inf.		39	-72	-14	
	Lingual gyrus	R	Inf.		-3	-82	-5	
B.								
Fearful faces > Fixation	Cuneus	R	Inf.	7969	18	-97	13	*
	Middle occipital gyrus	R	Inf.		39	-76	-14	
	Middle occipital gyrus	R	Inf.		45	-82	-5	
	Middle frontal gyrus	L	Inf.	8735	-48	47	-11	*
	Inferior frontal gyrus	L	7.81		-51	50	7	
	Inferior frontal gyrus	L	7.09		-57	17	4	
C.								
Happy faces > Fixation	Cuneus	R	Inf	16798	18	-97	13	*
	Lingual gyrus	R	Inf		0	-91	-11	
	Fusiform gyrus	R	Inf		36	-76	-20	
D.								
Neutral faces > Fixation	Cuneau	R	Inf	7392	18	-97	13	*
	Middle occipital gyrus	R	Inf		39	-76	-14	
	Middle occipital gyrus	R	Inf		45	-79	-8	
	Middle frontal gyrus	L	Inf	7265	-51	47	-5	*
	Inferior frontal gyrus	L	Inf		-48	53	4	
	Middle frontal gyrus	L	6.78		-39	62	10	
E.								
Fearful faces > Neutral faces	Middle occipital gyrus	R	Inf.	6401	27	-91	13	*
	Middle occipital gyrus	L	Inf.		-30	-88	4	
	Cuneus	R	7.70		12	-94	22	
	Inferior frontal gyrus	R	4.42	444	60	20	4	*
	Superior frontal gyrus	R	4.35		57	20	-17	

	Uncus	R	4.00	64	30	-1	-26	
	Inferior frontal gyrus	L	3.84	643	-51	20	7	*
	Middle frontal gyrus	L	3.04	24	-36	50	-8	
	Middle frontal gyrus	L	3.02	13	-36	41	19	
	Supramarginal gyrus	L	2.71	11	-57	-46	34	
F.								
Happy faces > Neutral faces	Middle occipital gyrus	R	Inf.	6255	21	-94	13	*
	Cuneus	L	Inf.		-15	-94	4	
	Culmen	R	5.65		24	-52	-20	
	Thalamus	L	2.94		-21	-19	10	
	Lentiform nucleus	L	3.52	56	-21	17	-5	
	Subcallosal gyrus	L	3.02		-15	11	-17	
	Middle temporal gyrus	L	3.30	101	-42	5	-38	
	Medial frontal gyrus	L	2.87		-6	53	13	
	Superior frontal gyrus	R	2.86		3	56	28	
	Parahippocampal gyrus	R	3.41	25	30	-10	-26	
	Precuneus	R	3.40	43	24	-61	34	
	Superior parietal lobule	R	2.92		24	-73	46	
	Subcallosal gyrus	R	3.23	21	6	14	-17	
	Superior temporal gyrus	L	2.94	12	-42	8	-20	
G.								
Fearful faces > Happy faces	Middle occipital gyrus	L	4.48	146	-39	-88	1	*
	Lingual gyrus	R	4.38	251	27	-73	-14	*
	Middle occipital gyrus	R	3.91		36	-88	1	
	Inferior frontal gyrus	L	4.26	19	-48	20	22	
	Superior temporal gyrus	R	4.12	56	66	-46	16	

	Middle frontal gyrus	R	4.03	145	57	32	19	*
	Inferior frontal gyrus	R	4.01		54	26	4	
	Inferior frontal gyrus	R	4.00		54	23	13	
	Superior frontal gyrus	R	3.93	31	45	-52	10	
	Inferior frontal gyrus	L	3.76	26	-48	32	-2	
	Middle temporal gyrus	R	3.67	24	51	-16	-8	
	Superior temporal gyrus	R	3.60		48	-28	-5	
H.								
Happy faces > Fearful faces	Medial frontal gyrus	R	5.15	351	6	53	-5	*
	Anterior cingulate gyrus	L	4.18		-15	50	1	
	Culmen	R	4.57	62	18	-52	-23	
	Postcentral gyrus	L	4.34	255	-39	-43	64	*
	Postcentral gyrus	L	4.07		-51	-25	49	
	Inferior parietal lobule	L	3.97		-39	-34	43	
	Caudate	L	4.04		-12	17	13	
	Postcentral gyrus	L	4.01	35	-60	-16	13	
	Middle frontal gyrus	L	3.78	19	-27	-13	58	
	Middle frontal gyrus	L	3.40		-24	-10	49	
	Superior parietal lobule	R	3.42	13	18	-64	64	
	Superior parietal lobule	R	3.28		18	-70	58	

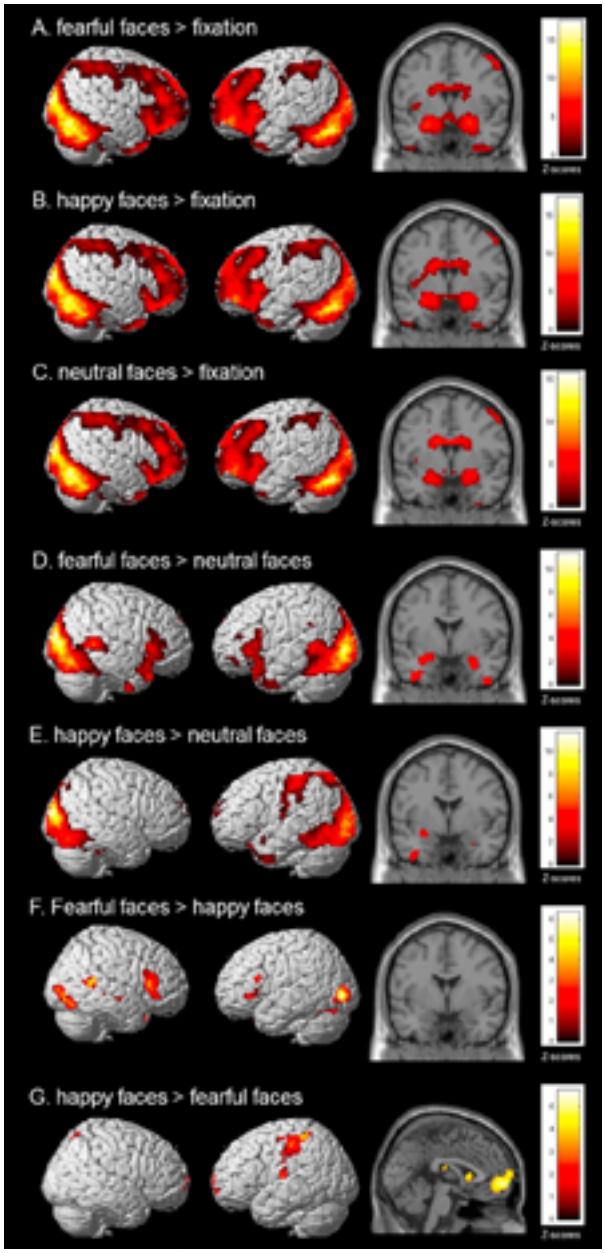

Fig. S1. **Whole brain contrast showing task effects for the contrasts A. all faces>fixation, B. fearful faces>fixation, C. happy faces>fixation, D. neutral faces>fixation, E. fearful faces>neutral faces, F. happy faces>neutral faces, G. fearful faces>happy faces and H. happy faces>fearful faces.** The contrasts were derived from full factorial models with one factor for group (3 levels; total N=71) and demeaned age and estimated total IQ as covariates. Thresholding: FDR corrected, $p<0.05$ with at least 10 contiguous voxels.

SECTION II:

ATTACHMENT, PSYCHOPATHOLOGY AND NEUROIMAGING

Safety and security don't just happen,
they are the result of collective consensus and public investment.
We owe our children, the most vulnerable citizens in our society,
a life free of violence and fear

Madiba - Nelson Rohlilahla Mandela
(1918, Mvezo – 2013, Johannesburg)

4

Unresolved-disorganized attachment associated with smaller hippocampus and increased functional connectivity beyond psychopathology

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ABSTRACT

Loss and abuse in children can lead to unresolved-disorganized attachment (Ud). How this condition relates to brain structure and functional connectivity (FC) is not known. We therefore aimed to investigate gray matter volume (GMV) and resting state functional connectivity (RSFC) correlates of Ud in adolescents. Based on previous neuroimaging studies of trauma effects, we hypothesized that structure of the amygdala and hippocampus and FC of the latter would be linked to Ud. Anatomical and RSFC data were collected from a mixed group of adolescents (*N* =74) with symptoms of posttraumatic stress disorder related to childhood sexual abuse (CSA-related PTSD), anxiety/depressive symptoms and without psychiatric disorder as part of the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA). Bilateral volumes of amygdala and hippocampus were measured using FSL, and RSFC of the hippocampus was assessed using seed-based correlation. Ud was measured using the Adult Attachment Interview (AAI). Hierarchical regression and correlation were used to assess the associations between Ud (continuous and categorical), brain structure and FC, adjusting for a general psychopathology factor, puberty stage, gender, age, and IQ. Ud was associated with a smaller left hippocampal volume (R^2=.23) and greater FC between the hippocampus and the middle temporal gyrus and lateral occipital cortex. The association of Ud with specific brain structure and FC across psychopathological classifications shows promise for dimensional complements to the dominant classificatory approach in clinical research and practice.

INTRODUCTION

The loss of an attachment figure or the abuse within an attachment relationship are adverse childhood events that may have lifelong somatic, psychiatric and psychosocial consequences for the individual (Anda et al., 2006; Felitti et al., 1998). From an attachment theory perspective (Bowlby, 1969; 1980; Hesse, 2016), loss and abuse increase the likelihood of unresolved-disorganized attachment (UD): the child may show signs of current mental impact from loss of loved ones or abuse, or the child may apply contradictory approach-avoidance strategies to relationships with parents or other attachment figures. For example, the child may simultaneously display proximity seeking and avoidant behaviors. This UD attachment is considered a (momentary) breakdown of an organized strategy to deal with stressful situations. It results from abuse or another traumatic experience within the attachment relationship, thus confronting the child with a paradox, as the parent is both a source of comfort and fear at the same time for the child (Lyons-Ruth & Jacobvitz, 2016). Not all children are able to resolve these traumatic attachment experiences. Some adolescents show signs of disorientation and disorganization while discussing early traumatic attachment events, indicating that they are still overwhelmed by the trauma

or the loss experience (Hesse, 2016; Lyons-Ruth & Jacobvitz, 2016). This UD mental representation may negatively impact current and future attachment relationships and the transition to adult functioning (Hesse, & Main, 2000).

Previous research had indicated that experiences of loss and abuse increase an individual's risk for psychopathology, including posttraumatic stress disorder (PTSD), as well as anxiety or depressive disorders (Cloitre et al. 2009; Gospodarevskaya, 2013; McLaughlin, Sheridan, & Lambert, 2014b). This may be at least partially attributable to the profound adverse effects of early life stress on brain development, particularly the hippocampus, a stress-sensitive brain region that plays a role in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis. Previous studies found evidence for a smaller hippocampal volume in healthy adults with experiences of abuse but not in children (Calem, Bromis, McGuire, Morgan, & Kemptona, 2017; Hart, & Rubia, 2012; Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015; Rinne-Albers, Van der Wee, Lamers-Winkelman, & Vermeiren, 2013). A reduced hippocampal volume has also been found in adults with PTSD (Chen, & Etkin, 2013). Studies examining brain structure in patients with anxiety and depressive disorders have shown diverging results, from a larger amygdala volume to a smaller left hippocampal volume (DeBellis et al., 2000; Koolschijn, Van IJzendoorn, Bakermans-Kranenburg, & Crone, 2013; MacMillan et al., 2003; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014; Schmaal et al., 2016). It is, however, possible that experiences of trauma account for hippocampal abnormalities in patients with PTSD, anxiety, and depressive disorders, since a reduced hippocampal volume has been found in maltreated individuals, regardless of psychopathology. In addition to structural differences, abnormalities in resting state functional connectivity (RSFC) of the hippocampus have been found in individuals with childhood adversity (Philip et al., 2013) and in a variety of neuro-psychiatric disorders known to be related to childhood adversity, such as PTSD (Tursich et al., 2015), depression and anxiety (Veer et al., 2010). More specifically, individuals who have experienced childhood adversity with or without psychopathology show aberrant resting-state connectivity between the amygdala and frontal regions (for a review, see Teicher, & Samson, 2016; Teicher, Samson, Anderson, & Ohashi, 2016). However, there is a lack of research examining the role of attachment in structural and functional brain abnormalities in adolescents with psychopathology, possibly because simultaneous assessment of psychopathology and attachment representations in adolescents is scarce (Van Hoof, van Lang, Speekenbrink, van IJzendoorn, & Vermeiren, 2015).

Attachment is best described as the innate system that motivates humans to develop an affective bond with a protective caregiver as a secure haven and a safe base to explore the environment (Bowlby, 1969). Caregiver protection against dangers and stresses along with stimulation of exploration shape the child's emotion regulation and the ability to build trusting relationships with others (Cassidy, 2016). According to attachment theory, interactions with attachment figures in childhood develop into inner working models of the

self and others (Bretherton, & Munholland, 2016). Attachment in adolescents and adults can be assessed with the well-validated Adult Attachment Interview (AAI) (Hesse, 2016; Main et al., 1985), which asks respondents for current mental representations of childhood attachment experiences. In the case of adversity such as loss of an attachment figure or the experience of child abuse, attachment representations may be characterized as UD (Hesse, 2016; Lyons-Ruth, & Jacobvitz, 2016), indicated by incoherent, that is disoriented and disorganized, speech in response to questions about losses or other potentially traumatic events, independent from assessed psychopathology. This UD representation is considered a trans-diagnostic risk factor that may increase vulnerability to a range of psychiatric disorders. Indeed, the authors of a meta-analysis found UD had a prevalence of 43% in combined clinical samples, with elevated rates of unresolved loss and trauma in all clinical groups (Bakermans-Kranenburg, & Van IJzendoorn, 2009).

Some studies point to an association between disorganized attachment and structural brain abnormalities. For example, maltreatment reported in the AAI was associated with smaller hippocampal volume in a study in female adult twin pairs (Riem et al., 2015). Recently, Lyons-Ruth, Pechtel, Yoon, Anderson, and Teicher (2016) showed that both maternal and infant components of disorganized attachment interaction in infancy were associated with increased left amygdala volume later in adulthood in a sample of impoverished, highly stressed families. However, it is yet unknown whether attachment representation as assessed with the 'gold standard' AAI (Hesse, 2016; Main et al., 1985) is associated with structural brain abnormalities. Moreover, whereas there is sparse literature on the relationship between attachment and brain morphology, studies on attachment representation and functional connectivity in the brain are lacking. Examining how UD attachment relates to brain structure and functional connectivity will extend previous neuroimaging research on childhood trauma, as previous studies assessed trauma retrospectively and have not examined whether or not it matters if the trauma has been resolved. UD attachment represents a *current* state of mind with respect to childhood attachment experiences. It is yet unknown how this current state relates to brain measures.

Although there is evidence that UD attachment increases vulnerability to psychopathology in general, it is unknown how unresolved status relates to the abnormalities in brain structure and function that are commonly found in patients with psychopathology (Caspi et al., 2014; Lahey et al., 2017). In the current study, we therefore examined whether UD attachment is related to brain abnormalities across multiple psychiatric diagnoses. Thus, we applied a dimensional approach to examine grey matter and resting-state abnormalities related to UD attachment across different psychopathological conditions. Although traditionally psychiatric disorders have been viewed as categorical psychopathological conditions, recent research shows accumulating evidence for a dimensional approach of psychopathology and points to overarching features and trans-diagnostic factors. This dimensional approach to the structure of psychopathology may explain high levels of

comorbidity among mental disorders. However, clinical neuroscience has not kept pace with these advances (Zald & Lahey, 2017). Neuroimaging studies examining biomarkers for psychopathological conditions point to similar structural and functional brain abnormalities across psychopathological conditions (Zald & Lahey, 2017). These shared brain abnormalities may be explained by high levels of comorbidity or shared trans-diagnostic risk factors, such as UD attachment.

Therefore, the aim of the present study was to investigate whether UD attachment representation is associated with gray matter volume (GMV) of the hippocampus and amygdala in a sample of adolescents, after adjusting for psychiatric symptomatology. We chose the hippocampus and amygdala as regions of interest, based on previous studies showing abnormalities in these regions in individuals with experiences of childhood trauma. In addition, we examined whether brain regions that show structural alterations related to UD attachment are also associated with different functional resting state connectivity. In sum, we examined the neural correlates of unresolved for loss or trauma as assessed with the AAI (Main et al., 1985). Our hypothesis is that UD attachment would be correlated with a smaller hippocampal volume and a larger amygdala (Brenning, & Braet, 2013; Brown, & Morey, 2012) and that brain structures associated with UD attachment would also show alterations in functional connectivity.

METHOD

Participants and procedure

Sample

Participants. The current study involved 74 participants from the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA) (Van Hoof, et al., 2015; *N*=77) were involved in the current study. They were recruited according to specified inclusion and exclusion criteria (Van den Bulk et al., 2013; Van Hoof et al., 2015; see supplemental material) and available coded AAIs (Main et al., 1985). Drop-out was due to anomalous magnetic resonance imaging (MRI) findings (*n*=2), technical scanning problems or poor imaging data quality (*n*=2). Within this group, there were 21 adolescents with PTSD related to childhood sexual abuse (CSA), 28 adolescents with anxiety and/or depressive disorders (DEP) and 25 non-clinical adolescents (CNTR). All adolescents with experiences of CSA had PTSD. Some adolescents in the DEP and CNTR group were exposed to other types of trauma (see supplemental material) but not to CSA. Inclusion criteria for the CSA group were having experienced sexual abuse during their lifetime more than once by one or more perpetrators in- or outside the family, and being referred for treatment. See Van Hoof and colleagues (2015) for a detailed description. The sample was originally recruited based on

whether they had experienced CSA, had an anxiety and/or depressive disorder or had no clinical symptoms in order to be able to compare groups cross-sectionally (see Van Hoof et al., 2015). In the current study, the CSA, DEP, and CNTR groups were analyzed together as the aim was to examine whether UD attachment is related to brain abnormalities across multiple psychiatric diagnoses.

Power analysis using G* power (linear multiple regression) showed that the power needed to examine effects of UD and the general psychopathology factor (GPF) on brain structure was met with an alpha value set to .05 and a power of .80, with an expected medium effect size $f = 0.15$ (Calem et al., 2017), and two predictors (UD and GPF), with a required sample size of 68.

The study sample comprised 63 females (85.1%), with 18 in the CSA group, 24 in the DEP group, and 21 in the CNTR group. Participants' mean age was 15.42 years (SD 1.67, range 12-20), and they had a total mean IQ of 103.28 (SD 8.89, range 81-119). Regarding cultural background, 1.4% of participants were Asian (CSA *n*=1), 93.2% were Caucasian (CSA *n*=20, DEP *n*=25, CNTR *n*=24), 1.4% were Surinamese (DEP *n*=1), 2.7% were Latin-American (DEP *n*=2). Four adolescents (5.4%; CSA *n*=2, DEP *n*=2) reported stable selective serotonine reuptake inhibitor use (*n*=3 on fluoxetine, *n*=1 on sertraline). Puberty stage was assessed using the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) according tot he following categories: prepubertal (CSA *n* =1), midpubertal (CNTR *n* =5), late pubertal (CSA *n* =7, DEP *n* =11, CNTR *n*=12), postpubertal (CSA *n* =10, DEP *n* =9, CNTR *n* =5). Information about pubertal status was missing for 10 participants; for these participants, pubertal status was imputed using gender and age. Attachment and clinical characteristics of the original larger total sample (*N*=77) not using imaging data, have been reported separately (Van Hoof et al., 2015).

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 this study. After adolescents and their parents had given assent and consent to participate in the EPISCA study, they filled out questionnaires (usually at home), and were tested for IQ and interviewed for classification of any disorder according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) and attachment representation at the clinic in separate appointments. Scanning was usually performed separate from the aforementioned appointments, depending on availability of the scanner.

Measures

Attachment

Adult Attachment Interview. The AAI (Main et al., 1985; see Supplemental Material) is a clinician-administered semi-structured interview, validated for adolescents, that takes

approximately 1 hr to administer. The AAI asks interviewees how they think about their relationship with parents or other primary caregivers in their youth, how these experiences have influenced them, how their actual relationship with parents or other primary caregivers is, and whether there were any experiences of illness, separation, fear, trauma or loss. Interviewees are asked to give specific examples supporting each evaluation. The coherence of the narrative rather than its autobiographical content is of most importance.

After transcription and coding of the AAI according to the manual (Hesse, 2016) by a certified coder, an attachment representation classification can be given. In organized attachment representations there is one coherent mental strategy with regard to attachment figures, either secure-autonomous or insecure. In UD attachment representations, different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradicting one another, which becomes apparent when coding the narrative. The AAI includes a dimensional subscale entitled Unresolved for Loss or Trauma; AAI narratives are assigned scores on this dimension between 1 and 9, with score of 9 indicating verbal behavior with highly incoherent speech characteristics in the narrative around loss or trauma experiences. A scale score for Unresolved Loss or Trauma of 5.5 or above also renders an individual UD (see Supplemental Material).

General Psychopathology Factor

To control for the effects of psychopathology, we decided to use the GPF. The GPF represents the lesser-to-greater severity of psychopathology associated with negative emotionality (Tackett et al., 2013), compromised brain integrity (Caspi et al., 2014), lower IQ, higher levels of negative affectivity, and lower levels of effortful control shown in 1,954 children between 6 and 8 years of age from a birth cohort (Jaddoe et al., 2012; Neumann et al., 2016). The GPF shows a significant Single Nucleotide Polymorphism (SNP) heritability of 38% (SE=0.16), p=.008. The use of the GPF has also been shown to be valid in girls (Lahey et al., 2015) and in young adolescents (Patalay et al., 2015). In our sample, the GPF was estimated using parent and self-report measurements for behavioral and emotional problems in children and adolescents: the Youth Self Report (YSR; Achenbach, 1991a; Verhulst, Ende, & van der Koot, 1997), Child Behavior CheckList (CBCL; Achenbach, 1991b; Verhulst, Ende, & van der Koot, 1996), Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000; Oldehinkel, 2000), Trauma Symptom Checklist for Children (TSCC; Briere, 1996), Children's Depression Inventory (CDI; Kovačs, 1992), and Adolescent Dissociative Experiences Scale (A-DES; Armstrong, Putnam, Carlson, Libero, & Smith, 1997). Principal Component Analysis was performed using these scales and appropriate subscales, and one component explaining 61.6% was extracted, all loadings > .56, see Supplementary Table S3). Factor scores were calculated in order to estimate the GPF (Franke, 2016; Lahey et al., 2012; Lahey, Zald, et al., 2017; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). See Supplemental Material for a detailed

description of the questionnaires used to estimate the GPF.

Image data acquisition

Images were acquired on a Philips 3T MRI system (Philips Healthcare, Best, the Netherlands), equipped with a SENSE-8 head coil. Scanning took place at the Leiden University Medical Centre. Prior to scanning, all participants were prepared for scanning by lying in a dummy scanner and hearing scanner sounds. For each participant, a sagittal 3-dimensional gradient-echo T1-weighted image was acquired (repetition time=9.8 ms; echo time=4.6 ms; flip angle=8°; 140 sagittal slices; no slice gap; field of view = 256 × 256 mm; 1.17 × 1.17 × 1.2 mm voxels; duration= 4:56 min) as part of a larger, fixed imaging protocol. Resting-state functional MRI (fMRI) data were acquired, using T2*-weighted gradient-echo echo-planar imaging (160 whole-brain volumes; repetition time 2,200 ms; echo time 30 ms; flip angle 80°; 38 transverse slices; no slice gap; field of view 220 mm; in-plane voxel size 2.75 x 2.75 mm; slice thickness 2.72 mm; total duration of the resting-state run = 6 min). Participants were instructed to lie still with their eyes closed and not to fall asleep.

Data analysis

Hippocampal and amygdala volumes. Volumes of the left and right hippocampus and amygdala were assessed using FMRIB's Integrated Registration and Segmentation Tool (FIRST; Patenaude, Smith, Kennedy, & Jenkinson, 2011), part of FSL FMRIB's Software Library, http://www.FMRIb.ox.ac.uk/fsl (Smith et al., 2004). Hippocampal volumes were extracted after affine registration to standard space and subcortical structure segmentation. Registrations and segmentations were visually inspected, and no errors were observed. After hippocampal volume extraction, fslstats was used to assess volumes of the left and right hippocampus and amygdala. Brain tissue volume, normalized for participant head size, was estimated with SIENAX (Smith, De Stefano, Jenkinson, & Matthews, 2001; Smith, 2002). Brain and skull images were extracted from the single whole-head input data (Jenkinson, Bannister, Brady, & Smith, 2002). The brain image was then affine registered to MNI152 space (Jenkinson et al., 2002), after which tissue-type segmentation with partial volume estimation was carried out in order to calculate total brain volume, including separate estimates of volumes of gray matter, white matter, peripheral gray matter and ventricular CSF (Zhang, Brady, & Smith, 2001). Volumes of the left and right hippocampus and amygdala and total brain volume (mm^3) were exported to SPSS.

First, four hierarchical regression analyses with left and right hippocampal volume and left and right amygdala volume were performed with the GPF, sex, composite score age/pubertal status (see Supplemental Material), total IQ score, and whole brain volume in the Step 1 and unresolved loss or trauma (categorical UD vs. non-UD and unresolved

continuous scale in two separate models) in Step 2. All participants were included in the UD versus non UD comparison, and analyses were performed with the clinical groups combined, as the aim of the study was to apply a dimensional approach. In addition to age, pubertal status was also included because variance in pubertal status may be related to different brain structures than variance in age. A composite score for age and pubertal status was calculated in order to control for multicollinearity (Giedd et al., 2006). Statistics indicated no multicollinearity, largest Variance Inflation Factor (VIF) ≤ 1.20, tolerance > .83). The four hierarchical regression analyses were repeated with the GPF as an additional covariate in the first step. Vertex analysis was performed using first_utils (Patenaude et al., 2011) in order to localize and visualize effects of Unresolved status. Exploratory whole brain VBM analyses were performed.

Functional connectivity. Contrasts of interest were the parameter estimates corresponding to the regressor of the region that was significantly related to unresolved loss and trauma (a subregion of the left hippocampus; see Figure 2), which represents functional connectivity with that region. Thus, the left hippocampus was used as the seed region. After transforming the mask to native space, the mean time series for each participant was extracted from the left hippocampus using *fslmeants*. The time series was then used as a regressor in the model. In addition, CSF, white matter and the global signal (see Supplemental Material) were added as regressors to the model in order to reduce the influence of artifacts caused by physiological signal sources on the results (Fox, & Raichle, 2007). The temporal derivative of each regressor was added to the model, which resulted in eight regressors in each model. Motion parameters were also added to the model. First-level analyses were performed in native space. These first-level contrast images and the corresponding variance images were transformed to standard space and submitted to second-level mixed-effects group whole brain analyses. The positive and negative correlation between hippocampal connectivity and unresolved loss and trauma score were assessed as were the contrasts UD greater than nonUD and UD smaller than nonUD. Thus, we contrasted UD with non-UD and applied a dimensional analysis of UD. We included the GPF, composite score age and pubertal status, sex, and IQ as confound regressors in the model. The statistical images were corrected for multiple comparisons at the cluster level in FSL, with a cluster-forming threshold of $Z > 2.3$ and a cluster-corrected significance of $p < .050$ (Worsley, 2001). This threshold was chosen to balance Type I and Type II error, as has been recommended (Hopfinger, 2017; Slotnick, 2017). Harvard-Oxford cortical structural atlas was used to localize hippocampal connectivity.

RESULTS

Clinical sample characteristics

See Table 1 for the clinical sample characteristics. Based on the AAI (Cassidy, 2016) 36.5% of the adolescents were classified as secure (CNTR *n*=13, DEP *n*=11, CSA *n*=3), 41.9% as dismissive (CNTR *n*=11, DEP *n*=11, CSA *n*=9), and 21.6% as UD (CNTR *n*=1, DEP *n*=6, CSA *n*=9). Unresolved-disorganized attachment was found in 16 (21.6%) participants. Of these unresolved participants, six adolescents had anxiety and/or depressive disorders, and nine had CSA-related PTSD. See Supplementary Table S1 for psychopathology scores for the separate groups (CSA-PTSD, internalizing, control and U vs. nonU).

Table 1. *Psychiatric Symptom Scores for the Whole Sample, Measured with the YSR, CBCL, RCADS, TSSC, CDI, and A-DES.*

Clinical characteristic	M	SD	Range
Depression	12.84	9.17	0-40
Posttraumatic stress	34.13	22.72	0-98
Anxiety	25.88	14.96	0-70
Dissociation	1.44	1.42	0-6.37
Internalizing youth report	18.78	11.13	0-44
Internalizing parent report	13.60	9.68	0-42
Unresolved attachment	2.40	1.18	1-8

Volumetric measurement of amygdala and hippocampus

Hierarchical regression analyses showed a significant effect of UD versus non UD on left hippocampal volume ($F_{(5,68)}$ = 3.94, p = .003, R^2 = .17), but not on right hippocampal volume or on amygdala volume (left or right; see Supplementary Table S2). Hierarchical regression analyses were repeated with the GPF as an additional covariate. Again, there was a significant effect of the categorical UD versus non UD on left hippocampal volume beyond psychopathology ($F_{(6,67)}$ = 3.37, p = .014, R^2 = .23). Participants who were classified as UD showed a smaller left hippocampal volume (M = 3,574.33, SD = 510.99 for UD; M = 3,921.81, SD = 344.29 for non-UD). The effect of UD remained significant after excluding one control participant with UD status. Hierarchical regression analysis with the continuous variable unresolved for loss or trauma (U) as predictor did not show a significant effect of U on bilateral hippocampal volumes beyond psychopathology (see Table 2). No effect was found of UD versus non UD on right hippocampal volume (see Table 2) or in the hierarchical regression analyses with the amygdala as the dependent variable (see Table 3). Vertex analysis to localize and visualize the effect of UD in specific subfields of the hippocampus was marginally significant, p < .100, corrected for multiple comparisons. The hippocampal region of interest is shown in Figure 1. Exploratory whole brain analyses yielded no results.

Table 2. *Results of Hierarchical Regression Analyses with Hippocampal Volume (L/R) as the Dependent Variable, Adjusting for Sex, Age/Pubertal Status, Total IQ Score, General Psychopathology Factor (GPF) in Step 1 and Unresolved Loss or Trauma Status in Step 2.*

	Left hippocampus					Right hippocampus				
	B	SE	ß	*p*	delta R^2	B	SE	ß	*p*	delta I
Step 1					.16*					.14
Sex	-195.73	132.21	-.17	.143		-277.48	140.85	-.23	.053	
Age-Puberty	-4.90	43.83	-.01	.911		9.87	46.70	.03	.833	
WBV	0.00	0.01	.00	.970		0.00	0.00	.10	.407	
TIQ	16.38	5.15	.36	.002		12.27	5.49	.25	.029	
GPF	19.99	47.76	.05	.677		-7.20	50.88	-.02	.888	
Step 2					.03					.03
Ud versus non Ud	-282.99	111.64	-.29	.014		-197.54	122.45	-.19	.111	
U continuous	-262.78	158.58	-.20	.102		-274.67	169.08	-.20	.109	

Note. Age-puberty is composite score of age and puberty status; WBV =Whole Brain Volume ; TIQ = Total Intelligence Quotient ; Ud = unresolved–disorganized attachment (categorical); U = unresolved loss or trauma (continuous) .

Table 3. *Results of Hierarchical Regression Analyses with Amygdala Volume (L/R) as the Dependent Variable, Adjusting for Sex, Age/Pubertal status, Total IQ Score, and General Psychopathology Factor (GPF) in Step 1 and Unresolved Loss or Trauma Status in Step 2.*

	Left amygdala					Right amygdala				
	B	SE	ß	*p*	delta R^2	B	SE	ß	*p*	delta R^2
Step 1					.07					.03
Sex	-131.26	70.93	-.23	.069		95.77	86.26	-.14	.271	
Age-Puberty	27.32	23.52	.15	.249		14.67	28.60	.07	.610	
WBV	0.00	.00	.10	.412		0.00	0.00	-.80	.513	
TIQ	2.06	2.76	.09	.458		0.14	3.36	.01	.966	
GPF	6.83	25.62	.03	.790		11.87	31.16	.05	.704	
Step 2										
Ud vs. non Ud	79.68	61.94	-.16	.203	.02	-109.89	75.06	-.18	.148	.03
U continuous	-6.78	86.80	-.01	.938	.00	39.08	105.46	-.05	.712	.00

Note. Age-puberty is composite score of age and puberty status; WBV = Whole Brain Volume ; TIQ = Total Intelligence Quotient ; Ud = unresolved–disorganized attachment (categorical); U = unresolved loss or trauma (continuous) .

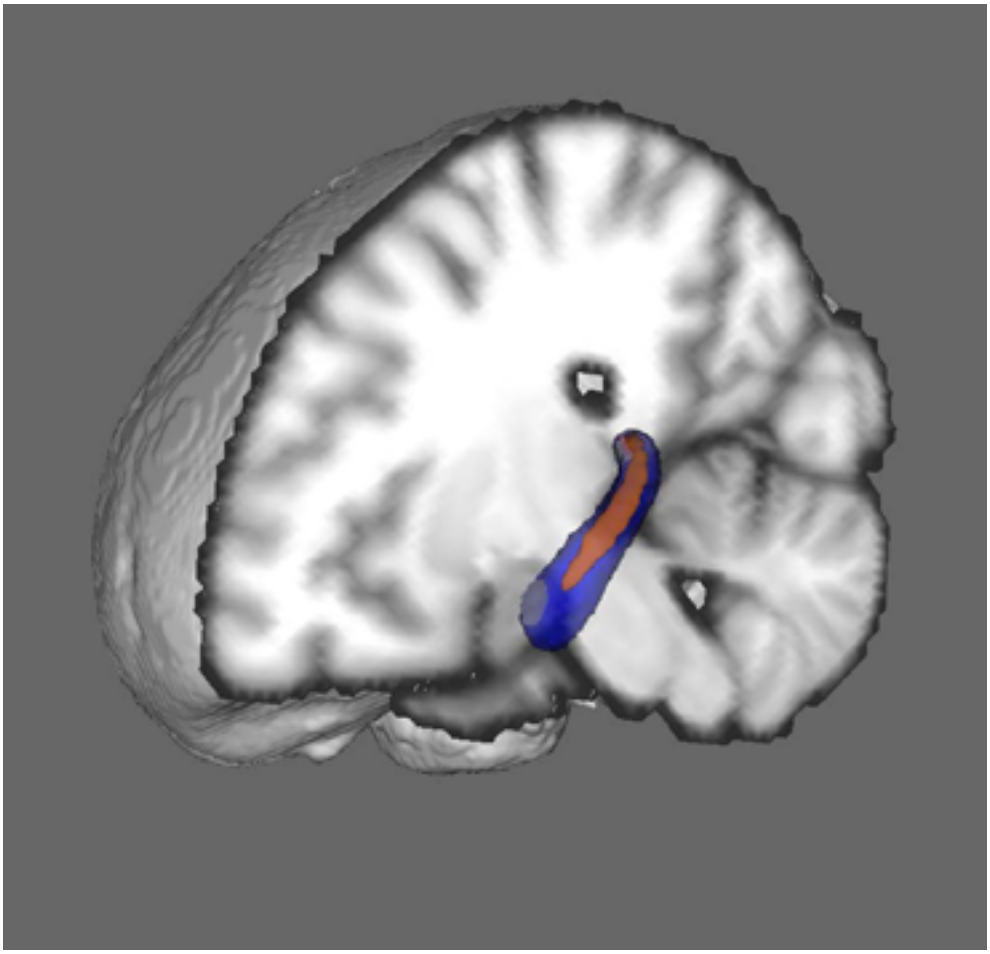

Figure 1. Red shading shows reduced hippocampal volume in adolescents with an unresolved-disorganized (UD) status compared to adolescents without a UD status, $p < .100$ (corrected for multiple comparisons). Blue shading shows study-specific mask of the left hippocampus.

Resting state functional connectivity

Analyses of RSFC showed that Unresolved loss or trauma was positively related to connectivity between the left hippocampus and the right middle temporal gyrus (MTG) and the lateral occipital cortex (LOC), cluster size = 654 voxels; peak Z = 3.55; MNI coordinates x,y,z (mm) = 40, -60, 10 (see Figure 2). In addition to the analysis with the dimensional measure of UD, we contrasted UD versus non UD, but there was no significant difference in hippocampal connectivity between the UD versus the non UD group.

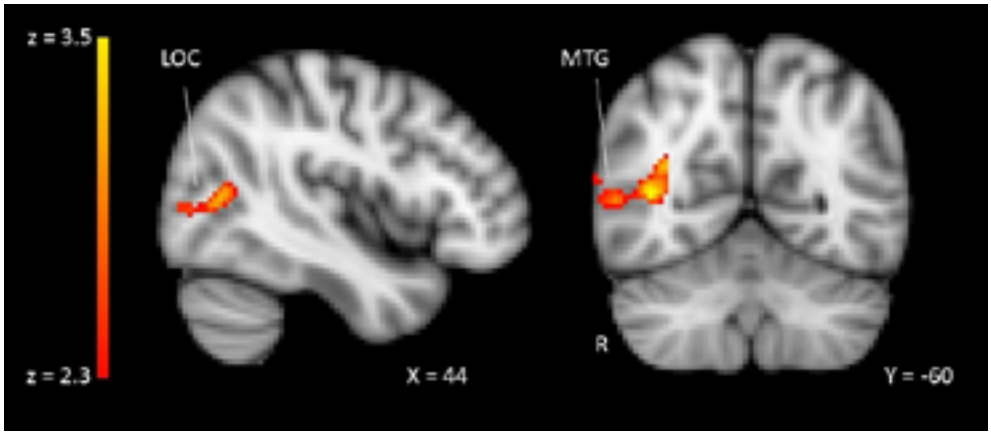

Figure 2. Results of the resting-state functional connectivity analysis. Unresolved loss and trauma is positively associated with connectivity between the left hippocampus and the middle temporal gyrus (MTG) and the lateral occipital cortex (LOC). Cluster thresholded $Z > 2.3$, $p < 0.050$.

DISCUSSION

The aim of this study was to investigate whether UD attachment representation as assessed with the AAI was associated with different volumes of hippocampus and amygdala as well as with related differential connectivity in hippocampus or amygdala-based RSFC networks in adolescents with CSA-related PTSD, anxiety and/or depressive disorders and those without psychiatric symptoms. As recent research shows accumulating evidence for a dimensional approach of psychopathology and points to overarching features and trans-diagnostic factors, we applied a dimensional approach to examine grey matter and resting-state abnormalities related to UD attachment across different psychopathological conditions. Unresolved versus resolved group status was associated with a significantly smaller left hippocampal volume after adjusting for general psychopathology, puberty status, age, gender, and IQ. In addition, there was a positive correlation between UD attachment score and left hippocampal functional connectivity with the right MTG and LOC. No associations were found between UD attachment and right hippocampus or amygdala volumes.

Our findings are consistent with research showing that UD attachment is a trans-diagnostic risk factor that increases vulnerability to psychopathology in general. Moreover, these findings indicate that hippocampal abnormalities previously found in patients with PTSD, depression or anxiety disorders are not a specific biomarker for individual mental disorders, but instead are common to several disorders, and could be related to etiological factors rooted in childhood attachment experiences. The hippocampus is one of the most stress-sensitive structures in the brain, as it modulates the HPA axis responsiveness to stress (Bernard, Lind, & Dozier, 2014). Early life stress such as child abuse and neglect

may reduce the number of hippocampal glucocorticoid receptors, prevent neurogenesis, and distort synaptic pruning (Sapolsky, Krey, & McEwan, 1985; Sapolsky, Uno, Rebert, & Finch,1990). In response to stress, the hypothalamus releases corticotrophin-releasing hormone and arginine vasopressin. This leads to the secretion of adrenocorticotrophic hormone and increased cortisol release. When cortisol binds to glucocorticoid receptors in the hippocampus, hypothalamus, and the pituitary, inhibitory feedback is given which returns the system to homeostasis (Koss, & Gunnar, 2018). Damage to the hippocampus results in reduced glucocorticoid-mediated feedback control of the HPA axis, leading to hyper- or hypo-responsiveness to mild stressors (McCrory, De Brito, & Viding, 2011), which in turn may explain poor emotion regulation and increased risk for psychopathology in individuals with unresolved trauma.

We found smaller left hippocampal volume in the UD versus organized adolescent group. This finding is in line with previous findings showing a smaller left hippocampal volume in adults with experiences of maltreatment (Riem et al., 2015). Maltreatment-related PTSD in children, however, was not related to hippocampal volume in a meta-analytic study (Woon, & Hedges, 2008); additionally, a study on the neurobiological effects of poor caregiving in orphanage reared children did not demonstrate a smaller hippocampus (Tottenham et al., 2010). One explanation could be that the sexual and physical abuse reported in the current study took place from early childhood to adolescence, a developmental period that is most sensitive to negative effects of maltreatment (Riem et al., 2015). Thus, the timing of the abuse may matter. Also, the reported abuse was often severe, cumulative and protracted, and the treatment gap between the abuse and start of treatment was sometimes rather large (Van Hoof et al., 2015), all of which may have negatively impacted the hippocampal volume due to severe and prolonged stress. Moreover, neuro-anatomic findings according to age in adolescents may already more closely resemble those in adults than in children. Another plausible explanation may be that UD attachment indeed constitutes a different concept than PTSD or maltreatment and shows different findings in relation to the brain when general psychopathology has been controlled for.

In addition, we found that UD attachment was related to the left hippocampus functional connectivity with the MTG and the LOC. In a meta-analysis Sabatinelli and colleagues (Sabatinelli et al., 2011) found activation in both regions related to processing of emotional information. The LOC has been shown to be implicated in higher level visual processing, including emotional scene perception, whereas the MTG seems to be associated with the processing of emotional faces, including faces provoking social aversion (Krause et al., 2016). However, enhanced connectivity between the hippocampus, MTG and LOC was found during rest, which is surprising since the MTG and LOC are not part of the limbic or default mode network. Thus, our finding indicates that UD attachment is related to atypical hippocampal limbic or default mode network connectivity. Future studies should investigate whether neural processing of emotions in individuals with UD attachment is due

to their Unresolved status or psychopathology, as altered MTG and LOC activity may also be associated with atypical processing of emotional stimuli of various kinds. Also, individuals with UD attachment may be more vulnerable to associate negative emotional stimuli with their current mental representation of traumatic sexual and/or physical experiences or past losses. The smaller hippocampal volume associated with unresolved loss or trauma may indicate a less effective HPA-axis feedback loop (Gupta, & Morley, 2014) leading to a lowered threshold for experiencing stress through perceptions or memories of loss or trauma.

Contrary to our hypothesis, we did not find an association between UD attachment and amygdala volumes. Our adolescent sample showed left hippocampal reduction but no (left) amygdala enlargement, as would have been in line with what was reported by Lyons-Ruth and colleagues (Lyons-Ruth et al., 2016), who found an association with both maternal and infant disorganization (but not child abuse per se) with larger left amygdala volume in adolescence in a sample of impoverished, highly stressed families. One explanation for the absence of the relation between unresolved status and amygdala volume in the current study is that acute threat and anxiety rather than childhood trauma could be related to amygdala enlargement. This is consistent with neuroimaging studies on affective disorders (Rinne-Albers et al., 2013; Van den Bulk, 2015) and suggested by normal development of hippocampus and amygdala (Tottenham, & Sheridan, 2010).

A previous study that used the same sample but did not include the AAI showed that abnormal amygdalar connectivity related to diminished grey matter of the basolateral and centrolateral subnuclei in the amygdala was associated with psychopathology (Aghajani et al., 2016). In contrast, the current study removed variance associated with psychopathology; therefore, it makes sense that amygdala abnormalities were not detected. The unique contribution of UD attachment on top of this psychopathology seems only related to hippocampal volume and hippocampal functional connectivity with the MTG and LOC which are involved in visual processing.

To the best of our knowledge this is the first study linking adolescent attachment status to amygdala and hippocampal volumes and GMV in the adolescent brains of both clinical and non-clinical individuals. There are, however, some limitations to consider. The generalizability of results may be limited due to the fairly small sample size and the restricted ranges of age, IQ, gender, and ethnicity. Also, this is a cross-sectional study, so reversed causality can easily shape the interpretation of results and definitive conclusions about cause and effects cannot be drawn. Finally, to be rendered UD on the AAI one must have experienced (interpersonal) trauma or loss that is volunteered in responding to some loss- and trauma-related questions on the AAI. Without such a trigger for narrative incoherence in the speech around loss or trauma, it is only possible to rate the individual on the continuous or categorical UD variable as showing the absence of unresolved status.

In conclusion, our study suggests that across diagnoses, UD attachment is

associated with structural and functional connectivity abnormalities of the hippocampus, a brain structure involved with regulation of the HPA axis, memory consolidation, and emotion regulation.

DECLARATION OF CONFLICTING INTERESTS
The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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SUPPLEMENTAL MATERIAL CHAPTER 4 (as published online)

METHODS

In- and exclusion criteria EPISCA

The adolescents were part of the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents), a longitudinal study in which adolescents were followed over a six-month period. The adolescents with and without clinical symptoms underwent a diagnostic assessment and an MRI scanning protocol at three points in time (at baseline, 3 months, 6 months)(Van den Bulk et al., 2013). AAI (Main et al., 1985) and clinical characteristics of the group and neuroimaging data were reported previously (Van Hoof et al., 2015; 2017).

Related to the neuroimaging protocol all participants met the following inclusion criteria: aged between 12 and 20 years, estimated full scale IQ ≥ 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). The adolescents with childhood sexual abuse (CSA) were recruited at two psychotrauma centres of child and adolescent psychiatric institutes in the Leiden region in the Netherlands. Inclusion for CSA was 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 psychotrauma centre. The 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 (Silverman et al., 2001) and no history of CSA (see Aghajani et al. ,2013; Pannekoek et al., 2014a; 2014b). Exclusion criteria for both clinical groups 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) amphetamine medication on the day of scanning or current use of psychotropic medication other than stable use of SSRI's; and (3) current substance abuse. The non-clinical adolescents were recruited through local advertisement, with the following inclusion criteria: no clinical scores on validated mood and behavioral questionnaires or past or current DSM-IV classification, no history of traumatic experiences and no current psychotherapeutic intervention of any kind.

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. Most adolescents with CSA (87%) reported during the AAI serious and/or longstanding physical sexual contact including repeated or group rape, in 63.6% by a person other than an attachment figure. In addition, 36.4% of the CSA group also experienced physical abuse, 22.7% by a person other than an attachment figure, 9.1% by an attachment figure, in one case by both. Sexual abuse was reported to the police in 60.9%, child welfare was involved in 56.5% of the cases, while 17.4% had a child protection measure (family custody). None of the participating non-clinical adolescents and those with anxiety and/or depressive disorders had experienced CSA, but they did mention physical and emotional abuse, bullying, and other incidents. Non-clinical adolescents had not been involved with police, child welfare or child protection, while 23% of the adolescents with anxiety and/or depressive disorders had child welfare involvement.

From the original sample of 82 adolescents, three participants were excluded due to technical problems, i.e. failed voice and video recording (one adolescent with CSA), unintelligible recording (one non-clinical adolescent), incorrect interview technique (one non-clinical adolescent). Two participants (one non-clinical adolescent and one adolescent with anxiety/depressive disorder) were excluded because they refused the AAI because of the interview itself. Of the *N*=77 in the remaining sample, 86% were girls. All CSA adolescents fulfilled the DSM-IV criteria for PTSD, according to the ADIS (Silverman et al. 2001), however one adolescent missed a point on the interference score to fully qualify for PTSD. SSRI's were used by four of the adolescents with CSA and two of those with anxiety and/or depressive disorder.

YSR: Youth Self-Report (Achenbach, 1991a) and CBCL: Child Behaviour Checklist (Achenbach, 1991b), with Dutch translations by Verhulst and colleagues (Verhulst et al., 1996; 1997). The YSR and CBCL are self-report questionnaires using a 3-point scale to assess social-emotional and behavioural problems in adolescents. The CBCL is the questionnaire for parents, the YSR for adolescents 11 years and older. There are 9 subscales and 3 main scales (total score, externalizing problemscore and internalizing problemscore). In this study, we used the internalizing problemscores of the YSR and CBCL.

ADIS: The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS C/P; Silverman et al., 2001) are semi structured interviews designed specifically for DSM-IV classification of anxiety and other related disorders such as depression and PTSD in children and adolescents. Strong test-retest reliability was shown for combined and individual ADIS-C/P diagnoses. Intra-class correlations were excellent. Interrater reliability between child and parent versions of the ADIS was reported to be excellent. In this study, the ADIS was applied to all participants by certified trained clinicians and researchers.

TSCC: The Trauma Symptom Checklist for Children (TSCC)(Briere, 1996) is a 54-item self-report for children and adolescents aged 8-17, which measures trauma-related symptoms. In the present study, only the TSCC total score was used as subscales overlapped significantly, with a Cronbach's alpha coefficient of .96.

A-DES: The Adolescent Dissociative Experiences Scale (Armstrong et al., 1997) is a self-report for adolescents aged 11-18 measuring possible dissociation. The A-DES has good reliability and validity. In this study, the mean total score on the A-DES was used as a measure of dissociation, which had a Cronbach's alpha coefficient of .95.

CDI: The Children's Depression Inventory (Kovačs, 1992) is a 27-item, self-rated, depression symptoms-oriented scale suitable for youths aged 7 to 17. The CDI has good psychometric properties of validity and reliability (Cronbach's alpha .71 to .86)(Timbremont et al., 2004) though discriminant validity has been subject to discussion. In this study, the total CDI score had a Cronbach's alpha coefficient of .93.

RCADS: The Revised Child Anxiety and Depression Scale (Chorpita et al., 2000; Oldehinkel, 2000) is a self-rated, anxiety and depressive symptoms-oriented 47-item-scale for children aged 6 to 18. Items are scored based on a four-point scale and grouped as depressive disorder, generalized anxiety disorder, social phobia, anxiety disorder NAO and obsessive-compulsive disorder. Chorpita et al. (2000) reported evidence for validity and reliability of the RCADS in clinical and healthy control adolescents. In this study, the total score of the RCADS was used as a measure for severity of experienced symptomatology (Cronbach's α = .95). Besides, the depression scale (Cronbach's α = .89) and the cumulative anxiety scales (Cronbach's α = .94) were used.

AAI: the Adult Attachment Interview (Main et al., 1985) is coded according to the DEFU system (Hesse, 2016): dismissive (Ds), preoccupied (E), secure-autonomous (F), unresolved-disorganized (Ud). Ds, E and F classifications are organized forms of attachment, while Ud represents disorganized forms of attachment. In organized attachment representations there is one coherent mental strategy with regard to attachment figures, either secure-autonomous (F) or insecure (Ds or E). In disorganized attachment-representation different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory. A high to moderate coherence of the narrative is seen in secure-autonomous (F) attachment interviews in which the interviewee can give ample evidence for general evaluative statements made regarding attachment relationships and attachment experiences whether good or bad. In case of unresolved loss or trauma, the attachment representation is labeled unresolved-disorganized (Ud). This classification can be given in addition to a Ds, E or F classification. A fifth category, cannot classify (CC), is used when the interviewee presents contrasting attachment strategies for attachment figures in the course of the interview resulting in very low coherence of narrative. In most studies U and CC are combined in one category, Unresolved-disorganized. Coherence of mind and unresolved for loss or trauma (Ulosstrauma) are two dimensional scales of the AAI which are assigned scores rated between 1-9. Lowest score for Coherence means there is little or no coherence of mind, highest score for Ulosstrauma means there is high impact of loss or trauma.

The AAI has been administered to more than 10,000 respondents since its development (Bakermans-Kranenburg, & Van IJzendoorn, 2009). The AAI is found to have remarkably good test-retest, discriminant reliability as well as predictive validity. In this

study, the AAI was administered by MJvH and CIG, verbatim transcribed according to protocol, and coded by GK (trained by Diane and Dave Pederson), and SdH (trained by Diane and Dave Pederson, and June Sroufe). Both reached intercoder reliability standards in the AAI classification system. Ten cases were also coded by MJBK. Interrater agreement in this sample was 80% for F-nonF, 90% for Ud-nonUd and 70% for four-way classification (DEFU). Kappa's for coding F-nonF (.59) and Ud-nonUd (.62) were both statistically significant and reasonable to satisfactory (see also Van Hoof et al., 2015).

WISC-III-NL and WAIS-III: Short versions of the Wechsler Intelligence Scale for Dutch Children aged 6-16 years, WISC-III-NL (Wechsler, 1991; Crawford et al., 1996) and adolescents aged 16 and above and adults, the Wechsler Adult Intelligence Scale, WAIS-III, (Wechsler, 1997) were used. They consisted of six subtests: picture completion, similarities, picture arrangement, arithmetic, block design and comprehension. In earlier studies, these subtests were found to give a valid and reliable IQ estimate (reliability coefficient > .90) (Kaufman et al., 1996).

PDS: The Pubertal Development Scale (Petersen et al., 1988) measures the actual level of physical development during puberty. It is a 5-item self-report that measures items like body growth, body hair, skin changes for both sexes. For boys, there are items on beard growth and voice changes. For girls, there are items on breast growth and menstrual bleeding. Items can be answered on a 5-point scale with a total score range of 0-20. Internal consistency is adequate for both sexes, consistent across samples, while the predictive validity of the PDS is satisfactory (Robertson et al., 1992) The PDS was filled out by 92.3% of participants in this study.

Statistical analysis

Structural analysis. Besides the dimensional scales scores for unresolved loss or trauma and coherence of mind we used the categorical variable Ud-nondUd for unresolved-disorganized attachment versus resolved organized attachment in both the exploratory whole brain analysis, and the ROI analyses. No significant results were found.

Resting state analysis. The following pre-statistics processing was applied: motion correction (Jenskinson et al., 2002), non-brain removal (Smith et al., 2001), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 6.0 mm, and high-pass temporal filtering (highpass filter cutoff = 100.0 s). Functional scans were registered to the T1-weighted images, which were registered to standard space in order to calculate the transformation matrix for the higher-level group analysis (Jenkinson et al., 2002). The global signal was added to the model. It should be noted that there is no consensus regarding the global signal for resting state functional connectivity analyses (Murphy, & Fox, 2017). Adding the global signal to resting state analyses has both advantages and disadvantages. We added the

global signal in the analyses of the current study in order to increase comparability with a previous resting state study with partly the same sample (Pannekoek et al., 2014b).

Functional connectivity Pre-statistics processing was applied before functional connectivity analyses, see supplemental material. A seed based correlation approach was used for the current study (Murphy, & Fox, 2007). We created a binary mask of the brain region that was significantly related to Unresolved loss and trauma: the left hippocampus. This region was used as seed region. After transforming the mask to native space, the mean time series for each participant were extracted from the left hippocampus. These times series were then used as a regressor in the model. In addition, CSF, white matter and the global signal (see supplemental material) were added as regressors to the model in order to reduce the influence of artifacts caused by physiological signal sources on the results (Fox, & Raichle, 2007). The temporal derivative of each regressor was added to the model resulting in 8 regressors in each model. Motion parameters were also added to the model.

Voxel-based morphometry. An exploratory whole brain analysis of the association of Unresolved loss or trauma with regional volume was performed with FSL-VBM (http://fsl.fmrib.o.ac.uk/fsl/fslwiki/FSLVBM) (Smith et al., 2004; Douaud et al., 2007). First, structural images were brain-extracted and gray matter-segmented before being registered to the MNI 152 standard space using non-linear registration. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific gray matter template. Second, all native gray matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. After preprocessing steps, the association between unresolved loss or trauma and GMV was investigated using a GLM including the general psychopathology factor, sex, composite score age and pubertal status, total IQ score as confound regressors. A voxel-wise GLM was applied using permutation-based (5000 permutations) non-parametric testing and Threshold-Free Cluster Enhancement (Smith, & Nichols, 2009) was used to correct for multiple comparisons at the cluster level ($p<0.05$).

RESULTS

Voxel-based morphometry

VBM analyses did not show a significant relation between Unresolved status and gray matter volume.

Coherence of mind

We hypothesized that coherence of mind besides unresolved loss or trauma would

correlate with a smaller hippocampal volume and a larger amygdala (Brown, & Morey, 2012; Brenning, & Braet, 2013), and that brain structures associated with coherence of mind would also show atypical functional connectivity. Similar to the analyses on Unresolved-disorganized attachment we analyzed whether coherence was associated with hippocampal and amygdalar volumes, and connectivities. No association was found between Coherence and hippocampal or amygdala volumes, nor with grey matter of the adolescent brain. Therefore, an association between Coherence and resting state functional connectivity (RSFC) was not further explored.

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Table S1. Mean (SD) general psychopathology scores for the internalizing, CSA-PTSD, and control group, and U versus nonU groups.

Group	N	M	SD	Range
Internalizing	21	0.46	0.83	-.88 – 2.34
CSA-PTSD	28	0.49	0.86	-.86 – 1.90
Control	25	-0.92	0.57	-1.66 – 0.39
U	16	0.38	.97	-1.31 – 1.90
nonU	58	-0.11	.99	-1.66 – 2.35

Table S2. Results of hierarchical regression analyses with hippocampal volume (L/R) and amygdala volume (L/R) as dependent variable, sex, age/pubertal status, total IQ score, and whole brain volume in the first step and Unresolved loss or trauma status (Ud versus non Ud/U continuous) in the second step.

	Ud-nonUd				U continuous			
	B	SE	ß	*p*	B	SE	ß	*p*
Left hippocampus	-269.99	110.15	-.27	.02	-237.39	154.57	-.18	.13
Right hippocampus	-195.87	119.96	-.19	.11	-267.52	164.14	-.19	.11
Left amygdala	-75.60	60.92	-.15	.22	-1.76	84.29	-.00	.98
Right amygdala	-103.40	73.91	-.17	.17	-29.17	102.50	-.04	.77

Table S3. Factor loadings for the Trauma Symptom Checklist for Children (TSCC), Children's Depression Inventory (CDI), Revised Child Anxiety and Depression Scale (RCADS), Adolescent Dissociative Experiences Scale (A-DES),Youth Self Report (YSR), and Child Behavior Check List (CBCL), resulting from the Principal Component Analysis.

Subscale	Loading
RCADS separation anxiety	.79
RCADS social phobia	.80
RCADS panic disorder	.69
RCADS generalized anxiety disorder	.74
RCADS obsessive compulsive disorder	.79
RCADS depressive disorder	.89
CDI	.84
YSR internalizing problems	.88
CBCL internalizing problems	.63
TSCC_depression	.92
TSCC anxiety	.75
TSCC_PTSD	.87
TSCC dissociation	.83
TSCC sexual concerns	.56
ADES	.70

5

General psychopathology factor and unresolved-disorganized attachment uniquely correlated to white matter integrity using diffusion tensor imaging

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ABSTRACT

Background: A dimensional approach of psychopathology focuses on features and risk factors that are shared across diagnoses. In support for this dimensional approach, studies point to a general psychopathology factor (GPF) associated with risk for multiple psychiatric disorders. It is, however, unknown how GPF relates to white matter integrity (WMI). In the current diffusion tensor imaging (DTI) study, we examined how GPF relates to abnormalities in a skeleton representation of white matter tracts, taking into account a trans-diagnostic risk factor: unresolved-disorganized attachment (Ud) resulting from loss or trauma.

Methods: Unique associations between GPF, Ud, and WMI were examined in a combined sample of adolescents ($N = 63$) with childhood sexual abuse-related posttraumatic stress disorder ($N = 18$), anxiety and depressive disorders ($N = 26$) and without psychiatric disorder ($N = 19$). WMI was measured using DTI. Ud was measured using the Adult Attachment Interview. We controlled for puberty stage, gender, age, and IQ.

Results: Controlling for GPF, Ud was associated with reduced fractional anisotropy (FA) in the splenium and inferior fronto-occipital fasciculus (IFOF). Controlling for Ud, GPF was associated with reduced FA in the genu and body of the corpus callosum.

Conclusions: Decreasing WMI in the genu and body with increasing psychopathology across diagnoses suggests demyelinization in these areas and may underlie comorbidity and presence of symptoms that transcend psychopathological diagnoses. In contrast, trauma-related WMI reductions in the splenium and IFOF may account for heterogeneity within diagnostic categories as a function of childhood trauma. These findings support the importance of a dimensional approach in addition to traditional diagnostic classifications in clinical research and practice.

1. INTRODUCTION

Psychiatric disorders have traditionally been viewed as categorical and distinct psychopathological conditions. However, recent research on mental health shows accumulating evidence for a dimensional approach of psychopathology and points to overarching features and trans-diagnostic factors (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Caspi, Houts, Belsky, Goldman-Mellor, Harrington, Israel, et al., 2014; Lahey, Rathouz, Keenan, Stepp, Loeber, & Hipwell, 2015). Given the high rates of comorbidity among mental disorders and the evidence that many disorders exist on a continuum, it has been argued that the underlying structure of psychopathology is reflected by a general psychopathology factor (GPF) that represents lesser-to-greater severity of psychopathology (Caspi et al., 2014). Although there is increasing attention for this novel dimensional approach for psychopathology in mental health research, clinical neuroscience is only beginning to investigate the neural mechanisms underlying mental disorders across traditional diagnostic

classifications of psychopathology (Zald, & Lahey, 2017). Numerous neuroimaging studies in search for biomarkers for psychopathological conditions point to structural and functional brain abnormalities (Hanson, Knodt, Brigidi, & Hariri, 2018; Miller, Hamilton, Sacchet, & Gotlib, 2015), but fail to find neural features with specificity to individual disorders, possibly because of comorbidity and the existence of a GPF (Zald, & Lahey, 2017).

The high comorbidity rates among mental disorders concur with the observation that risk for psychopathology is not disorder specific. For example, a recent study indicates that the GPF shows a significant Single Nucleotide Polymorphism (SNP) heritability of 38% in children (Neumann, Pappa, Lahey, Verhulst, Medina-Gomez, Jaddoe, et al., 2016). Thus, genetic factors may enhance the risk for psychopathology in general rather than or in addition to heritability of specific disorders. Similarly, environmental influences contribute to a general risk for psychopathology. More specifically, childhood trauma has been shown to increase the risk for a range of psychiatric disorders, including depression, anxiety disorders and posttraumatic stress disorder (PTSD)(Green, McLaughlin, Berglund, et al., 2010), possibly because it interacts with genetic risk factors to interfere with brain development (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Consistent with this suggestion, studies on white matter integrity (WMI) in PTSD due to maltreatment show reduced WMI in structures subserving emotional, learning, and memory functions, such as the cingulum, corpus callosum and associated fasciculi. For example, Rinne-Albers and colleagues (Rinne-Albers, Van der Werff, Van Hoof, Van Lang, Lamers-Winkelman, Rombouts, et al., 2016) found abnormalities of WMI in the genu, body and splenium of the corpus callosum in adolescents with PTSD related to childhood sexual abuse (CSA) compared to a control group. Abnormalities of the integrity of the corpus callosum may be the consequence of stress hormones associated with maltreatment earlier in life and may underlie deficits in emotional dysregulation that are often experienced by these individuals (Heim et al., 2008; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002).

Structural brain abnormalities have also been found in healthy individuals with experiences of maltreatment, regardless of psycho-pathology (Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015). This indicates that previous neuroimaging findings with clinical and non-clinical samples are possibly confounded by neurobiological consequences of childhood trauma. Indeed, research shows that the hippocampal volume reductions that are often observed in depressed patients are only found in patients diagnosed with depression and experiences of childhood maltreatment, but not in depressed patients without experiences of maltreatment (Heim et al., 2008). This finding has been interpreted as support for the existence of heterogeneity within psychopathological diagnoses as a function of childhood trauma (Teicher, & Samson, 2013) and is in line with clinical observations that depression with maltreatment is often more severe and predicts an unfavorable treatment outcome (Nanni, Uher, & Danese, 2012). Thus, childhood trauma may explain heterogeneity within diagnoses and may be related to neural substrates that are nonspecifically related to

multiple psychopathological conditions.

Not all maltreated individuals develop a mental disorder. A substantial number of children are resilient and develop well in the context of adversity (Masten, Best, & Garmezy, 1990). Multiple resilience factors, such as IQ, personality, genetic factors, parenting or positive experiences in attachment relationships, may explain individual variability in the pathways from trauma to (mal)adaptation (Masten, Best, & Garmezy, 1990). Good quality relationships with parents, peers, and romantic partners across childhood, adolescence and adulthood appear especially important predictors of a good prognosis after childhood trauma and may help in resolving issues related to childhood trauma (Collishaw, Pickles, Messer, Rutter, Shearer, & Maughan, 2007). Previous neuroimaging studies on the neurobiological effects of maltreatment have not taken into account the role of *current* state of mind with respect to childhood attachment experiences. Childhood trauma is mostly assessed retrospectively in studies examining brain structure in maltreated individuals and it is unknown whether it matters if the trauma has been resolved or not, for example through psychotherapy or resilience factors. From an attachment theory perspective, unresolved loss or trauma is characterized by a disorganized/disoriented attachment representation, that is, a disorganized/disoriented mental state with respect to childhood attachment relationships. It results from loss of or being abused by a trusted caregiver or another very traumatic incident (Hesse, 2016). Individuals with a disorganized state of mind show signs of incoherence, that is disorientation and disorganization, in their speech when they are questioned about traumatic events and/or they may present contradictory approach-avoidance strategies towards parents and other attachment figures (Hesse, 2016). Previous meta-analytic results show a prevalence of unresolved-disorganized attachment of 43% in clinical samples (Bakermans-Kranenburg, & Van IJzendoorn, 2009) and suggest that unresolved-disorganized attachment may be a trans-diagnostic risk factor for increased vulnerability to multiple psychiatric disorders. It is, however, not known whether and how psychopathology and unresolved-disorganized attachment differentially relate to brain structure and functioning.

In the current Diffusion Tensor Imaging (DTI) study, we will examine whether unresolved loss and trauma, and GPF are differentially related to WMI abnormalities in specific tracts. The current study is the first attempt to examine the unique neural correlates of a GPF in a combined clinical sample consisting of adolescents with CSA-related PTSD, anxiety and/or depressive disorders, and healthy controls. To our knowledge, only one previous study examined the association between general psychopathology and structural abnormalities (Romer, Knodt, Houts, Brigidi, Moffitt, Caspi, et al., 2017). Romer and colleagues (Romer et al., 2017) showed that general liability for psychopathology correlated with structural alterations in a cortico-cerebellar circuitry in a sample of adolescents (> 18 years) without psychiatric diagnoses, but it is unclear whether this finding can be generalized to individuals with more severe psychiatric symptoms since the sample consisted of non-

clinical adolescents and psychiatric symptoms were not measured extensively. Moreover, trans-diagnostic risk factors for psychopathology were not examined. In the current study, we use the Adult Attachment Interview (AAI) (Hesse, 2016) to assess trans-diagnostic risk factors. We hypothesize that 1) a GPF and unresolved-disorganized attachment (Ud) are differentially related to white matter abnormalities, and 2) after adjusting for a GPF, Unresolved attachment is associated with a reduction in WMI in regions that have previously been associated with childhood adversity, that is, the cingulum, corpus callosum and the superior longitudinal fasciculus (Daniels, Lamke, Gaebler, Walter, & Scheel, 2013).

2. METHODS AND MATERIALS

2.1. Participants

Sixty-three participants from the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents; *N* = 77;(Van Hoof, Van Lang, Speekenbrink, Van IJzendoorn, & Vermeiren, 2015) were recruited according to specified in- and exclusion criteria (Van den Bulk, Koolschijn, Meens, Van Lang, Van der Wee, Rombouts, et al., 2013) (see also supplemental material). They were further selected based on availability of an AAI and a DTI scan (*N* = 72). Drop-out occurred due to poor imaging data quality and artifacts on DTI scans (*N* = 9). Within the final group there were 18 adolescents with childhood sexual abuse related posttraumatic stress disorder (CSA-PTSD), 26 adolescents with anxiety and/or depressive disorders (DEP) and 19 non-clinical adolescents (CNTR).

Our study sample consisted of 53 females and 10 males. Mean age was 15.49 years (SD 1.72, range 12–20) and total mean IQ was 103.25 (SD 8.77, range 81–119). As to cultural background, 1.6% was Asian, 92.1% was Caucasian, 4.8% was Surinamese, 1.6% was Latin-American. Four adolescents (CSA-PTSD *N* = 2, DEP *N* = 2) were on stable SSRI use (three fluoxetine, one sertraline). Puberty stage was assessed according to the following categories using the Pubertal Development Scale (PDS; (Petersen, Crockett, Richards, & Boxer, 1988), see supplemental material). Attachment and clinical characteristics of the originally larger total EPISCA sample (*N* = 77) without neuroimaging data were reported separately (Van Hoof, et al., 2015).

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).

2.2. *Adult attachment interview*

The Adult Attachment Interview (AAI; Hesse, 2016); see also supplemental material) is a one hour long administered semi-structured interview, validated for adolescents (Allen, Moore, Kuperminc, & Bell, 1998). The AAI asks how the interviewee thinks about the relationship with parents or other primary caregivers in his or her childhood, how these experiences have influenced him or her, how the actual relationship with parents or other primary caregivers is currently and whether there were any childhood experiences of illness, separation, fear, trauma or loss. The interviewee is asked to give specific examples supporting each evaluation. The coherence of the narrative determines the score, not its autobiographical content (Hesse, 2016).

After verbatim transcription of the AAI a certified coder rates the interview and assigns an attachment representation classification described by Hesse (2016). In organized attachment representations there is one coherent mental strategy with regard to attachment figures, either secure-autonomous or insecure. In unresolved-disorganized attachment representations different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory (Hesse, 2016). Individuals receive a scale score for Unresolved loss or trauma and a score of 5.5 or above leads to a classification of unresolved-disorganized (Hesse, 2016) (see Supplemental material)

2.3. *General psychopathology factor*

The general psychopathology factor represents lesser-to-greater severity of psychopathology that is associated with higher negative affectivity, life impairment and compromised brain integrity (Caspi et al., 2014). The use of the general psychopathology factor was also shown to be valid in previous studies with adolescents [e.g. 3]. A GPF was estimated using parent and self-report measurements for behavioral and emotional problems in children and adolescents: Trauma Symptom Checklist for Children (TSCC; Briere, 1996), Children's Depression Inventory (CDI; Kovačs, 1992), Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000; Oldehinkel, 2000), Adolescent Dissociative Experiences Scale (A-DES; Armstrong, Putnam, Carlson, Libero, & Smith, 1997),Youth Self Report (YSR; Achenbach, 1991b; Verhulst, Van der Ende, & Koot, 1997), and Child Behavior CheckList (CBCL; Achenbach, 1991a; Verhulst, Van der Ende, & Koot, 1996). A Principal Component Analysis was performed using these (sub)scales. The Kaiser-Meyer-Olkin statistic showed sampling adequacy (KMO = 0.92). 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 ex- plaining 61.63% (see Table 1 for an overview of the loadings). Individual factor scores were calculated in order to estimate the general psychopathology factor (Caspi et al., 2014; Franke, 2016; Lahey, Applegate, Hakes, Zald, Hariri, & Rathouz, 2012; Lahey, et al., 2015).

Table 1

Factor loadings and factor score coefficients for the Trauma Symptom Checklist for Children (TSCC), Children's Depression Inventory (CDI), Revised Child Anxiety and Depression Scale (RCADS), Adolescent Dissociative Experiences Scale (A-DES),Youth Self Report (YSR), and Child Behavior Check List (CBCL), resulting from the Principal Component Analysis.

Subscale	Loading	Factor score coefficients
RCADS separation anxiety	0.79	0.09
RCADS social phobia	0.80	0.09
RCADS panic disorder	0.69	0.07
RCADS generalized anxiety disorder	0.74	0.08
RCADS obsessive compulsive disorder	0.79	0.09
RCADS depressive disorder	0.89	0.10
YSR internalizing problems	0.88	0.10
CBCL internalizing problems	0.63	0.07
TSCC_depression	0.92	0.10
TSCC_anxiety	0.75	0.08
TSCC_PTSD	0.87	0.09
TSCC_dissociation	0.83	0.09
TSCC_sexual concerns	0.56	0.06
A-DES	0.70	0.08

Factor score coefficients were calculated using the regression method (see Table 1). These coefficients were multiplied with the (sub)scale scores to obtain factor scores, which represent individual standardized scores on the GPF, based on their scores on the constituent questionnaires. All calculations were performed in SPSS with Principal Component Analysis. See Table S1 and Fig. S1 in the supplemental material for the mean psychopathology scores across the psychopathology groups.

2.4. Data acquisition and analysis

DTI data were collected using a Philips 3.0T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) with an eight-channel SENSE (Sensitivity Encoding) head coil. A single-shot echo-planar imaging sequence was used with the following scan parameters: re- petition time = 11,000 ms, echo time = 56 ms, flip angle = 90°, b- factor = 1000s/mm2, voxel dimensions = 2.3 mm isotropic, number of slices = 73, and no slice gap. DTI data were acquired along 32 directions, together with a baseline image having no diffusion weighting (b = 0). The total scanning time was ~7.5 min. DTI data is not publicly available.

The Oxford Centre for Functional MRI of the Brain (FMRIB) software library was used to preprocess (see supplemental material) and analyze DTI data. Voxel-wise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics (Smith, Jenkinson, Johansen-Berg, Rueckert, Nichols, Mackay, et al., 2006), part of FSL (Smith, Jenkinson, Woolrich, Beckmann, Behrens, Johansen-Berg, et al., 2004) First, FA images were created by fitting a tensor model to the diffusion data using FMRIB's Diffusion Toolbox. All subjects' FA images were then registered to a common space using nonlinear registration (see supplemental material). Next, the mean FA image was created and a mean FA skeleton was created which represents the centers of all tracts common to the group. Each subject's registered FA image was then projected onto this skeleton and the resulting data fed into voxel-wise group analysis.

We performed an ROI analysis in order to examine whether Ud was related to white matter integrity of regions that have previously been associated with childhood adversity, that is, the cingulum, corpus callosum (splenium, body, and genu) and the superior longitudinal fasciculus (Daniels, et al., 2013). A mask containing these three regions was created using the Johns Hopkins University (JHU) white matter atlas provided by FSL (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005). This mask was applied to the mean FA skeleton so that only voxels in the mean FA skeleton were included.

Voxel-wise statistical group analysis was performed using the General Linear Model and inference was performed with Randomise, (see supplemental material). Our model included the GPF as a continuous variable, Unresolved status (Ud versus non-Ud), and covariates of no interest were sex, IQ, and a composite score combining age and pubertal status. Unresolved status and GPF were included in the same model as the aim of the current study was to examine unique correlates of Ud and GPF. We assessed the contrasts 1) Ud > nonUd; 2) Ud < nonUd; 3) positive association with GPF; 4) negative association with GPF. Significant voxels were determined using Threshold-Free Cluster Enhancement (TFCE)(Smith, & Nichols, 2009) with family wise error correction for multiple comparisons ($p < .05$). In order to visualize the associations between GPF, Ud, and white matter integrity in graphs, FA values were extracted using fslmeants for voxels of regions that were significantly related to GPF or unresolved status. In addition to ROI analysis, we also performed whole brain analyses with the same contrasts.

FA is a non-specific marker for WMI, meaning that it gives no information about underlying tissue structure. Therefore, post-hoc analyses were performed to examine mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in the voxels that were significantly related to GPF or unresolved-disorganized attachment in the ROI analysis. Increases in MD and RD reflect demyelination (Alexander, Lee, Lazar, & Field, 2007; Horsfield, & Jones, 2002), whereas decreased AD values reflect axonal loss (Budde, Xie, Cross, & Song, 2009).

Table 2
Mean (SD) general psychopathology scores, age, PDS, and total IQ scores for the Ud versus non-Ud group.

	UD (*N*=12)		Non-UD (*N*=51)	
	M	SD	M	SD
GPF	0.23	1.03	-0.04	1.00
Age	15.58	1.68	15.47	1.75
Total IQ	101.67	7.99	103.63	8.98
PDS-scores	4.25	1.14	4.25	0.74

3. RESULTS

3.1. Clinical characteristics

Clinical assessment (as detailed in Supplemental material) revealed that the mean score found for post-traumatic symptoms was 34.49 (TSCC, SD 23.36; range 0–98), for depression 13.00 (CDI, SD 9.42; range 0–4), for anxiety 25.97 (RCADS, SD 14.93; range 0–70), for dissociation 1.39 (A-DES, SD 1.38; range 0–6.4), for self-report problems by youth 19.10 (YSR, SD 11.03; range 0–44) and for parent reported internalizing problems 13.99 (CBCL; SD 9.08; range 0–37).

Based on the AAI, 34.9% of the adolescents in this sample was classified as secure (N = 22), 46.0% as dismissive (N = 29), 19.0% as Unresolved-disorganized (Ud) (N = 12; CNTR N = 1, DEP N = 5, CSA-PTSD N = 6). Correlational analysis showed that there was no significant relation between Unresolved-Disorganized status and GPF (r = .21, p = .11). Adolescents with Unresolved-Disorganized status did not have higher GPF scores than adolescents without Unresolved-Disorganized status ($t(61)$ = -.84, p = .40). Neither was there a significant difference in puberty phase, age, or IQ between the Ud and non-Ud group (p's > .49, see Table 2) or in the number of male and female participants in the Ud and non-Ud group (Ud: women N = 11, men N = 1, non-Ud: women N = 42, men N = 9, $\chi^2(1)$ = .63, p = .38).

3.2. DTI results

3.2.1. ROI analysis

ROI analysis showed reduced FA values in the splenium in individuals with Unresolved loss and trauma (p < .05, FWE corrected for multiple comparisons, controlling for GPF, age, puberty status, IQ, and sex, see Fig. 1), but no association between Unresolved status and FA values was found in the cingulum or superior longitudinal fasciculus. Furthermore, ROI analysis revealed a negative association between GPF scores and FA values in the genu and body of the corpus callosum (p < .05, FWE corrected for multiple comparisons, controlling for Ud, age, puberty status, IQ, and sex), but not in the splenium

(see Fig. 2). Neither was there an association between GPF scores and FA values in the cingulum or superior longitudinal fasciculus.

3.2.2. Post-hoc analyses

Post-hoc analyses were performed to examine MD, RD, and AD in the voxels that were significantly related to GPF scores or unresolved loss and trauma in the ROI analysis. Unresolved status was not significantly related to MD, RD, and AD. However, we found a positive association between GPF scores and MD, RD, and AD in the body of the corpus callosum ($p < .05$, FWE corrected for multiple comparisons, controlling for Ud, age, puberty status, IQ, and sex). Additional analyses were performed to examine the relation between FA, MD, RD, AD and GPF and unresolved status in girls only because of sex differences in white matter integrity (Inano, Takao, Hayashi, Abe, & Ohtomo, et al., 2011). In the sample with only girls, the association between FA, MD, RD and GPF scores remained significant (controlling for Ud, age, puberty status, and IQ), but AD was not significantly related to psychopathology (see supplemental material). In addition, girls with an unresolved status showed significantly lower FA values than girls without Unresolved status, controlling for GPF, age/ puberty, and IQ ($F_{(1,48)} = 16.57$, $p < .001$).

3.2.3. Whole brain analysis

The whole brain voxel-wise analysis showed that adolescents who were classified as Unresolved had reduced FA values in the splenium and the inferior fronto-occipital fasciculus (IFOF) (whole brain analysis, $p < .05$, FWE corrected for multiple comparisons, controlling for GPF, age, puberty status, IQ, and sex) (see Fig. 1). Whole brain analysis did not reveal an association between GPF scores and FA values, controlling for Ud, age, puberty status, IQ, and sex.

4. DISCUSSION

The current study is the first to examine white matter correlates of unresolved-disorganized attachment and a measure of general psychopathology (GPF). With DTI, we showed that unresolved-disorganized attachment representation (Ud), i.e. unresolved loss or trauma as assessed with the AAI, and GPF are differentially related to abnormalities in a skeleton representation of white matter tracts. We studied a mixed group of adolescents with CSA-related PTSD, anxiety and depressive disorders and without psychiatric symptoms. We found that unresolved loss and trauma was associated with reduced FA values in the inferior fronto-occipital longitudinal fasciculus and the splenium of the corpus callosum, whereas our ROI analysis showed that GPF was associated with reduced white matter integrity in the

genu and body of the corpus callosum. This is consistent with our hypothesis that a GPF and Ud are differentially related to white matter abnormalities. Our findings provide evidence for a WMI correlate of Ud within the splenium of the corpus callosum ROI, and indicate that reduced white matter integrity in the genu and body is a trans-diagnostic biomarker of multiple psychopathological symptoms.

As white matter develops over at least three decades following birth, it is thought to be a brain structure prone to be influenced by psychopathology as well as childhood maltreatment (Andersen, 2003; Ayling, Aghajani. Fouche, & Van der Wee, 2012). Previous neuroimaging studies found white matter reductions in the corpus callosum in patients with several mental disorders, including PTSD, major de- pression, anxiety disorders, borderline personality disorder and bipolar disorder, for a review see (Thomason, & Thompson, 2011). However, corpus callosum reductions have been found in healthy individuals with a history of maltreatment, regardless of psychopathology (Teicher, & Samson, 2016). It has therefore been suggested that brain abnormalities in each diagnostic group may be restricted to a maltreatment ecophenotype (Teicher, & Samson, 2016). Indeed, a study by Bücker and col- leagues (2014) showed that corpus callosum reductions were associated with bipolar disorder, but were limited to patients with experiences of maltreatment. Thus, in the past few decades, neuroimaging studies may have confounded childhood trauma and psychopathological symptoms (Van der Kolk, 2016). Our findings are consistent with and extend this suggestion and indicate that white matter integrity of the splenium of the corpus callosum is specifically related to unresolved-disorganized attachment, which is a result of childhood loss or trauma, while psychopathology is linked to the genu and body of the corpus callosum.

The corpus callosum is crucial for interhemispheric communication and is the largest white matter tract in the human brain. Thickness of the corpus callosum has been associated with measures of IQ and problem solving (Luders, Narr, Bilder, Thompson, Szeszko, Hamilton, et al., 2007). Although the number of fibers in the corpus callosum is already determined at birth, structural changes continue to occur during childhood and adolescence due to axonal myelination, pruning, and redirection (Luders, Thompson, & Toga, 2010; Galaburda, Rosen, & Sherman, 1990; Luo, & O'Leary, 2005). The same degree of growth is, however, not the same for each subregion. Luders and colleagues (Luders et al., 2010) show a more pronounced growth of the splenium compared to other regions of the corpus callosum in children between 5 and 18 years of age. This is consistent with studies showing greater age-related changes in posterior regions than in anterior regions of the corpus callosum in other age groups (Giedd, Rumsey, Castellanos, Rajapakse, Kaysen, Vaituzis, et al., 1996; Chung, Worsley, Paus, Cherif, Collings, Giedd, et al., 2001). Accelerated development of the splenium during childhood and adolescence may lead to greater vulnerability to childhood stressors, which may explain the association with unresolved-disorganized

attachment related to loss and trauma in the current study. Rodent studies show that these callosal abnormalities are related to imbalance in oligodendrocyte proliferation in reaction to high cortisol stress levels due to chronic exposure to stress (Alonso, 2000; Miyata, Koyama, Takemoto, Yoshikawa, Ishikawa, Taniguchi, et al., 2011).

Our finding that reduced white matter integrity in the splenium of the corpus callosum and IFOF was specific for individuals with Ud (after controlling for the GPF) could be explained in alternate ways. One possibility is that reduced white matter integrity in the splenium of the corpus callosum and IFOF may reflect a pre-existing vulnerability factor that increases sensitivity to deleterious effects of childhood abuse, resulting in unresolved loss and trauma. In fact, reduced callosal size has been negatively associated with IQ and cognitive functioning (Luders, et al., 2007), which may in turn hinder recovery from trauma (Masten, Hubbard, Gest, Tellegen, Garmezy, & Ramirez, 1999; Masten, et al., 2008). Another ex- planation is that a secure parent-child relationship may help in resolving a traumatic experience and may stimulate recovery or compensatory changes. There is some evidence showing that resilience after childhood trauma is associated with compensatory neurobiological mechanisms (Galinowski, Miranda, Lemaitre, Paillere Martinot, Artiges, Vulser, et al., 2015). Future studies should therefore examine WMI in individuals with traumatic childhood experiences with longitudinal intervention designs in order to shed light on trauma- and attachment-related neurobiological changes and which interventions help best to recover in patients with versus without Ud.

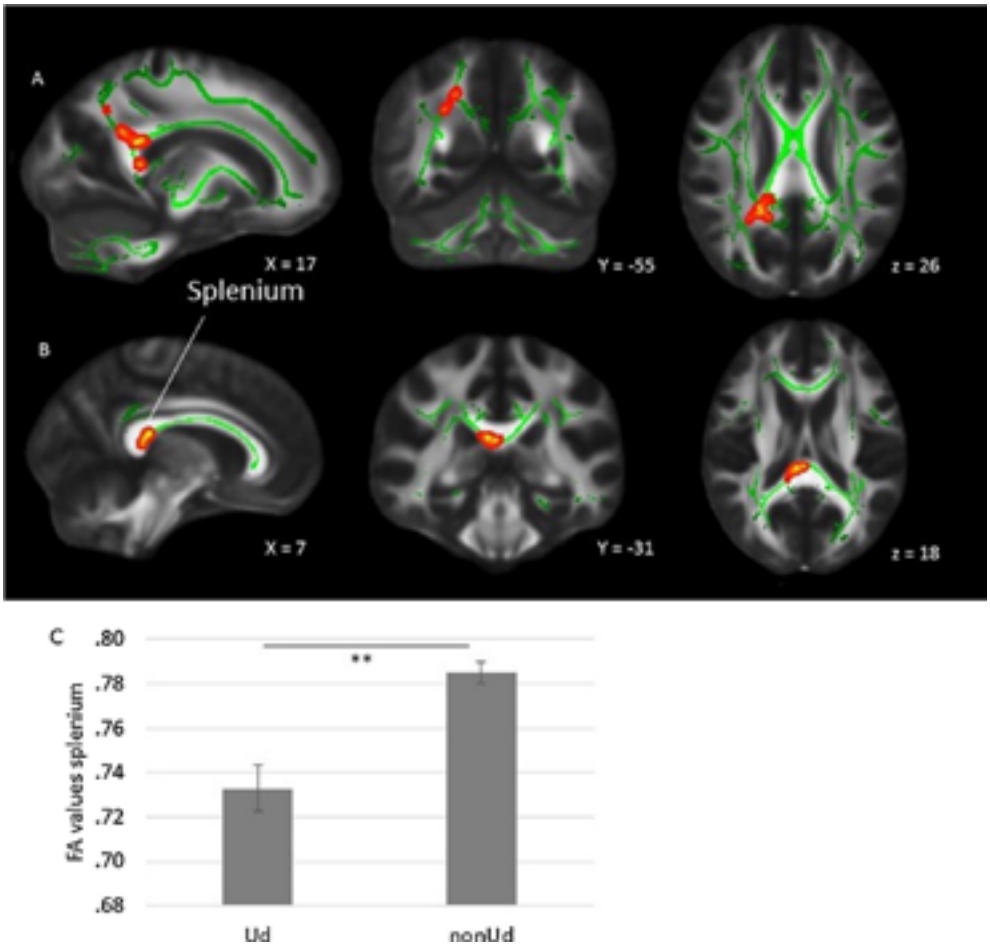

Fig. 1. Reduced FA values in individuals with Ud. Upper panel A: whole brain analysis; lower panel B: ROI analysis. Depicted in green is the white matter skeleton superimposed on the FMRIB58_FA_1 mm standard brain (gray). Depicted in yellow are the regions in which FA values were significantly lower in individuals with Ud (N = 12), compared to individuals without Ud (N = 51), $p < 0.05$, TFCE corrected. The results are thickened (in red) using the "tbss-fill" command. The right side of the image corresponds to the left hemisphere of the brain and vice versa. Panel C shows mean (SE) FA values of the subregion of the splenium that was significantly related to unresolved status (extracted for illustrative purposes) for individuals with and without Ud, controlled for TIQ, composite score age and puberty, sex, and GPF (** $p < .001$).

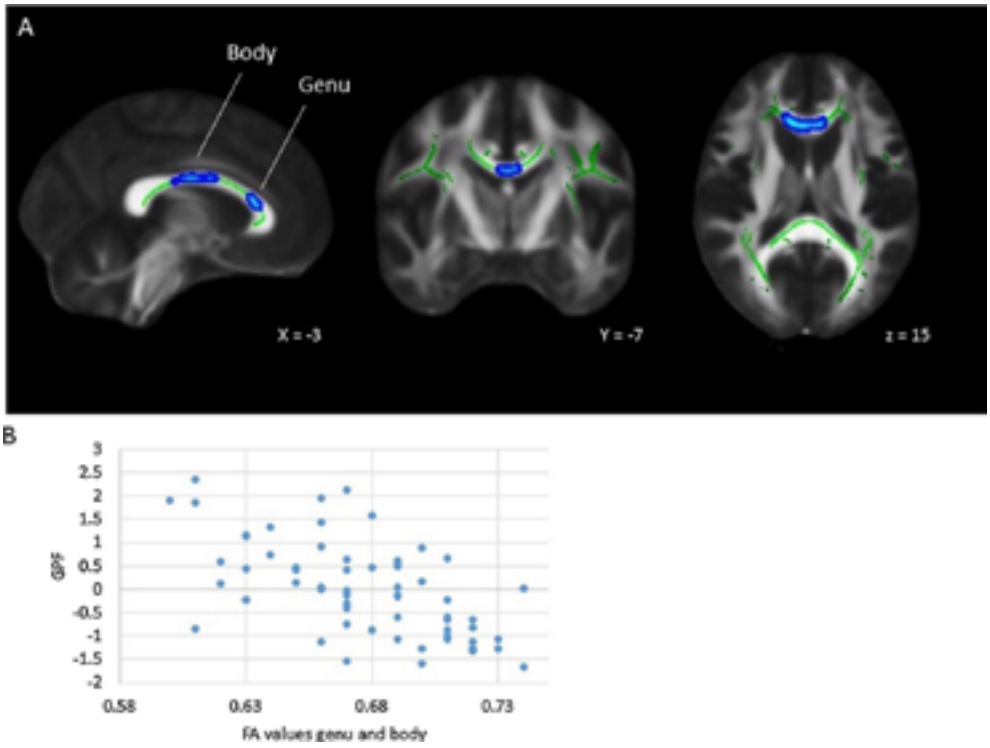

Fig. 2. Panel A: Negative association between general psychopathology factor (GPF) and FA values in the genu and body of the corpus callosum (ROI analysis). Depicted in green is the white matter skeleton superimposed on the FMRIB58_FA_1 mm standard brain (gray). Depicted in light blue are the regions in which FA values were significantly related to GPF, $p < 0.05$, TFCE corrected. Panel B: A scatterplot of extracted voxel values, for illustrative purposes only, showing the negative association between GPF and FA values in the genu and body.

When traumatic childhood attachment experiences remain unresolved it may account for reduced white matter integrity of the splenium, but abnormalities of the genu and body of the corpus callosum may be the consequence of a general vulnerability for psycho- pathology that might be a result of genetic influences (Patel, Kelly, Wright, Gupta, Arias-Vasquez, Perrone-Bizzozero, et al., 2015) or prenatal stress (Jensen, Pangelinan, Björnholm, Klasnja, Leemans, Drakesmith, et al., 2018). Our findings indicated that the smaller FA values in the genu and body were due to increases in AD, RD, and MD. RD and MD are known to reflect demyelinization (Alexander et al., 2007), whereas the positive association between GPF and AD values may reflect altered axonal integrity (Budde et al., 2009). However, caution with interpretation of these WMI indicators is warranted because causality still has to be established.

Some limitations should be mentioned. The generalizability of results may be limited due to the relatively small sample size and the restricted ranges of age, IQ, and gender. Future studies should examine neural correlates of unresolved loss and trauma and a GPF in a more diverse sample with a broader range of psychopathological symptoms, for example including more externalizing symptoms. In addition, the study was cross-sectional which makes conclusions regarding causality speculative. Furthermore, we did not make use of fieldmap corrections for susceptibility artifacts. Lastly, although studies with different age categories (children, adolescents, adults) and countries using different report sources (self-report, parent or teacher report) all confirm the existence of a GPF (see Caspi, & Moffitt, 2018 for a review), it is still unclear what causes the correlation among disorders and symptoms. The GPF has been compared with the general factor in intelligence (the "g" factor) (Caspi, & Moffitt, 2018), which accounts for correlated scores on different cognitive tests, whereas more domain-specific factors explain shared variance among smaller subsets of tests. A similar bifactor model specifying both a general factor and specific internalizing and externalizing factors has been proposed for the structure of psychopathology, although alternative models for the correlation among symptoms should also be tested (Caspi, & Moffitt, 2018). The findings of the current study may suggest that GPF has a neurobiological basis, similar to the "g" factor (Duncan, Seitz, Kolodny, Bor, Herzog, Ahmed, et al., 2000). However, it is still unclear what GPF exactly means and whether it is a g like *causal* factor. Caspi and Moffitt therefore call for a neuroimaging approach in the investigation of GPF. Exploring brain correlates of GPF could potentially be a step forward in the discovery of biological psychiatry as it may be a new route to identify the causes shared by psychiatric disorders (Caspi, & Moffitt, 2018).

5. CONCLUSIONS

In conclusion, we showed that a GPF and unresolved loss or trauma have unique associations with white matter integrity. Our findings indicate that reduced white matter integrity in the genu and body is a trans-diagnostic biomarker of multiple psychopathological symptoms, which may be related to comorbidity and presence of symptoms that transcend specific psychopathological diagnoses. In contrast, reduced white matter integrity of the splenium and IFOF seem to reflect consequences of unresolved childhood loss or other trauma and may account for heterogeneity within diagnostic categories. Together, these findings suggests that a dimensional approach may complement the traditional classificatory approach in clinical research and practice.

DISCLOSURES

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2018.10.014.

SUPPLEMENTAL MATERIAL CHAPTER 5 (as published)

A.1 Supplemental material

A.1.1 Introduction

It should be noted that the combination of PTSD with experiences of interpersonal adversities such as childhood trauma warrants a diagnosis of complex PTSD [A.1] or according to the American Psychiatric Association 'PTSD with dissociative symptoms' [A.2] and shows a different clinical presentation (e.g. dissociation, behavioral symptoms, emotional dysregulation) than PTSD without childhood trauma.

A.1.2 In- and exclusion criteria EPISCA

The adolescents were part of the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents), a longitudinal study in which adolescents were followed over a six-month period. The adolescents with and without clinical symptoms underwent a diagnostic assessment and an MRI scanning protocol at three points in time (at baseline, 3 months, 6 months; Van den Bulk et al., 2013). AAI (Hesse, 2016) and clinical characteristics of the group and neuroimaging data were reported previously (e.g. Van Hoof et al., 2015; A.3).

Related to the neuroimaging protocol all participants 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 [A.4](WISC-III) or Adults [A.5](WAIS-III), 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). The adolescents with childhood sexual abuse (CSA) were recruited at two psychotrauma centres of child and adolescent psychiatric institutes in the Leiden region in the Netherlands. Inclusion for CSA was having experienced sexual abuse during their life time more than once by one or more perpetrators in- or outside the family, and being referred for treatment at the psychotrauma centre. The 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 [A.6] and no history of CSA (see [A.7, A.8, A.9]. Exclusion criteria for both clinical groups 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) amphetamine medication on the day of scanning or current use of psychotropic medication other than stable use of SSRI's; and 3) current substance abuse. The non-clinical adolescents were recruited through local advertisement, with the following inclusion criteria: no clinical scores on validated mood and behavioral questionnaires or past or current DSM-IV classification, no history of traumatic experiences and no current

psychotherapeutic intervention of any kind.

To objectify any abuse or neglect as well as risk for functional impairment and morbidity [A.10], 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. Most adolescents with CSA (87%) reported during the AAI serious and/or longstanding physical sexual contact including repeated or group rape, in 63.6% by a person other than an attachment figure. In addition, 36.4% of the CSA group also experienced physical abuse, 22.7% by a person other than an attachment figure, 9.1% by an attachment figure, in one case by both. Sexual abuse was reported to the police in 60.9%, child welfare was involved in 56.5% of the cases, while 17.4% had a child protection measure (family custody). None of the participating non-clinical adolescents and those with anxiety and/or depressive disorders had experienced CSA, but they did mention physical and emotional abuse, bullying, and other incidents. Non-clinical adolescents had not been involved with police, child welfare or child protection, while 23% of the adolescents with anxiety and/or depressive disorders had child welfare involvement.

From the original sample of 82 adolescents, three participants were excluded due to technical problems, i.e. failed voice and video recording (one adolescent with CSA), unintelligible recording (one non-clinical adolescent), incorrect interview technique (one non-clinical adolescent). Two participants (one non-clinical adolescent and one adolescent with anxiety/depressive disorder) were excluded because they refused the AAI because of the interview itself. Of the *N*=77 in the remaining sample, 86% were girls. All CSA adolescents fulfilled the DSM-IV criteria for PTSD, according to the ADIS [A.6], however one adolescent missed a point on the interference score to fully qualify for PTSD. SSRI's were used by four of the adolescents with CSA and two of those with anxiety and/or depressive disorder.

A.1.3 Questionnaires and tests

A.1.3.1 YSR: Youth Self-Report [Achenbach, 1991] and CBCL: Child Behavior Checklist (Achenbach, 1991), with Dutch translations by Verhulst and colleagues (Verhulst, Van den Ende, & Koot, 1996; 1997). The YSR and CBCL are self-report questionnaires using a 3-point scale to assess social-emotional and behavioral problems in adolescents. The CBCL is the questionnaire for parents, the YSR for adolescents 11 years and older. There are 9 subscales and 3 main scales (total score, externalizing problem score and internalizing problem score) In this study we used the internalizing problem scores of the YSR and CBCL.

A.1.3.2 ADIS: The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS C/P) [A.7] are semi structured interviews designed specifically for DSM-IV classification of anxiety and other related disorders such as depression and PTSD in children and adolescents. Strong test-retest reliability was shown for combined and individual ADIS-C/P

diagnoses. Intra-class correlations were excellent. Interrater reliability between child and parent versions of the ADIS was reported to be excellent. In this study, the ADIS was applied to all participants by certified trained clinicians and researchers.

A.1.3.3 TSCC: The Trauma Symptom Checklist for Children (TSCC)(Briere, 1996) is a 54-item self-report for children and adolescents aged 8-17, which measures trauma-related symptoms. In the present study, only the TSCC total score was used as subscales overlapped significantly, with a Cronbach's alpha coefficient of .96.

A.1.3.4 A-DES: The Adolescent Dissociative Experiences Scale (Armstrong, et al., 1997) is a self-report for adolescents aged 11-18 measuring possible dissociation. The A-DES has good reliability and validity. In this study, the mean total score on the A-DES was used as a measure of dissociation, which had a Cronbach's alpha coefficient of .95.

A.1.3.5 CDI: The Children's Depression Inventory (Kovačs, 1992) is a 27-item, self-rated, depression symptoms-oriented scale suitable for youths aged 7 to 17. The CDI has good psychometric properties of validity and reliability (Cronbach's alpha .71 to .86) [A.11], though discriminant validity has been subject to discussion. In this study, the total CDI score had a Cronbach's alpha coefficient of .93.

A.1.3.6 RCADS: The Revised Child Anxiety and Depression Scale (Chorpita, et al., 2000; Oldehinkel, 2000) is a self-rated, anxiety and depressive symptoms-oriented 47-item-scale for children aged 6 to 18. Items are scored based on a four-point scale and grouped as depressive disorder, generalized anxiety disorder, social phobia, anxiety disorder NAO and obsessive-compulsive disorder. Chorpita and colleagues (2000) reported evidence for validity and reliability of the RCADS in clinical and healthy control adolescents. In this study, the total score of the RCADS was used as a measure for severity of experienced symptomatology (Cronbach's α = .95). Besides, the depression scale (Cronbach's α = .89) and the cumulative anxiety scales (Cronbach's α = .94) were used.

A.1.3.7 AAI: the Adult Attachment Interview (Main, Kaplan, & Cassidy, 1985) is coded according to the DEFU system (Hesse, 2016): dismissive (Ds), preoccupied (E), secure-autonomous (F), unresolved-disorganized (Ud). Ds, E and F classifications are organized forms of attachment, while Ud represents disorganized forms of attachment. In organized attachment representations, there is one coherent mental strategy with regard to attachment figures, either secure-autonomous (F) or insecure (Ds or E). In disorganized attachment-representation different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory. A high to moderate coherence of the narrative is seen in secure-autonomous (F) attachment interviews in which the interviewee

can give ample evidence for general evaluative statements made regarding attachment relationships and attachment experiences whether good or bad. In case of unresolved loss or trauma, the attachment representation is labeled unresolved-disorganized (Ud). This classification can be given in addition to a Ds, E or F classification. A fifth category, cannot classify (CC), is used when the interviewee presents contrasting attachment strategies for attachment figures in the course of the interview resulting in very low coherence of narrative. In most studies U and CC are combined in one category, Unresolved-disorganized. Coherence of mind and unresolved for loss or trauma (Ulosstrauma) are two dimensional scales of the AAI which are assigned scores rated between 1-9. Lowest score for Coherence means there is little or no coherence of mind, highest score for Ulosstrauma means there is high impact of loss or trauma.

The AAI has been administered to more than 10,000 respondents since its development (Bakermans-Kranenburg, & Van IJzendoorn, 2009). The AAI is found to have remarkably good test-retest, discriminant reliability as well as predictive validity. In this study, the AAI was administered by MJvH and CIG, verbatim transcribed according to protocol, and coded by GK (trained by Diane and Dave Pederson), and SdH (trained by Diane and Dave Pederson, and June Sroufe). Both reached intercoder reliability standards in the AAI classification system. Ten cases were also coded by MJBK. Interrater agreement in this sample was 80% for F-nonF, 90% for Ud-nonUd and 70% for four-way classification (DEFU). Kappa's for coding F-nonF (.59) and Ud-nonUd (.62) were both statistically significant and reasonable to satisfactory.

We focused our analyses on the unresolved versus non-unresolved (non-Ud) comparison because the distribution of continuous unresolved scores was skewed and because our previous study revealed structural and functional brain abnormalities in individuals with unresolved versus without unresolved classification [A.13].

A.1.3.8 WISC-III-NL and WAIS-III: Short versions of the Wechsler Intelligence Scale for Dutch Children aged 6-16 years, WISC-III-NL [A.4, A.14] and adolescents aged 16 and above and adults, the Wechsler Adult Intelligence Scale, WAIS-III [A.5] were used. They consisted of six subtests: picture completion, similarities, picture arrangement, arithmetic, block design and comprehension. In earlier studies, these subtests were found to give a valid and reliable IQ estimate (reliability coefficient > .90)[A.15].

A.1.3.9 PDS: The Pubertal Development Scale (Petersen, Corckett, Richards, Boxer, 1988) measures the actual level of physical development during puberty. It is a 5-item self-report that measures items like body growth, body hair, skin changes for both sexes. For boys, there are items on beard growth and voice changes. For girls, there are items on breast growth and menstrual bleeding. Items can be answered on a 5-point scale with a total score range of 0-20. Internal consistency is adequate for both sexes, consistent across samples, while

the predictive validity of the PDS is satisfactory [A.16]. The following distribution was found for the current sample: Prepubertal (N = 1), early pubertal (N = 1), midpubertal (N = 4), late pubertal (N = 22), postpubertal (N = 25). Information about pubertal status was missing for 10 participants. For these participants, pubertal status was imputed using gender and age.

A.1.4 Statistical analysis

A.1.4.1 Preprocessing. The Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) version 5.0.9 was used to preprocess and analyze DTI data. First, non-brain tissue was removed, using the Brain Extraction Tool [A.17]. DTI data were corrected for distortion and motion artifacts, induced by eddy currents, using affine registration of each diffusion weighted image to the b=0 reference image.

A.1.4.2 Analysis. Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics, (Smith, et al., 2006). First, FA images were created by fitting a tensor model to the diffusion data using FMRIB's Diffusion Toolbox, and then brain-extracted using BET [A.17]. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT [A.18, A.19], which uses a b-spline representation of the registration warp field [A.20]. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. Voxel-wise statistical group analysis was performed using the General Linear Model and inference was performed with Randomise, FSL's tool for nonparametric permutation inference on neuroimaging data [A.21].

A.1.5 RESULTS

The association between GPF scores and FA, MD, RD and remained significant in the sample with only girls (controlling for Ud, age, puberty status, and IQ, FA: $F_{(1,48)} = 22.31$, $p < .001$, MD: $F_{(1,48)} = 5.17$, $p < .05$, RD: $F_{(1,48)} = 6.86$, $p < .05$), but AD was not significantly related to psychopathology ($F_{(1,48)} = 2.34$, $p < .12$)).

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Table A.1. Mean (SD) general psychopathology scores for the anxiety/depression, CSA-related PTSD, and control group, and Ud versus non-Ud group.

Group	N	M	SD	range
Anxiety/depression	26	0.45	0.86	-0.88 – 2.34
CSA-PTSD	18	0.39	0.87	-0.86 – 1.90
Control	19	-0.95	0.54	-1.66 – 0.12
Ud	12	0.23	1.03	-1.31 – 1.90
Non-Ud	51	-0.04	1.00	-1.66 – 2.34

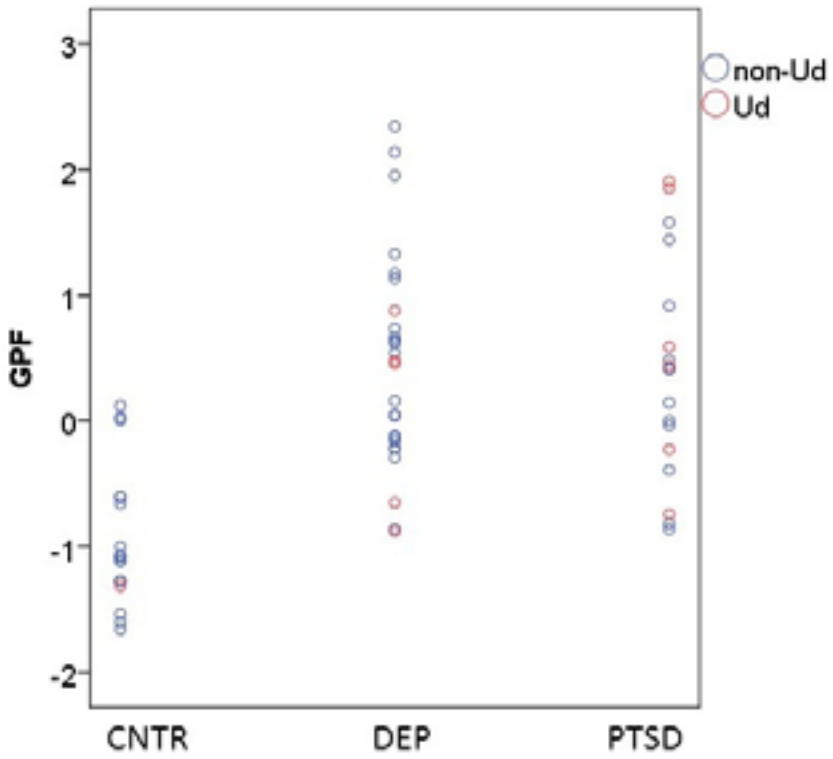

Figure A.1. Scatterplot of general psychopathology scores for the Ud, non-Ud, anxiety/depression (DEP), PTSD, and control group (CNTR).

6

Unresolved-disorganized attachment adjusted for a General Psychopathology Factor associated with atypical amygdala resting-state functional connectivity

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ABSTRACT

Background: Recent research has identified a general psychopathology factor (GPF), which explains overlap in presentation of psychopathological symptoms. Unresolved-disorganized attachment (Ud) is another transdiagnostic risk factor that may be relevant to explain differences in patient characteristics within diagnostic classifications.

Objective: In the current study, we examined unique relations of resting state functional connectivity with Ud and GPF.

Method: Resting state functional connectivity (RSFC) data were collected from a mixed group of adolescents (*N* =74) with and without psychiatric disorder, part of the Emotional Pathways' Imaging Study in Clinical Adolescents study. Ud was measured using the Adult Attachment Interview (AAI). Associations between Ud, GPF, and RSFC of the amygdala and anterior cingulate cortex (dACC) and with amygdala- medial frontal connectivity were examined.

Results: Ud was positively associated with greater functional connectivity between the left amygdala and the left lateral occipital cortex, precuneus, and superior parietal lobule. Furthermore, Ud was negatively associated with left amygdala-medial frontal cortex connectivity. GPF was not significantly associated with dACC or amygdala connectivity.

Conclusions: Atypical amygdala connectivity may reflect a vulnerability factor rather than a biomarker of psychopathology. The unique association of Ud and amygdala RSFC connectivity, adjusted for a GPF, across participants with and without various classifications of psychopathology illustrates that dimensional approaches based on the AAI may complement psychiatric classifications in clinical research and practice.

INTRODUCTION

Psychopathology and unresolved-disorganized attachment (Ud; Bowlby, 1969; 1980; Hesse & Main, 2000) are different yet interrelated clinical constructs (Lyons-Ruth, Pechtel, Yoon, Anderson, & Teicher, 2016; Patalay et al., 2015; Riem, Van Hoof, et al., 2019) that can impair adolescent functioning. Ud is characterized by signs of disoriented and/or dissociated, disorganized narratives in case of loss or abuse, that indicate simultaneous or sequential contradictory strategies to deal with the loss or other trauma, and often display a lack of reflective functioning (Fonagy, Steele, Moran, Steele, & Higgitt, 1991). Ud is thought to be a transdiagnostic risk factor that is relevant across psychopathologies (Lyons-Ruth & Jacobvitz, 2016; Riem, Van Hoof, et al, 2019) and accounts for patient characteristics not included in diagnostic categories. The General Psychopathology Factor (GPF), which represents lesser-to- greater severity of psychopathology across disorders, has also been identified as a transdiagnostic factor that represents clinical presentations on a continuum, contrary to diagnostic categorical classifications such as in the DSM-5 which are not optimal for research, partly because of the overlap between diagnostic categories and difficulty classifying individual patients (Caspi et al., 2014; Patalay et al., 2015; Tackett et al., 2013). The Ud and GPF transdiagnostic factors, however, may provide a useful measure for clinical research, particularly for neuroimaging studies of brain function, however, this prospect has not yet been fully explored.

Early life stress and adversity have negative consequences for physical and mental health, attachment and psychosocial adjustment across the lifespan (Anda et al., 2006; Felitti et al., 1998). As to mental health, experiences of loss and abuse increase the risk for psychopathology, including posttraumatic stress disorder (PTSD) and depressive disorders (Cloitre et al., 2009; 2014; Schmaal, et al., 2016). Neuroimaging studies of child and adult psychopathology are increasingly investigating the effects of early life stress on psychopathology, however they have neglected the role of attachment. Child maltreatment and neglect, particularly from parental perpetrators, may lead to Ud, which can be measured in patients as a disorganized/disoriented, incoherent, state of mind when narrating childhood attachment experiences (Bowlby, 1969;1980; Hesse & Main, 2000). Current and future attachment relationships and the transition to adult functioning is negatively impacted by Ud (Hesse, 2016). A meta-analysis of over 200 adult attachment studies showed that the prevalence of Ud within a mixed clinical sample was 43% , which was significantly higher than in normative groups (Bakermans-Kranenburg & Van IJzendoorn, 2009) evidence that Ud is a trans-diagnostic risk factor that may increase vulnerability to various psychiatric disorders. Furthermore, Ud has a higher representation among individuals with a history of abuse, serious other trauma or loss (Hesse, 2016; Hesse & Main, 2000).

In addition to negative effects on attachment relationships, early life adversity is associated with neurobiological alterations that may interfere with brain development (Rinne-Albers, Van der Wee, Lamers-Winkelman, & Vermeiren, 2013). Specifically, child abuse and neglect has been associated with altered resting state functional connectivity (RSFC) of the amygdala and dorsal anterior cingulate cortex (dACC), as well as attenuated cognitive control through the medial prefrontal cortex (Wang et al., 2014).

The amygdala and dACC are considered crucial brain structures in detecting and responding to threats (Graham & Milad, 2011; Phelps & LeDoux, 2005) and show heightened reactivity to emotionally negative stimuli in individuals with a history of maltreatment (Teicher , Samson, Anderson, & Ohashi, 2016). The dACC amplifies this fear response to threat through excitation of the amygdala, whereas the medial prefrontal cortex inhibits amygdala activation through a negative feedback cycle (Feng, Feng, Chen, & Lei, 2014; Schuwerk et al., 2014; Teicher et al., 2016), thereby reducing anxiety and the intensity of emotional reactions. However, there is evidence for impaired inhibition of the amygdala by the medial prefrontal cortex in individuals with a history of adversity (Wang et al., 2014). Impaired emotion regulation related to amygdala and dACC hyperactivation may in turn increase risk for the development of psychopathology.

Indeed, heightened activation of the amygdala and dACC has been implied in PTSD (Lyons-Ruth et al., 2016; Shalev, Liberzon, & Marmar, 2017; Vermetten & Lanius, 2012) and several other psychiatric disorders known to be related to childhood adversity, such as depression and anxiety (Grant et al., 2014; Strawn et al., 2012). For example, in anxiety and depressive disorders the dACC was shown to be involved in location-specific, fear network function and fear recovery (Lang et al., 2009; Mechias, Etkin, & Kalisch, 2010; Suarez-Jimenez et al., 2018) Interestingly, a meta-analysis observed abnormalities in the fronto-amygdala circuitry in individuals across the internalizing spectrum, possibly reflecting a general emotional disturbance that is shared across diagnostic classifications (Marusak et al., 2016).Thus, disruptions in the fronto-amygdala circuitry seem to play a general role in psychopathology and may underlie high levels of co-morbidity. It may therefore be a potential neural substrate underlying GPF. Another possibility is, however, that these resting state functional abnormalities are not a true biomarker of general psychopathology, but instead are the result of abuse experiences. Multiple studies provide evidence that brain abnormalities in maltreated individuals are not directly linked to psychopathology because they are found in maltreated individuals with psychopathology but also in resilient individuals with a history of maltreatment but without psychopathology (for a review see Teicher et al., 2016). This raises the question whether abuse experiences, Ud, and psychopathology have unique patterns of altered RSFC.

In the current study, we will therefore examine whether Ud and GPF show unique amygdala and dACC RSFC. We were specifically interested in amygdala and

dACC connectivity as previous research points to altered connectivity in these regions in maltreated individuals as well as in individuals with psychopathology (Teicher et al., 2016). As previous studies indicate that fronto-amygdala circuitry disruptions are shared by psychiatric disorders (Marusak et al., 2016), we investigated unique associations between Ud, GPF and connectivity with the amygdala and the medial frontal cortex as an a priori connection of interest. Ud was assessed with the 'gold standard' AAI (Cassidy, 2016; Hesse, 2016). ·It should be noted that Ud represents a *current* state of mind with respect to childhood attachment experiences, and is derived exclusively from the language used in the narrative about potentially traumatic experiences. Despite low levels of reflective functioning that might obscure self-reports on adverse experiences, the incoherence of the narrative may uncover mental distress not immediately accessible to the adolescent. Our study, therefore, adds to previous neuroimaging studies that examined neurobiological effects of abuse using retrospective self-report questionnaires, without taking into account whether the narrative about the trauma was (dis-)organized. We hypothesized that Ud and GPF would show unique RSFC of the amygdala and dACC.

METHODS

Design and sample

Seventy-four participants from the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA) study (Van Hoof, Van Lang, Speekenbrink, Van IJzendoorn, & Vermeiren, 2015) (*N*=77) were involved in the current study. They were recruited from mental health centers and local advertisements according to specified in- and exclusion criteria (Van den Bulk et al., 2013; Van Hoof et al., 2015)(see supplemental material) and available coded AAI (Hesse, 2016). Drop-out was due to anomalous MRI findings (*N*=2), technical scanning problems or poor imaging data quality (*N*=2). Within this group there were 21 adolescents with childhood sexual abuse (CSA), 28 adolescents with anxiety and/or depressive disorders (DEP) and 25 non-clinical adolescents (CNTR). Unresolved loss or trauma (continuous and categorical) was determined with the AAI coding system (Hesse, 2016). Information about pubertal status was missing for 10 participants. For these participants, pubertal status was imputed using sex and age.

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. P08.175).

Procedure

After adolescents and their parents had given assent and consent to participate in the EPISCA study they filled out questionnaires, usually at home, and were tested for IQ and interviewed for DSM-IV classification and attachment representation at the clinic in separate appointments. Scanning was usually performed on separate days, depending on availability of the scanner.

Adult Attachment Interview

The AAI (Hesse, 2016; see supplemental material) is a one hour long semi-structured interview, validated for adolescents. The AAI asks how the interviewee thinks about the relationship with parents or other primary caregivers in his or her youth, how these experiences have influenced him or her, how the actual relationship with parents or other primary caregivers is and whether there were any experiences of severe illness, separation, fear, trauma or loss. The interviewee is asked to give specific examples supporting each evaluation. Not its autobiographical content, but rather the coherence of the narrative matters.

After transcription and coding of the AAI according to the manual (Hesse, 2016) by a certified coder, an attachment representation classification can be given. In organized attachment representations there is one coherent mental strategy with regard to attachment figures, either secure-autonomous or insecure. In unresolved-disorganized attachment representations different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory, as becomes apparent when coding the narrative. A scale score for Unresolved loss or trauma of 5.5 or above also renders a classification unresolved-disorganized (Hesse, 2016; see supplemental material and manual). In the current study, unresolved trauma was examined as a continuous variable to enhance statistical power. A log transformation was applied because the distribution was skewed. Ud being hypothesized to be a trans-diagnostic factor for psychopathology like no other (in)secure attachment representation (Cassidy, 2016; Hesse, 2016), we choose to use Ud in our connectivity analyses.

General Psychopathology Factor

To estimate the effects of psychopathology separate from Ud we decided to use a general psychopathology factor. The general psychopathology factor represents lesser-to-greater severity of psychopathology that 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). The general psychopathology factor has also been shown a significant Single Nucleotide Polymorphism (SNP) heritability of 38% (SE=0.16, p=.008) (Neumann et al., 2016). The use of the general psychopathology factor was also shown to be valid in girls (Lahey et al., 2015) and in young adolescents (Patalay et al., 2015). The general psychopathology factor was estimated for our sample using parent and self-report measurements for behavioral and emotional problems in children and adolescents: Youth Self Report (YSR; Achenbach, 1991a), Child Behavior CheckList (CBCL; Achenbach, 1991b), Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000), Trauma Symptom Checklist for Children (TSCC; Briere, 1996), Children's Depression Inventory (CDI; Kovačs, 1992), Adolescent Dissociative Experiences Scale (A-DES; Armstrong, Putnam, Carlson, Libero, & Smith, 1997). Principal Component Analysis was performed using these (sub)scales. 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 Table S2 for an overview of the loadings). Individual factor scores were calculated in order to estimate the general psychopathology factor (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). Factor score coefficients were calculated using the regression method. These coefficients were multiplied with the (sub)scale scores to obtain factor scores, which 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. See Table S1 and Figure S1 in the supplemental material for the mean psychopathology scores across the psychopathology groups.

Image data acquisition

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

Resting-state functional MRI data were acquired, using T2*-weighted gradient-echo echo-planar imaging: 160 whole-brain volumes; repetition time 2200 ms; echo time 30 ms; flip angle 80°; 38 transverse slices; no slice gap; field of view 220 mm; in-plane voxel size 2.75x2.75 mm; slice thickness 2.72 mm; total duration of the resting-state run 6 min. Participants were instructed to lie still with their eyes closed and not to fall asleep.

Statistical analysis

Pre-statistics. The FEAT module of the FSL software (FMRIB's Software Library, http://www.FMRIb.ox.ac.uk/fsl; Smith et al., 2004) was used to apply the following pre-statistics processing: motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal using BET (Smith, De Stefano, Jenkinson, Matthews, 2001), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 6.0 mm, and high-pass temporal filtering (highpass filter cutoff = 100.0 s). Functional scans were registered to the T1- weighted images, which were registered to standard space in order to calculate the transformation matrix for the higher-level group analysis (Jenkinson et al., 2002).

Functional connectivity analysis. A seed based correlation approach was used for the current study (Murphy & Fox, 2017). We created binary masks of the left and right amygdala and left and right dACC. Coordinates of the seed regions were similar to a previous study examining resting-state connectivity in relation to depressive symptoms in partly the same sample (amygdala: x = ±22; y = -6; z = -16; dACC: x = ±6; y = 18; z = 28)(Pannekoek et al., 2014b). Masks were created as spheres (4 mm radius, similar to Pannekoek et al., 2014b) centered on these coordinates. After transforming the masks to native space, the mean time series for each participant were extracted from the voxels in the seed regions. The times series of the left and right amygdala were then entered as regressors in a GLM to examine amygdala connectivity and the left and right dACC time series were entered as regressors in a separate GLM to examine dACC connectivity. In addition, CSF, white matter and the global signal were added as regressors to the model in order to reduce the influence of artifacts caused by physiological signal sources on the results (Fox & Raichle, 2007).

The temporal derivative of each regressor was added to the model similar to Pannekoek et al., 2014b, resulting in 10 regressors in each model. Motion parameters were also added to the model. Contrasts of interest were the parameter estimates corresponding to the regressor of the left and right amygdala and left and right dACC, which represents functional connectivity with that region. First-level analyses were performed in native space. These first-level contrast images and the corresponding variance images of connectivity with each seed region were transformed to standard space and submitted to second-level mixed-effects group whole brain analyses using FMRIB's Local Analysis of Mixed Effects (FLAME). In the second-level analysis, the positive and negative correlation between amygdala and dACC connectivity and Unresolved loss and trauma score and GPF was assessed. Unresolved status and GPF were included in the same model as the aim of the current study was to examine unique correlates of Ud and GPF. Composite score age and pubertal status, sex, and IQ were confound regressors in the model. Non-parametric permutation inference was conducting using FSL's randomise with threshold- free cluster enhancement (TFCE) to obtain family-wise error corrected clusters ($p<.05$)(Winkler, Ridgway, Webster, Smith, &

Nichols, 2014). Finally, because of the prominence of the medial frontal cortex in previous studies of social-emotional processing (Crone, 2014; Waugh, Lemus, & Gotlib, 2014) and general psychopathology (Marusak et al., 2016), connectivity between the amygdala and a medial frontal cortex ROI was examined. The left and right medial frontal cortex was anatomically defined using the Harvard–Oxford cortical atlas (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and used as an inclusive mask for the analysis of amygdala connectivity.

RESULTS

Clinical sample characteristics

Mean age of the participants was 15.42 years (SD 1.67, range 12-20), and a total mean IQ of 103.28 (SD 8.89, range 81-119); 85.1% (*N*=63) of the participants were female. As to cultural background, 1.4% were Asian (CSA *N*=1), 93.2% were Caucasian (CSA *N*=20, DEP *N*=25, CNTR *N*=24), 1.4% were Surinamese (DEP *N*=1), 2.7% were Latin-American (DEP *N*=2). Four adolescents (5.4%; CSA *N*=2, DEP *N*=2) were on stable SSRI use (three fluoxetine, one sertraline). Puberty stage was assessed according to the following categories using the Pubertal Development Scale (PDS)(Petersen, Crockett, Richards, & Boxer, 1988): Prepubertal (CSA *N*=1), early pubertal (DEP: *N*=1), midpubertal (CNTR *N*=6, DEP *N*=1), late pubertal (CSA *N*=10, DEP *N*=14, CNTR *N*=13), postpubertal (CSA *N*=10, DEP *N*=12, CNTR *N*=6).

Clinical assessment of this sample (as detailed in supplemental material) revealed that the mean score found for post-traumatic symptoms was 34.13 (Briere, 1996; TSCC; SD 22.72; range 0-98), for depression 12.84 (Kovačs, 1992; CDI; SD 9.17; range 0-40), for anxiety 25.88 (Chorpita et al., 2009; RCADS; SD 14.96; range 0-70), for dissociation 1.44 (Armstrong et al., 1997; A-DES mean total score; SD 1.42; range 0-6.37), for self-report problems youth 18.78 (Achenbach, 1991b; YSR; SD 11.13; range 0-44) and for reported internalizing problems by parents 13.60 (Achenbach, 1991a; CBCL; SD 9.68; range 0-42).

Unresolved loss or trauma score (AAI)

The AAI (Hesse, 2016) mean score for unresolved loss or trauma in this sample was 2.42 (SD 1.81; range 1-8). Based on the AAI (Cassidy, 2016; Hesse, 2016) 36.5% of the adolescents were classified as secure (CNTR *N*=13, DEP *N*=11, CSA *N*=3), 41.9% as dismissive (CNTR *N*=11, DEP *N*=11, CSA *N*=9), 21.6% as Unresolved-disorganized (Ud) (CNTR *N*=1, DEP *N*=6, CSA *N*=9). No adolescents in this sample were classified as preoccupied (Cassidy, 2016; Van Hoof et al., 2015). See Table 1 for the mean GPF, age, IQ,

and PDS scores for the Ud and non-Ud groups and see Table S1 for general psychopathology scores for the separate groups (CSA-PTSD, internalizing, control and U versus nonU). There was no significant correlation between Ud and GPF (Pearson $r = .203$, $p = .083$, covariance 0.84).

Table 1. Mean (SD) general psychopathology scores (GPF), age, pubertal status (Pubertal Development Scale (PDS), and total IQ scores for the Ud versus non-Ud group. *$p < .05$

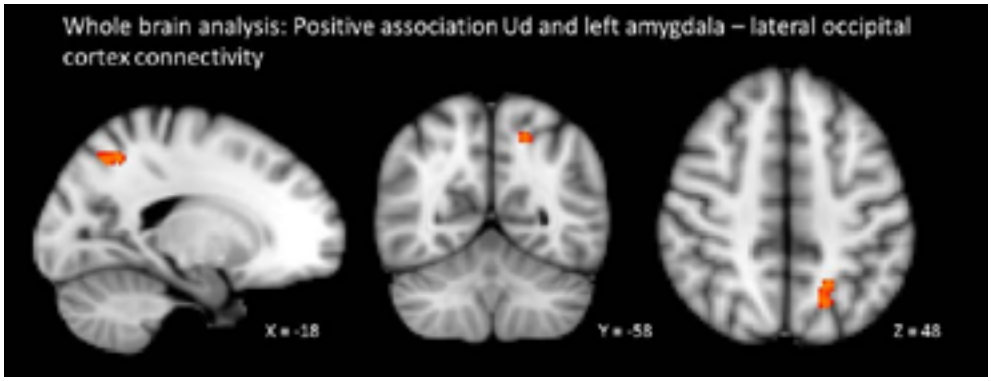
	UD (N=16)		Non-UD (N = 58)		
	M	*SD*	*M*	*SD*	*t*
GPF	0.38	0.97	-0.11	0.99	-1.76
Age	15.56	1.63	15.38	1.69	-0.39
Total IQ	99.38	8.40	104.36	8.89	2.03*
PDS scores	4.19	0.98	4.22	0.73	0.17

Amygdala connectivity

Whole brain analysis showed a significant positive association between Ud and connectivity of the left amygdala, with left lateral occipital cortex (LOC), precuneus, and superior parietal lobule (Brodmann Area 7) , after adjusting for GPF, age, puberty status, IQ, and sex (family-wise error corrected $p < .05$, see Table 2 and Figure 1A). The whole brain analysis did not reveal significant associations between amygdala connectivity and GPF.

Connectivity between the amygdala and the medial frontal ROI was significantly and negatively correlated with Ud, controlling for GPF, age, puberty status, IQ, and sex (family-wise error corrected $p < .05$, see Table 2 and Figure 1B), indicating reduced connectivity in individuals showing higher levels of Unresolved loss and trauma. No significant association was found between GPF and amygdala - medial frontal cortex connectivity.

A)



B)

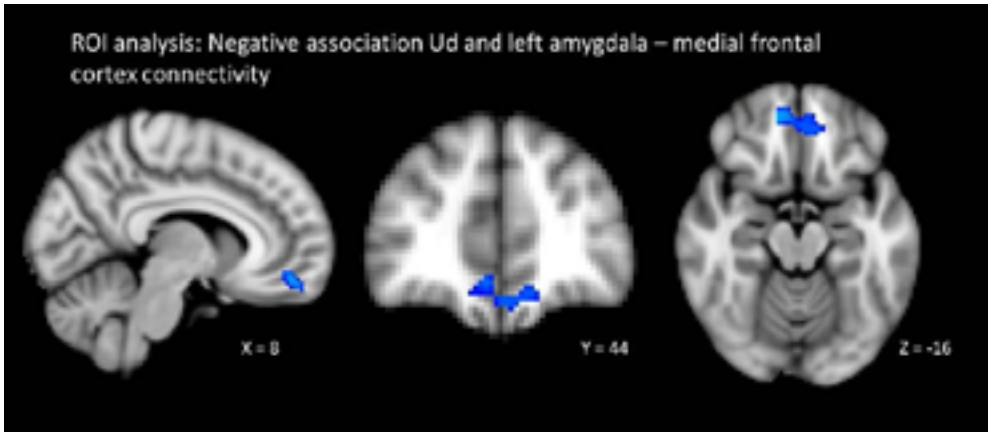


Figure 1. A) Significant positive association between Unresolved loss and trauma and left amygdala – lateral occipital cortex connectivity, resulting from the whole brain analysis, TFCE family-wise corrected, $p < .05$. **B)** Significant negative association between Unresolved loss and trauma and left amygdala – medial frontal cortex connectivity, resulting from the ROI analysis, TFCE family-wise corrected, $p < .05$. The right side of the brain corresponds to the left hemisphere and vice versa.

Table 2. Cluster size, lowest *p*-value, and coordinates of the significant clusters resulting from the analyses with the amygdala as seed region.

Contrast	Region	Voxels	*p*	x	y	z
Unresolved loss and trauma +	L Superior Parietal Lobule	80	0.02	-20	-56	48
	L Superior Parietal Lobule	25	0.04	-24	-52	34
	L Lateral Occipital Cortex	8	0.05	-28	-66	34
Unresolved loss and trauma[a] -	R Medial Frontal Cortex	189	0.02	12	50	-16

[a] Results from the ROI analysis with the medial frontal cortex as a priori defined region of interest.

dACC connectivity

The whole brain connectivity analyses with the dACC as seed region did not reveal associations with Ud or GPF (however, see Supplemental Material).

DISCUSSION

The aim of this study was to investigate whether unresolved loss or trauma (Ud) as assessed with the AAI and a general psychopathology factor (GPF) were differentially associated with amygdala and dACC functional connectivity in a mixed group of adolescents with CSA- related PTSD, anxiety and depressive disorders and without psychiatric symptoms. After adjusting for GPF, puberty status, age, sex, and IQ, we found that individuals with higher levels of Ud showed stronger left amygdala connectivity with the lateral occipital cortex, precuneus, and left superior parietal lobule compared to individuals with lower levels Ud. In addition, Ud was negatively associated with left amygdala-medial frontal cortex connectivity. Our study suggests that across diagnoses, Ud is associated with specific RSFC of the left amygdala. The finding means that individuals' functional connections vary according to attachment status, regardless of specific psychopathology.

The amygdala is part of the limbic network and involved in fear, fight, flight and freeze reactions to traumatic experiences controlled by the HPA-axis (Rinne-Albers et al., 2013). The urgency of these conditions as well as their long-term impact may hamper specific reflective functioning called mentalization, i.e. reflection about thoughts, emotions and behavior of the self and others (Luyten & Fonagy, 2015). A critical element of Ud is that individuals coded high for Ud often lack reflective functioning and awareness of their own

psychological states. Our findings for the connectivity of the amygdala may reflect a lack of awareness of fear states, rather than regulatory deficits alone. Because Ud is assessed through coding of language rather than self-reported psychopathology, this indirect method of assessing mental distress may reveal the neural basis of psychopathology better than self-reported mental health.

Our finding that amygdala connectivity with the lateral occipital cortex is enhanced in individuals with Ud shows parallels with our previous study that showed enhanced LOC- hippocampus connectivity in Ud (Van Hoof et al., *in press*). Altered LOC activity is associated with atypical processing of emotional stimuli and has been implicated in higher level visual processing, including emotional scene perception (Sabatinelli et al., 2011). In addition, we observed enhanced functional connectivity with the precuneus and the left superior parietal lobe in adolescents with Ud. The precuneus is part of the default mode network (resting consciousness) and has been associated with self-consciousness, memory, directing attention in space both when an individual makes movements and when imaging or preparing them, visuospatial mental operations, and mental imagery/modeling other people's views (Cattaneo & Rizzolatti, 2009; Cavanna, 2007; Cavanna & Trimble, 2006). The left superior parietal lobe is involved in spatial orientation, and visual and sensorimotor input from the hand. Both precuneus and superior parietal lobe involvement have been implicated in PTSD with symptoms of dissociation, depersonalization, and derealization (Nicholson et al., 2015) and in particular the precuneus may be associated with Ud and its relative lack of reflective functioning.

In addition, a negative association between Ud and amygdala connectivity with the medial frontal cortex was found, possibly indicating altered amygdala inhibition by the medial frontal cortex. Such an impaired functional connectivity within the amygdala-medial (pre)frontal circuit increases the propensity for excessive fear as it promotes amygdala hyperactivity and diminished medial prefrontal control. It suggests less rational, cortical control by the medial frontal cortex such as evaluating choices, handling errors and cognition of social interaction (Crone, 2014; Waugh et al., 2014) and may explain why emotions and behavior have dominance over cognitions in case of Ud. (Aghajani et al., 2016) previously suggested that disrupted basolateral amygdala-medial prefrontal connectivity might be a reliable neural marker of PTSD and a prominent feature of pediatric PTSD in part of the same sample (Rinne-Albers et al., 2013; Shin & Liberzon, 2010; Sripada et al., 2012; Wolf & Herringa, 2016). Our findings show that the atypical amygdala-medial (pre)frontal connectivity could additionally be a neural marker of Ud, as the current dysconnectivity was associated with Ud and not with GPF. As previous work demonstrated a rather strong association between PTSD and Ud, longitudinal research should investigate the developmental relationships between these phenomena and their underlying neural structures and functions (Harari et al., 2009).

Whereas the amygdala is part of the limbic network, the dACC is part of the salience network and involved in selection of stimuli that are deserving of our attention, judgment and discrimination, social sensitivity and many autonomic functions (motor and digestive functions, regulation of blood pressure and heart rate)(Seeley et al., 2007). The ACC contains spindle or so called Von Economo neurons (Von Economo & Koskinas, 1925), which allow rapid communications across areas, which aids the frontoparietal mirror neuron system in mentalization. The dACC connects primarily to cognitive brain regions such as the medial prefrontal cortex and is active in concert with the basolateral amygdala during appraisal and expression of fear (Etkin, Egmer, & Kalisch, 2011; Teicher et al., 2016).

Evidence for lateralization of amygdala function is accumulating (Baas, Aleman, & Kahn, 2004; Sergerie, Chochol, & Armony, 2008). The dominant notion seems to be that the right amygdala mediates relatively global and transient emotional responses, while the left amygdala seems to serve more specific and sustained forms of emotional responding. More in detail, the right basolateral amygdala is thought to encode precise affective features (e.g. punishment), while the left centromedial amygdala is thought to process general affective valence (e.g. good vs bad)(Styliadis, Ioannides, Bamids, & Papedelis, 2014). In this respect it is interesting that Ud was found to be associated with left amygdala, as attachment representation comprises a profound, sustained form of relating to others.

Our findings are consistent with our previous studies showing that unresolved loss or abuse is a trans-diagnostic risk factor for increased vulnerability to psychopathology in general (Lyons-Ruth et al., 2016; Riem, Van Hoof, et al., 2019). Moreover, these findings indicate that amygdala alterations previously found in patients with PTSD, depression or anxiety disorders are not a specific biomarker for individual mental disorders, but instead may be common to several disorders with overlapping psychopathological symptoms. Amygdala atypical RS connectivity seems to be related to underlying factors associated with childhood attachment experiences which may be predisposing for vulnerability to fear generation and mental disorders (Admon, Milad, & Hendler, 2013).

LIMITATIONS

Some limitations should be considered. Due to the fairly small sample size and the restricted ranges of age, IQ, sex, and ethnicity, results should be replicated in larger samples with a wider array of clinical diagnoses. The GPF was based on self-report of symptoms and not on clinical interview scores. Also, because of the cross-sectional design of our study, interpretation of results should be done with caution to avoid reverse causality and therefore, definitive conclusions about cause and effects cannot be drawn.

CONCLUSION

In conclusion, we found that Ud is uniquely related to amygdala RSFC connectivity across psychopathologies, possibly indicating that disrupted amygdala connectivity reflects a vulnerability factor rather than a biomarker of psychopathology. This study shows that the search for underlying dimensions of attachment and psychopathological symptoms across and beyond conventional diagnostic classifications might uncover commonalities and differences at the neural level explaining etiology of common disorders. Ud might be especially helpful in uncovering underlying dimensions of psychopathology since coding of the AAI is not dependent on the (conscious) content of the narrative about past experiences nor on a high level of reflective functioning about loss or trauma. Instead, the AAI is coded for coherence of mind, the (in-)coherent use of language of the verbatim transcribed interview, without the participants' awareness.

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DISCLOSURE STATEMENT

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SUPPLEMENTAL MATERIAL CHAPTER 6 (as published)

A.1 Supplemental material

A.1.1 Introduction

It should be noted that the combination of PTSD with experiences of interpersonal adversities such as childhood trauma warrants a diagnosis of complex PTSD (Ford, 2015) or according to the American Psychiatric Association 'PTSD with dissociative symptoms' (Choi et al., 2017) and shows a different clinical presentation (e.g. dissociation, behavioral symptoms, emotional dysregulation) than PTSD without childhood trauma.

A.1.2 In- and exclusion criteria EPISCA

The adolescents were part of the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA), a longitudinal study in which adolescents were followed over a six-month period. The adolescents with and without clinical symptoms underwent a diagnostic assessment and an MRI scanning protocol at three points in time (at baseline, 3 months, 6 months; Van den Bulk, 2013). AAI (Hesse, 2016) and clinical characteristics of the group and neuroimaging data were reported previously (e.g. Van Hoof et al., 2015; Pannekoek et al., 2014b; Aghajani et al., 2016).

Related to the neuroimaging protocol all participants 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). The adolescents with childhood sexual abuse (CSA) were recruited at two psychotraumacenters in the Leiden region of the Netherlands. Inclusion for CSA was having experienced sexual abuse during their life time more than once by one or more perpetrators in- or outside the family, and being referred for treatment at a psychotraumacenter. The 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 (Silverman, Saavedra, Pina, 2001) and no history of CSA (see Van Hoof et al., 2015). Exclusion criteria for both clinical groups 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) amphetamine medication on the day of scanning or current use of

psychotropic medication other than stable use of SSRI's; and 3) current substance abuse. The non-clinical adolescents were recruited through local advertisement, with the following inclusion criteria: no clinical scores on validated mood and behavioral questionnaires or past or current DSM-IV classification, no history of traumatic experiences and no current psychotherapeutic intervention of any kind.

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. Most adolescents with CSA (87%) reported during the AAI serious and/or longstanding physical sexual contact including repeated or group rape, in 63.6% by a person other than an attachment figure. In addition, 36.4% of the CSA group also experienced physical abuse, 22.7% by a person other than an attachment figure, 9.1% by an attachment figure, in one case by both. Sexual abuse was reported to the police in 60.9%, child welfare was involved in 56.5% of the cases, while 17.4% had a child protection measure (family custody). None of the participating non-clinical adolescents and those with anxiety and/or depressive disorders had experienced CSA, but they did mention physical and emotional abuse, bullying, and other incidents. Non-clinical adolescents had not been involved with police, child welfare or child protection, while 23% of the adolescents with anxiety and/or depressive disorders had child welfare involvement.

From the original sample of 82 adolescents, three participants were excluded due to technical problems, i.e. failed voice and video recording (one adolescent with CSA), unintelligible recording (one non-clinical adolescent), incorrect interview technique (one non-clinical adolescent). Two participants (one non-clinical adolescent and one adolescent with anxiety/depressive disorder) were excluded because they refused the AAI because of the interview itself. Of the N=77 in the remaining sample, 86% were girls. All CSA adolescents fulfilled the DSM-IV criteria for PTSD, according to the ADIS (Silverman et al., 2001), however one adolescent missed a point on the interference score to fully qualify for PTSD. SSRI's were used by four of the adolescents with CSA and two of those with anxiety and/or depressive disorder.

A.1.3 Questionnaires and tests

A.1.3.1 YSR: Youth Self-Report (Achenbach, 1991a) and CBCL: Child Behavior Checklist (Achenbach, 1991b), with Dutch translations by Verhulst and colleagues (Verhulst, Van der Ende, Koot, 1991; 1997). The YSR and CBCL are self-report questionnaires using a 3-point scale to assess social-emotional and behavioral problems in adolescents. The CBCL is the questionnaire for parents, the YSR for adolescents 11 years and older. There are 9 subscales and 3 main scales (total score, externalizing problem score and internalizing problem score) In this study we used the internalizing problem scores of the YSR and CBCL.

A.1.3.2 ADIS: The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS C/P; Silverman et al., 2001) are semi structured interviews designed specifically for DSM-IV classification of anxiety and other related disorders such as depression and PTSD in children and adolescents. Strong test-retest reliability was shown for combined and individual ADIS-C/P diagnoses. Intra-class correlations were excellent. Interrater reliability between child and parent versions of the ADIS was reported to be excellent. In this study, the ADIS was applied to all participants by certified trained clinicians and researchers.

A.1.3.3 TSCC: The Trauma Symptom Checklist for Children (TSCC; Briere, 1996) is a 54-item self-report for children and adolescents aged 8-17, which measures trauma-related symptoms. In the present study, only the TSCC total score was used as subscales overlapped significantly, with a Cronbach's alpha coefficient of .96. 10.3% of the total sample showed scores above the cut-off of 60 suggesting acute and chronic posttraumatic symptomatology (Briere, 1996).

A.1.3.4 A-DES: The Adolescent Dissociative Experiences Scale (Armstrong et al., 1997) is a self-report for adolescents aged 11-18 measuring possible dissociation. The A-DES has good reliability and validity. In this study, the mean total score on the A-DES was used as a measure of dissociation, which had a Cronbach's alpha coefficient of .95. 5.4% of the total sample showed scores above the cut-off of 4 suggesting pathological dissociation (Armstrong et al., 1997).

A.1.3.5 CDI: The Children's Depression Inventory (Kovačs, 1992) is a 27-item, self-rated, depression symptoms-oriented scale suitable for youths aged 7 to 17. The CDI has good psychometric properties of validity and reliability (Cronbach's alpha .71 to .86)(Timbremont, Braet, Dreessen, 2004), though discriminant validity has been subject to discussion. In this study, the total CDI score had a Cronbach's alpha coefficient of .93. 33.8% of the total sample showed scores above the recommended cut-off of 16 (Roelofs et al., 2010).

A.1.3.6 RCADS: The Revised Child Anxiety and Depression Scale (Chorpita et al., 2000; Oldehinkel, 2000) is a self-rated, anxiety and depressive symptoms-oriented 47-item-scale for children aged 6 to 18. Items are scored based on a four-point scale and grouped as depressive disorder, generalized anxiety disorder, social phobia, anxiety disorder NAO and obsessive-compulsive disorder. Chorpita and colleagues (2000) reported evidence for validity and reliability of the RCADS in clinical and healthy control adolescents. In this study, the total score of the RCADS was used as a measure for severity of experienced symptomatology (Cronbach's α = .95). Besides, the depression scale (Cronbach's α = .89) and the cumulative anxiety scales (Cronbach's α = .94) were used.

A.1.3.7 AAI: the Adult Attachment Interview (Main, Kaplan, & Cassidy, 1985) is coded according to the DEFU system (Hesse, 2016): dismissive (Ds), preoccupied (E), secure-autonomous (F), unresolved-disorganized (Ud). Ds, E and F classifications are organized forms of attachment, while Ud represents disorganized forms of attachment. In organized attachment representations, there is one coherent mental strategy with regard to attachment figures, either secure-autonomous (F) or insecure (Ds or E). In disorganized attachment-representation different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory. A high to moderate coherence of the narrative is seen in secure-autonomous (F) attachment interviews in which the interviewee can give ample evidence for general evaluative statements made regarding attachment relationships and attachment experiences whether good or bad. In case of unresolved loss or trauma, the attachment representation is labeled unresolved-disorganized (Ud). This classification can be given in addition to a Ds, E or F classification. A fifth category, cannot classify (CC), is used when the interviewee presents contrasting attachment strategies for attachment figures in the course of the interview resulting in very low coherence of narrative. In most studies U and CC are combined in one category, Unresolved-disorganized. Coherence of mind and unresolved for loss or trauma (Ulosstrauma) are two dimensional scales of the AAI which are assigned scores rated between 1-9. Lowest score for Coherence means there is little or no coherence of mind, highest score for Ulosstrauma means there is high impact of loss or trauma.

The AAI has been administered to more than 10,000 respondents since its development (Bakermans-Kranenburg, & Van IJzendoorn, 2009). The AAI is found to have remarkably good test-retest, discriminant reliability as well as predictive validity. In this study, the AAI was administered by MJvH and CIG, verbatim transcribed according to protocol, and coded by GK (trained by Diane and Dave Pederson), and SdH (trained by Diane and Dave Pederson, and June Sroufe). Both reached intercoder reliability standards in the AAI classification system. Ten cases were also coded by MJBK. Interrater agreement in this sample was 80% for F-nonF, 90% for Ud-nonUd and 70% for four-way classification (DEFU). Kappa's for coding F-nonF (.59) and Ud-nonUd (.62) were both statistically significant and reasonable to satisfactory.

We focused our analyses on the unresolved versus non-unresolved (non-Ud) comparison because the distribution of continuous unresolved scores was skewed and because our previous study revealed structural and functional brain abnormalities in individuals with unresolved versus without unresolved classification (Riem, Van Hoof, et al., 2019; Van Hoof et al., in press).

A.1.3.8 WISC-III-NL and WAIS-III: Short versions of the Wechsler Intelligence Scale for Dutch Children aged 6-16 years, WISC-III-NL (Wechsler, 1991; Kaufman, Kaufman,

Balgopal, & McLean, 1996) and adolescents aged 16 and above and adults, the Wechsler Adult Intelligence Scale, WAIS-III (Wechsler, 1997) were used. They consisted of six subtests: picture completion, similarities, picture arrangement, arithmetic, block design and comprehension. In earlier studies, these subtests were found to give a valid and reliable IQ estimate (reliability coefficient > .90)(Kaufman, et al., 1996).

A.1.3.9 PDS: The Pubertal Development Scale (Petersen et al., 1988) measures the actual level of physical development during puberty. It is a 5-item self-report that measures items like body growth, body hair, skin changes for both sexes. For boys, there are items on beard growth and voice changes. For girls, there are items on breast growth and menstrual bleeding. Items can be answered on a 5-point scale with a total score range of 0-20. Internal consistency is adequate for both sexes, consistent across samples, while the predictive validity of the PDS is satisfactory (Robertson et al., 1992). The following distribution was found for the current sample: Prepubertal (N = 1), early pubertal (N = 1), midpubertal (N = 4), late pubertal (N = 22), postpubertal (N = 25). Information about pubertal status was missing for 10 participants. For these participants, pubertal status was imputed using gender and age.

A.1.4. Statistical analysis

Functional connectivity analysis.

In addition to left and right amygdala, and left and right dACC time series, CSF, white matter and the global signal were added as regressors to the statistical model of a seed based correlation approach. The global signal was added to the model. It should be noted that there is no consensus regarding the global signal for RSFC analyses (Murphy & Fox, 2017). Adding the global signal to resting state analyses has both advantages and disadvantages. We added the global signal in the analyses of the current study in order to increase comparability with a previous resting state study with partly the same sample (Van Hoof et al., in press).

A.1.5 Results

dorsal anterior cingulate cortex (dACC)

As mentioned in the article itself, the whole brain connectivity analyses with the dACC as seed region did not reveal associations with Ud or GPF. However, there was a significant negative association between GPF and left dACC connectivity with the right body of the corpus callosum, right superior fronto-occipital fasciculus, and right corticospinal tract, controlling for Ud, age, puberty status, IQ, and sex (TFCE family-wise error corrected, $p < .05$, see Table A.2 and Figure A.2).

A.1.6 Discussion

Our current findings on GPF revealed a negative association of GPF with the left ACC functional connectivity with the right body of the corpus callosum, superior fronto-occipital fasciculus, and corticospinal tract (Peer, Nitzan, Bick, Levin, & Arzy, 2017). In a Diffusion Tensor Imaging (DTI) study on the same sample Riem, Van Hoof and colleagues (2019) found that GPF was associated with reduced fractional anisotropy in the genu and body of the corpus callosum, which suggests demyelinization in these areas. The findings of the current study indicate that a GPF is also related to functional white matter abnormalities. Although previous studies often discarded white matter signals as noise, recent evidence suggests that white matter tracts are correlated to grey matter resting-state networks (Ding et al., 2018; Peer et al., 2017). Thus, white matter activities and connectivities seem to have a functional role and disturbances in these networks may underlie a general vulnerability to psychopathology.

As we adjusted for white matter noise, we felt that the finding on GPF and dACC could however not be included in the main manuscript itself. However, there is discussion about the existence and meaning of connectivity between RSFC, grey matter and white matter (Ding et al., 2018). We therefore do mention our initial findings in the supplemental material, as our conclusion would have been different had we included the dACC-GPF connectivity finding in the main manuscript, namely that Ud and GPF both represent independent trans-diagnostic predisposing risk factors as follows from the argumentation below.

Since there is common heritability and large co-morbidity among mental disorders, it seems likely that a GPF may account for a general increase in vulnerability (Smith et al., 2001; Lahey, Applegate, Hakes, Zald, Hariri, & Rathouz, 2012; Lahey, Zald, Perkins, Villalta-Gil, Werts, Van Hulle, … & Waldman, 2018; Caspi & Moffitt, 2018). Whether an individual will develop a mental disorder may depend on individual resilience factors such as personality, IQ, (epi)genetic factors, coping strategies, parenting or positive attachment experiences, that may counterbalance risk factors that are present (Schuwerk et al., 2014). In this study, Ud and GPF were found to be related to atypical amygdala respectively dACC functional connectivity networks. Therefore, an alternative hypothesis for Ud being a trans-diagnostic factor (Riem, Van Hoof et al., 2019) may be that both Ud and GPF represent trans-diagnostic predisposing risk factors for developing stress-related and affective mental disorders (Caspi & Moffitt, 2018), though independently from each other as they did not correlate in this study. Caution is, however, required in drawing causal conclusions from this cross-sectional study, as unmeasured third factors or reversed causality may be also possible.

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A.1.8 Tables

Table S1. Mean (SD) general psychopathology scores for the anxiety/depression, CSA-related PTSD, and control group, and Ud versus non-Ud group.

Group	N	M	SD	range
Anxiety/depression	26	0.45	0.86	-0.88 – 2.34
CSA-PTSD	18	0.39	0.87	-0.86 – 1.90
Control	19	-0.95	0.54	-1.66 – 0.12
Ud	12	0.23	1.03	-1.31 – 1.90
Non-Ud	51	-0.04	1.00	-1.66 – 2.34

Table S2. Factor loadings for the Trauma Symptom Checklist for Children (TSCC), Children's Depression Inventory (CDI), Revised Child Anxiety and Depression Scale (RCADS), Adolescent Dissociative Experiences Scale (A-DES),Youth Self Report (YSR), and Child Behavior Check List (CBCL), resulting from the Principal Component Analysis.

Subscale	Loading
RCADS separation anxiety	.79
RCADS social phobia	.80
RCADS panic disorder	.69
RCADS generalized anxiety disorder	.74
RCADS obsessive compulsive disorder	.79
RCADS depressive disorder	.89
CDI	.84
YSR internalizing problems	.88
CBCL internalizing problems	.63
TSCC_depression	.92
TSCC anxiety	.75
TSCC_PTSD	.87
TSCC dissociation	.83
TSCC sexual concerns	.56
ADES	.70

Table A.1. Mean (SD) general psychopathology scores for the anxiety/depression, CSA-related PTSD, and control group, and Ud versus non-Ud group.

Group	N	M	SD	range
Anxiety/depression	26	0.45	0.86	-0.88 – 2.34
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Table A.2. Cluster size, lowest *p*-value, and coordinates of the significant clusters resulting from the analyses with the dACC as seed region.

Contrast	Region	Voxels	*p*	x	y	z
GPF -	R Corticospinal tract	50	0.03	22	-16	30

Legend: GPF = General Psychopathology Factor

A.1.9 Figures

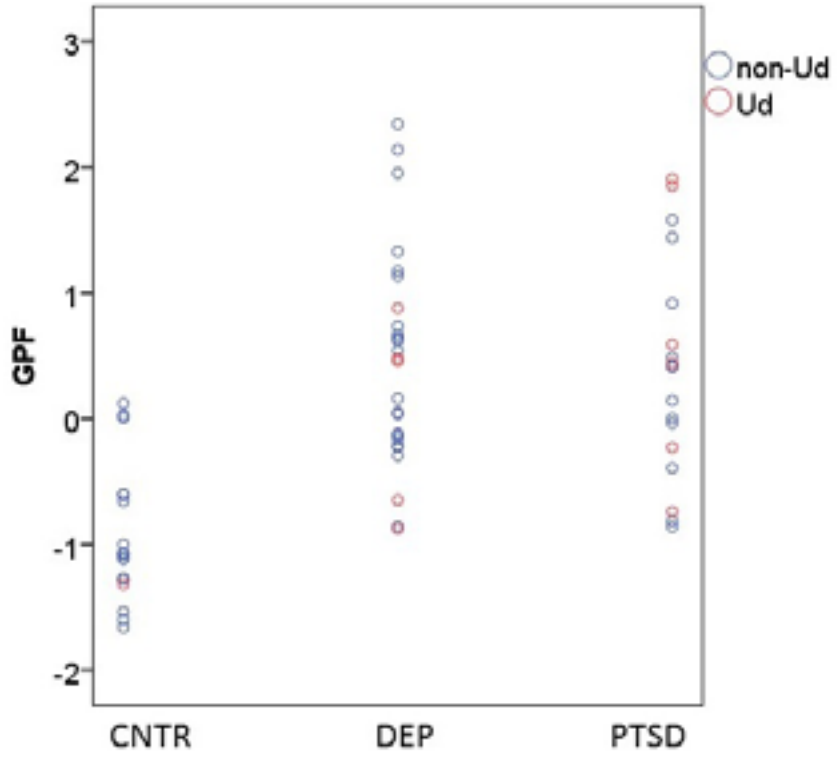

Figure A.1. Scatterplot of general psychopathology scores for the Ud, non-Ud, anxiety/depression (DEP), PTSD, and control group (CNTR)

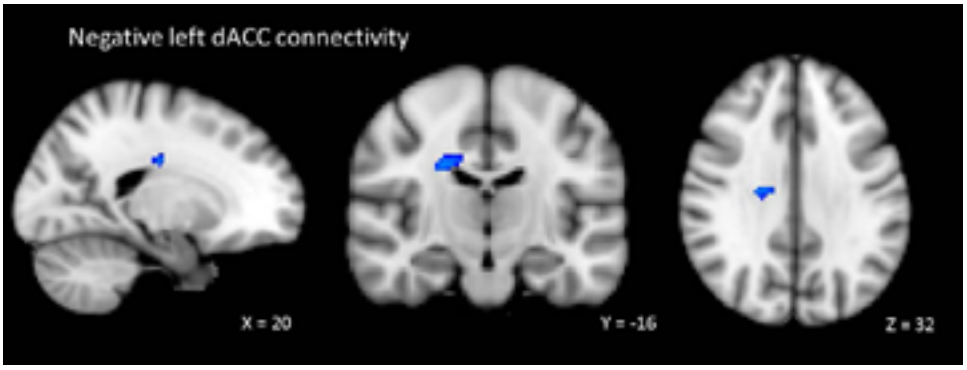

Figure A.2. Significant negative connectivity between GPF and left dACC and the right body of the corpus callosum, superior fronto-occipital fasciculus, and corticospinal tract, TFCE family-wise corrected, $p < .05$. The right side of the brain corresponds to the left hemisphere and vice versa.

SUMMARY AND GENERAL DISCUSSION

Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more,
so that we may fear less.

Marie Curie (1867, Warsaw - 1934, Paris)

CHAPTER 7: SUMMARY AND GENERAL DISCUSSION

AIM

This thesis focuses on attachment, trauma and emotion regulation and their interrelatedness and therefore aimed to investigate: 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 used a mixed sample of adolescents with childhood sexual abuse related posttraumatic stress disorder (CSA-related PTSD) or clinical depression as well as population based control group, either comparing diagnostic groups with controls or analysing the sample as a whole.

SUMMARY

The studies presented in **Chapters 2-6** are based on a sample of mainly female adolescents (86%, age 12-20 years) participating in the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents; Van den Bulk et al., 2013).

Attachment representation refers to how one perceives the relationship with parents or caregivers in his or her youth which can be narrated during the Adult Attachment Interview (AAI; Main, Kaplan, & Cassidy, 1985). Although attachment is a concept bearing substantial clinical relevance for child mental health, attachment representation and psychiatric symptoms have barely been examined simultaneously in clinical adolescent groups (Bakermans-Kranenburg & Van IJzendoorn, 2009).

In **Chapter 1** we introduced the topic of this thesis.

In **Chapter 2** The aim of this study was to investigate whether attachment representation differentiated adolescents with CSA from those with clinical depression and non-clinical controls beyond psychiatric symptomatology.

First, we found that the CSA group was most often unresolved-disorganized as classified with the AAI, compared to both the clinical depression and control groups. Overrepresentation of unresolved trauma and "Cannot Classify" classifications (U/CC) accounted for this unresolved-disorganized attachment classification. Secondly, clinical symptomatology correlated with unresolved status, but not with coherence of mind. Third,

being unresolved was scored highest and coherence of mind lowest in the CSA group, compared to the clinical depression group and the controls. Only coherence of mind uniquely differentiated the CSA group from both the clinical depression group and controls, when co-varied for age, IQ and psychiatric symptomatology. The unresolved loss or trauma scale differentiated both clinical groups from the controls.

In **Chapter 3** we investigated the neural mechanisms of emotional face processing in adolescents with CSA-related PTSD versus clinical depression and non-clinical controls using fMRI and dimensional measures of psychiatric symptoms (TSCC, A-DES and CDI). First, we found that the CSA-related PTSD group was significantly slower to react to all emotional faces across all questions than the clinical depression group. All participants reacted slower to fearful and neutral faces than to happy faces when asked 'How afraid are you?'. Besides, both clinical groups felt higher subjective anxiety in response to fearful faces than to happy faces when asked how afraid they were compared to non-clinical controls. Furthermore, the CSA-related PTSD group reported higher anxiety to neutral faces than both the clinical depression group and non-clinical controls. Asked how happy they were, both clinical groups reported being less happy when viewing fearful faces than non-clinical controls. Happy faces elicited relatively faster reaction times than fearful and neutral faces within the state 'how afraid are you?'. However, no significant differences between groups were found on whole brain and ROI level, nor between levels of self-reported symptoms and brain activation, except for a few single positive correlations with TSCC subscales. Therefore, our second and third hypothesis were not supported.

In **Chapter 4** the aim was to investigate whether unresolved-disorganized attachment representation, controlled for a general psychopathology factor (GPF) was associated with amygdala and hippocampus volume and associated resting state functional connectivity (RSFC) in a group of adolescents with CSA-related PTSD, clinical depression and non-clinical controls, using VBM and RSFC. We investigated GMV using FIRST with regard to being unresolved (continuous), and disorganized versus organized attachment classification (Ud-nonUd), co-varied for IQ, age, sex, and a GPF.

According to our hypothesis, we found that unresolved loss or trauma related to a smaller hippocampal volume and associated functional connectivity. More specifically, we found that the categorical but not the continuous Ud was associated with a smaller left hippocampal volume, and greater functional connectivity with the middle temporal gyrus (MTG) and lateral occipital cortex (LOC). No association was found for unresolved status with right hippocampal volume nor left or right amygdala volume.

In **Chapter 5** we aimed to evaluate whether there were differences in white matter integrity (WMI) of white matter tracts, in particular the genu and body of the corpus

callosum and the splenium and inferior fronto-occipital fasciculus (IFOF). In support of our hypothesis, we found that, controlling for GPF, Ud was associated with reduced fractional anisotropy (FA) in the splenium (ROI and whole brain analyses) and IFOF (whole brain analyses). Controlling for Ud, GPF was negatively associated with reduced FA in the genu and body of the corpus callosum (ROI analysis, not whole brain analysis). Correlational analysis showed that there was no significant relation between Ud status and GPF. Contrary to our hypothesis, no association was found between unresolved status nor GPF and FA values in the cingulum or superior longitudinal fasciculus.

In **Chapter 6** we aimed to evaluate whether there were differences in RSFC of the amygdala and dorsal anterior cingulate cortex (dACC) with regard to unresolved-disorganized attachment representation and a general psychopathology factor (GPF) in a group of adolescents with CSA-related PTSD, clinical depression and non-clinical controls. We hypothesized that Ud and GPF would be related to unique RSFC networks of the amygdala and dACC. Ud was positively associated with greater functional connectivity between the left amygdala and the left lateral occipital cortex, precuneus, and superior parietal lobule. Furthermore, Ud was negatively associated with left amygdala-medial frontal cortex connectivity. In contrast, GPF was not significantly associated with dACC or amygdala connectivity. There was no significant correlation between Ud and GPF.

GENERAL DISCUSSION

Regarding the **first aim** of this dissertation, investigating ***behavioural and mental health*** correlates of attachment and emotion regulation (i.e. attention bias) in adolescence, we found significant differences between traumatized and non-traumatized adolescents regarding unresolved-disorganized attachment, but only partially regarding self-reported psychopathological symptoms across diagnostic groups. Though there was a significant difference in symptomatology between the clinical groups (adolescents with CSA-related PTSD or depressive/anxiety disorders) and the non-clinical group, posttraumatic stress, depressive/anxious, and dissociative symptoms did not differ significantly across diagnostic categories (Chapter 2). ***Regarding attachment***, we specifically found the unresolved-disorganized cannot classify category (Ud/CC) to be overrepresented in the CSA-related PTSD group, indicating severe disturbance of attachment representation (Chapter 2). The dual approach of using categorical as well as dimensional variables of the AAI to examine attachment resulted not only in identification of an association between the CC classification and CSA, but also in the identification of the role of coherence of mind in differentiating CSA from the clinical depression group and controls. In contrast to coherence of mind, the unresolved scale did not differentiate the CSA from the clinical depression group (see for the debate: Roisman, Fraley, & Booth-LaForce, 2014; Van IJzendoorn & Bakermans-

Kranenburg, 2014).

This study increased insight into the associations between trauma, dissociation, and disorganized attachment representations by adding evidence to theories addressing ways in which individuals (fail to) cope with traumatic experiences (Cassidy & Mohr, 2001; Hesse, 2008; Liotti, 2004; Lyons-Ruth et al., 1999, 2006). Given the fact that the CSA group displayed serious and/or longstanding physical sexual contact including repeated or group rape and implicit emotional abuse and neglect, physical abuse, losses, bullying and other traumatic incidents, combined with high levels of posttraumatic stress, dissociative and depressive symptoms, a substantial percentage of adolescents with CSA clinically appeared to suffer from complex PTSD (Herman, 1992; Jonkman, Verlinden, Bolle, Boer, & Lindauer, 2013; Karam et al., 2014) or "PTSD with prominent dissociative symptoms" (DSM-5; American Psychiatric Association [APA], 2013). Complex PTSD was, however, not part of the inclusion criteria, but rather a post hoc finding in part of the participants in a cross-sectional study design. Therefore, though we suspect a substantial percentage of complex PTSD and interrelatedness of posttraumatic stress, dissociative and depressive symptoms in the CSA-related PTSD group of our sample, we cannot draw any definitive generalized, scientific conclusions from our findings with regard to Liotti's diathesis-stress model of trauma, dissociation and disorganized attachment (2004).

We can however conclude that in our sample 1) we found in part significant associations between unresolved-disorganized attachment, dissociation, posttraumatic stress and depressive symptoms, (see tables 1 and 2, Chapter 2); 2) there was an overrepresentation of the CC attachment classification in the CSA group and 43% of adolescents with CSA had Ud vs 21% of adolescents with clinical depression, and 4% of adolescents in the control group, while all adolescents with CSA were classified as having PTSD and 17% of adolescents in the clinical depression group had a secondary diagnosis of PTSD for other trauma than CSA (Chapter 2); 3) significant differential correlations with grey and white matter and RSFC of the brain were found for Ud and GPF (including posttraumatic stress, dissociative and depressive symptoms among others). This suggests underlying differentiating brain mechanisms for clinical presentations, based on either the perspective of attachment or that of psychopathology (Chapters 4-6).

We hypothesize that either 1) disorganization may have been elevated in case of CSA due to pre-existent incoherence of mind as a consequence of highly insensitive parenting or atypical parental behaviours such as neglect, or that 2) CSA specifically or trauma by itself may have caused disorganization. Of course, these speculative interpretations should be tested in a longitudinal study, testing the diathesis-stress model of trauma (Ingram & Luxton, 2005; Liotti, 2004; Zuckerman, 1999), versus the differential susceptibility hypothesis (Bakermans-Kranenburg & Van IJzendoorn, 2007; Belsky, 1997a; 1997b). According to the

latter hypothesis children develop and grow up influenced by differential environmental factors and genetic make-up more or less resilient cq. susceptible, "for better or for worse".

Regarding attention bias as a proxy for emotion regulation, we found significant correlations of diagnostic group to attention bias in emotional face processing, adolescents with CSA-related PTSD processing fearful and neutral emotions more slowly than adolescents from the clinical depression and non-clinical group (Chapter 3). We explain this negative attention bias to be the result of a combination of automatic and strategic emotional face processing, involving heightened threat detection and difficulty to disengage (Cisler and Koster, 2010). A negative attention bias is consistent with studies in maltreated children and adolescents that showed them to process threat-related information more slowly than controls, using a non-morphed emotional faces task like we did (Monk et al., 2006; Pine et al., 2005). Inconsistency in attention bias between studies (e.g. Masten et al., 2008; Romens & Pollak, 2012) may be due to use of a heterogeneous sample that may use different attention bias components and strategies, a different paradigm (e.g. visual probe, visual discrimination and identification, or morphed facial emotion identification task), or a different presentation of emotional cues and questions posed.

Critical questions that can be posed are:

- whether all participants should have been extensively analysed for any possible loss or trauma, involving any abuse or neglect and grouped according to presence or absence of loss or trauma instead of according to diagnostic group;
- whether anxiety and depressive disorders should have been taken together under one diagnostic group as 'clinical depression';
- whether differentiation should have been made between participants with a single and with cumulative loss or trauma;
- whether attention bias is a true proxy for emotion regulation, as it involves a motor response;
- whether diagnostic interviews rather than self-report questionnaires should have been used to assess symptoms and correlate these to behavioural, mental health, and neural correlates.

Regarding the **second aim**, investigating ***neural*** correlates of emotional face processing (as a proxy of emotion regulation) in adolescence, we did not find any significant whole-brain or ROI group differences, differential amygdala activation between groups, nor any significant relation between levels of self-reported posttraumatic stress, dissociation or depression symptoms and ROI activation with regard to emotional face processing, despite having used a valid and functionally correctly used paradigm and previous findings by

Nooner and colleagues (2013) and Garrett and colleagues (2012) (Chapter 3).

One reason may be that there was rapid amygdala habituation to emotional faces in adolescents with CSA-related PTSD, as we found in a later analysis of our findings (Van den Bulk et al., 2016). A second reason may be that the applied statistical method used so many covariates, including three psychiatric symptom questionnaires, that reaching significance was hampered. Using a General Psychopathology Factor (GPF, see p. 13; Caspi et al., 2014; Lahey et al., 2015; 2017; Zald & Lahey, 2017) we might have had different results. An additional reason why we did not find significant relations between self-reported symptomatology and brain activation might be that the CSA-related PTSD and clinical depression groups did not significantly differ in dimensionally assessed psychiatric symptomatology, supposedly associated with post-hoc confirmed secondary PTSD in a subgroup of the clinical depression group.

In his somatic marker theory Damasio (1996) proposed that emotions and their biological underpinnings guide internal working models of social cognition. Until recently, attention bias in CSA-related PTSD and clinical depression has been predominantly studied in observational, non-fMRI studies, focusing for example on reaction time when looking at emotional faces. In these experiments, it was shown that emotional face processing is distinct in CSA as compared to non-abused children and adolescents (e.g. Masten et al., 2008; Monk et al., 2006; Pine et al., 2005; Romens & Pollak, 2012). Our study being one of the few emotional face processing studies trying to identify neural correlates of emotion regulation in clinical and non-clinical adolescent groups, we could only partially confirm differential emotion regulation in adolescents with CSA-related PTSD: on the behaviour level there was negative attention bias in the CSA-related PTSD group, on the neural level we had zero significant findings regarding emotional face processing between diagnostic groups.

Improved knowledge about the concepts of attachment and emotion regulation and their working mechanisms in case of psychopathology and/or Ud, can aid clinical and scientific applications that need further investigation. It is essential to derive and refine diagnostics and treatment strategies based on attachment as well as psychopathology, to remove irrelevant strategies and develop novel, holistic, integrated approaches that are more efficacious and effective than current treatments (Nemeroff, 2016; Van der Kolk, 2014). Knowledge of the working mechanisms could also improve precision in tailoring psychotherapy to the needs of individuals, thereby optimising treatment outcomes (Nemeroff, 2016; Van der Kolk, 2014).

Critical questions that can be raised are e.g.:

- whether the concepts of attachment and emotion regulation are culturally sensitive and need cultural adaptation;
- whether trauma, dissociation and unresolved-disorganized attachment are indeed

three strands of a single braid as Liotti theorized (2004) and therefore should be systematically reclassified from a psychopathology and an attachment perspective;
- whether diagnostic classifications provide the right framework to find differences in attachment and emotion regulation between groups;
- whether attachment in the individual child or adolescent can be well enough understood without diagnostics of parental attachment representation and observation of the parent-child interaction.

Considering the **third aim**: investigating differential neural correlates of attachment and psychopathology, the differential relationship of Ud and GPF, adjusted for each other, was established in this thesis for grey matter, white matter tracts and resting state functional connectivity (Chapters 4-6). Specifically, we found significant correlations of Ud and a GPF to grey matter volume (smaller left hippocampus and associated resting state functional connectivity; Chapter 4), white matter integrity of white matter tracts (splenium and IFOF for unresolved-disorganized attachment; genu and body of the corpus callosum for GPF; Chapter 5), and left amygdala and associated resting state functional connectivity for Ud besides a negative association with left amygdala-medial frontal cortex connectivity (Chapter 6). With regard to associations with Ud, there seemed to be lateralization of the brain to the left with regard to amygdala RSFC and hippocampal volume (Chapter 6 respectively 4).

Though we had a relatively small sample, the importance of attachment, specifically Ud, as a trans-diagnostic factor in relation to brain structure, volume and functioning was shown, adjusted for and separate from GPF. This finding is interesting against the background of the connectome wide functional signature of trans-diagnostic risk to mental illness Elliott and colleagues (2018) found for a GPF. Our studies were the first to compare attachment and psychopathology in the same (adolescent) sample and the first to test differential relationships for Ud and GPF in relation to the (adolescent) brain, along the way stressing the importance of using both dimensional and categorical variables in attachment and clinical psychopathology research. Since even at rest Ud is associated with amygdala functional connectivity, it means that an individual's functional connections in the brain may vary according to attachment status regardless of psychopathology as reflected by the GPF.

Since GPF on the contrary, was not found to be significantly associated with either amygdala or dACC functional connectivity (Chapter 5; see Ding et al.. 2018; Peer, Nitzan, Bick Levin, & Arzy, 2017 for a discussion on white matter signals and evidence of white matter tracts correlation to grey matter and resting-state networks), we do not know whether presence of more or less psychopathological symptoms per se, regardless of attachment status, impact an individual's functional connections in the brain. Therefore, we cannot conclude from our studies that GPF, just as Ud, also represents an independent, predisposing, trans-diagnostic risk factor for developing stress-related and affective mental

disorders as Elliott and colleagues (2018) demonstrated. Since third factors or reversed causality cannot be excluded in the cross-sectional study we performed, there is no definite conclusion to the discussion whether white matter signals should be regarded as noise or as significant activity. Therefore, we did not add this statement to our main conclusions in this dissertation.

With regard to Ud we found Ud had associations with structures in the brain associated with:

1) stress such as reduced hippocampal volume and *reduced WMI of certain parts of white matter tracts (splenium and IFOF)* (Chapter 4 and 5);
2) areas functionally connected in resting state, associated with processing emotional information, respectively mentalization, specifically *left middle temporal gyrus (MTG), left lateral occipital cortex (LOC), respectively LOC, precuneus, and superior parietal lobule* (Chapters 4 and 6);
3) *decreased connectivity with medial (pre)frontal areas of the brain* that ascertain cognitive control (Chapters 4 and 6);
4) *enhanced connectivity between the amygdala and areas of the brain* regulating negative emotions (Chapters 4 and 6).

These Ud-associated structures and areas in the brain can explain:

1. greater vulnerability to childhood stressors such as loss or trauma due to:
    a. hippocampal glucocorticoid receptor reduction associated with increased cortisol and reduced hippocampal volume (Sapolsky et al., 1985; 1990) and
    b. accelerated oligodendrocyte proliferation in the splenium, part of the corpus callosum (Alonso, 2000; Galaburda et al., 1990; Luders et al., 2010; Luo & O'Leary, 2005; Miyata, Koyama, Takemoto, Yoshikawa, Ishikawa, Taniguchi, et al., 2011), in reaction to high cortisol stress levels, in case of chronic exposure to stress which creates imbalance and callosal abnormalities (Tanti, Kim, Wakid, Davoli, Turecki, & Mechawar, 2017). These neural sequelae of loss and trauma may explain poor emotion regulation with a lowered threshold for experiencing stress or increased risk for psychopathology. In other words it may explain why emotions and behaviour have dominance over cognitions in case of Ud.;
2. less prefrontal cortical control, which may explain a higher level of impulsivity, emotional instability, stress vulnerability and risk for psychopathology;
3. atypical emotional responding (Baas et al., 2004; Sergerie et al., 2008) and emotional face processing (Krause et al., 2016);
4. general affective valence (Styliadis et al., 2014);
5. atypical processing of emotional stimuli and higher-level visual processing, including emotional scene perception (Sabatinelli et al, 2011);
6. impaired resting self-consciousness, memory, visuospatial orientation and mental

operations/modelling other people's views (Cattaneo & Rizzolatti, 2009; Cavanna, 2007; Cavanna & Trimble, 2006), visual and sensorimotor input from the hand, depersonalization, derealization and dissociation (Nicholson et al., 2015).

With regard to GPF we found GPF had associations with:

- increases in radial, mean and axial diffusivity, reflecting demyelination (Alexander et al., 2007) and altered axonal integrity of WMI (Budde et al., 2009), specifically in the genu and body of the corpus callosum. These abnormalities may be caused by a general vulnerability for psychopathology as a result of genetic influences (Patel et al., 2015) or prenatal stress (Jensen et al., 2018).
- the left ACC functional connectivity with the right body of the corpus callosum, superior fronto-occipital fasciculus, and corticospinal tract (Peer et al., 2017). Despite significance and cumulative evidence for existing associations between white and grey matter and RSFC, these associations were interpreted carefully as just noise according to common interpretation of white matter signals as such (Ding et al., 2018; Peer et al., 2017).

Critical questions that can be posed are:

- whether Ud and a GPF would differentially relate to the (adolescent) brain:
    1. in repeat (larger) studies;
    2. in other age, IQ, ethnic and socio-economic categories;
    3. in a different percentage males/females;
    4. when using other self-reports constructing a GPF;
    5. if the preoccupied attachment representation would have been present in the EPISCA sample;
    6. if diagnostic interviews instead of self-reports were used, e.g. for PTSD, the CAPS-CA (Diehle, de Roos, Boer, Lindauer, 2015; Nader et al., 1996; Van Meijel, Verlinden, Diehle, & Lindauer, 2014) and for dissociation, the Dissociative Disorders Interview Schedule (Ross et al.,1989);
    7. in all sorts of diagnostic categories, whether trauma-related or not-trauma related, e.g. complex PTSD, PTSD, trauma only, but also psychosis, eating disorder, and neuropsychiatric disorders as autism, ADHD, or tic disorder.
- Also, one might question the use of the AAI, and therefore Ud, as a meaningful variable, or the use of the GPF or the way this GPF was composed.
- In addition one could argue that the association of GPF with left ACC and right WMI should have been interpreted as significant and meaningful, which could have meant GPF is a trans-diagnostic factor beside Ud.
- Another critical question might be easier to answer in additional, larger samples: whether Ud, dissociation and PTSD overlap or form part of each other within the

concept 'complex trauma, 'complex PTSD' or 'PTSD with dissociation'.

- An additional question is whether altered MTG and LOC activity are associated with atypical processing of emotional stimuli of various kinds in general or whether this specific atypical processing of negative emotional stimuli is due to unresolved loss or trauma.

Clinical research and practice could benefit from clarity in conceptualization and further revelation of working brain mechanisms.

A RADICALLY EMBODIED NEUROSCIENCE OF ATTACHMENT?

Summarizing the discussion in this thesis, one study, using fMRI and multiple psychiatric symptoms as covariates, did not yield significant brain functioning results, however, there was attention bias, that is reactivity towards fearful and neural faces, which was slower and elicited most anxiety in the CSA-related PTSD group. The attachment representation profile and GMV, RSFC and DTI studies each did add at least some evidence to the theory of embodied trauma previously suggested by Van der Kolk (2014) and the theory of radically embodied neuroscience of attachment proposed by Beckes, IJzerman and Tops (2015). The latter outlined a hybrid concept of the radically embodied neuroscience of attachment, suggesting attachment is intrinsically interweaved with neurobiological metabolism and functioning. As the studies are of cross-sectional nature and third factors aren't measured nor do correlations imply causality, further longitudinal intervention research in larger samples will be needed to gain more insight.

In Figure 1 below a graphic representation shows different sequelae of loss and abuse in a way we assume that they may correlate from an attachment point of view, based on Main, Goldwyn, & Hesse, 2003 [unpublished manuscript], see Hesse, 2016, with clinical notions from diagnostic classifications as DSM-5 and ICD-11:

Intra-individual sequelae, i.e.

- affective sequelae of loss and abuse, mostly known as psychiatric symptoms of PTSD, depressive or anxiety disorders according to the DSM;
- behavioural sequelae of loss and abuse, mostly known as psychiatric symptoms of PTSD, and behavioural disorders according to the DSM;
- disorganized, disoriented and reported extreme behaviour sequelae, classifying attachment representation as determined with the AAI as unresolved-disorganized or cannot classify;
- somatic sequelae (as shown in the ACE study; Felitti et al., 1998);

II. Individual external financial, social, educational and career sequelae (see e.g. Shonkhoff et al., 2012).

To be investigated in future research, all these sequelae may take place simultaneously or consecutively and they may interact. How these sequelae interact is not known yet. As mentioned in the General Introduction of this thesis cumulative ACEs (Felitti et al., 1998) have been found to predict unresolved-disorganized attachment in 67% (Murphy et al., 2014) and have been shown to be the strongest predictor of symptom complexity above adult- and childhood experiences of complex trauma (Cloitre et al., 2009). Disorganized sequelae of trauma, i.e. disorganized attachment representation (Hesse, 2016), seem to be relatively independent from affective and behavioural sequelae and a better differentiator between adolescent groups than psychiatric symptoms, as suggested by our study in Chapter 2. Also, Ud and GPF have been shown to differentially relate to grey matter, white matter and resting state functional connectivity in our studies (Chapters 4-6).

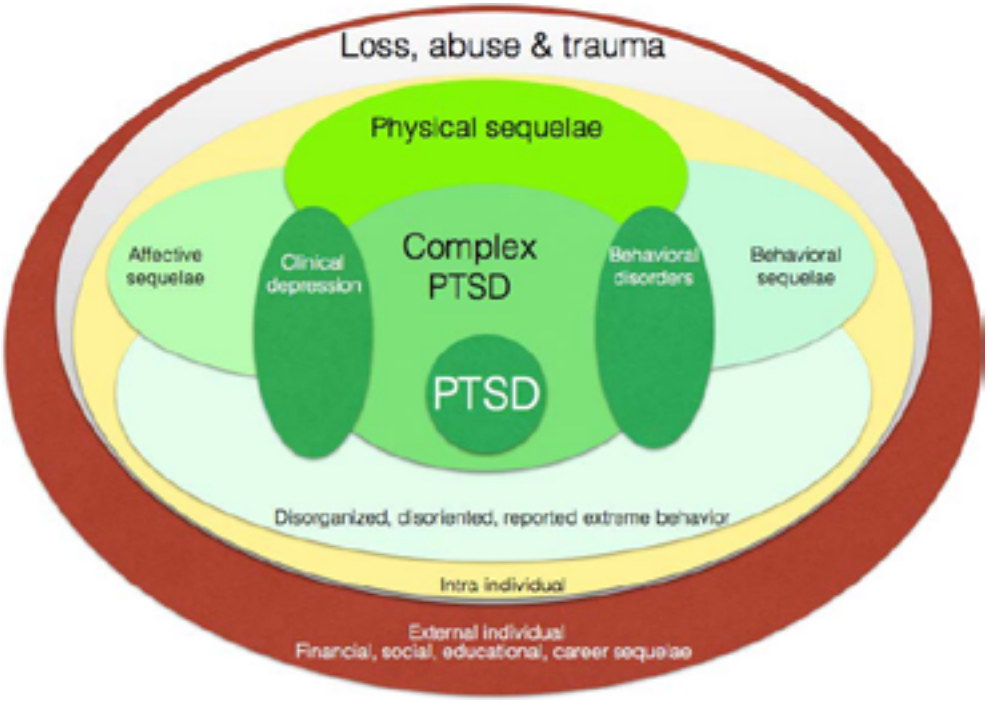

Figure 1. Graphic representation of intra-individual and external sequelae of loss, abuse and trauma and their overlap with psychiatric disorders

LIMITATIONS

General limitations of the studies in this thesis are:

1. generalizability of results due to:
    a) a relatively large but for the purpose of testing certain hypotheses still fairly small sample size;
    b) diagnostic group heterogeneity;
    c) selective, referred, willing to participate sample;
    d) restricted age, IQ, gender, diagnostic groups and ethnicity;
2. Being a cross-sectional study, conclusions about cause and time aspects cannot be drawn since unmeasured third factors may play a role.

Furthermore, *study-specific* limitations were that:

3. coding of the AAI was restricted to the established classifications and scales by Main and Hesse (Hesse, 2016), leaving out complementary Helplessness/Hostility (HH) coding (Lyons-Ruth, 2003);

4. The fMRI task may not be sensitive enough to detect clinical group differences on the neural level. The original face attention paradigm was used in anxious children and displayed anger as emotion and the question 'how hostile is the face?', while our adapted version was administered to traumatized and clinically depressed adolescents. This change in perspective may account for differences in the possibility to detect group differences of neural correlates;
5. the fMRI task was not tailored to content specificity of attachment or emotion regulation in clinical groups. As a recent meta-analysis suggests (Bar-Haim et al. 2007; Cisler et al., 2010), greater attention bias toward disorder-congruent relative to disorder incongruent threat stimuli might have made a difference;
6. we possibly measured the wrong proxy for emotion regulation, i.e. attention bias instead of attention bias variability, i.e. attention fluctuations alternating toward and away from threat (Iacoviello et al., 2014; Naim et al., 2015). The latter might have revealed group differences where attention bias did not;
7. the use of self-report questionnaires instead of diagnostic interviews may have biased the GPF: the use of self report questionnaires for a post-hoc GPF may not be apt.

RESEARCH DIRECTIONS

To start with, simultaneous assessment of psychiatric and attachment variables in clinical groups, using either type or combination of multimodal, multi-informant, longitudinal, experimental, fundamental, and/or practice-based designs is needed to determine how assessment of attachment should be implemented into (child)psychiatric practice.

As to use of a GPF, we estimated a GPF based on parent and self-report measurements for behavioral and emotional problems in children and adolescents using the TSCC, CDI, RCADS, A-DES, YSR, and CBCL. A Principal Component Analysis was performed using these (sub)scales. Validity of a GPF has been shown in a longitudinal, population-based study, e.g. Neumann and colleagues (2016) previously found a single nucleotide polymorphism heritability of a GPF in children also using the CBCL parent version to be valid and reliable. Zald and Lahey (2018) reviewed use of a GPF in relation to neuroimaging as particularly useful, surpassing taxonomic issues, lower-order and previously excluded diagnostic factors, as well as diagnostic interview skip-out shortcomings, taking a common genetic basis of higher-order factors into account. Elliott and colleagues (2018) showed that the trans-diagnostic risk for common forms of mental illness is associated with patterns of inefficient connectome-wide intrinsic connectivity between visual association cortex and networks involved in executive control and self-referential processes. These networks are often impaired across categorical disorders.

However, the GPF has initially been based on dimensional scores derived from diagnostic interviews as the CAPS (Child and Adolescent Psychopathology Scale; Lahey et al., 2004) and Diagnostic Interview Schedule (DIS; Robins, Cottler, Bucholz, & Compton, 1995)(Caspi et al., 2014; Lahey et al. 2012). Caution is therefore needed in interpretation of a parent and self-report based GPF as conclusive regarding findings. More research would be needed in order to investigate the reliability and validity of a parent and self-report based GPF against a clinical diagnostic interview based GPF. Also, in order to test replicability of a GPF independent from statistical methods applied, studies using a GPF should apply several statistical methods such as principal component analysis (PCA), confirmatory factor analysis (CFA) and structural equation modeling (SEM) to compare for statistical differences inherent in the method used. At the same time the kind of parent-, third informant- and self-reports and diagnostic interviews included in a GPF should be scrutinized carefully.

As assessment of Ud and incoherence in the narrative of the AAI is based on disoriented and disorganized (i.e. dissociative) indices (Hesse, 2016) and referring to literature on dissociation (e.g. Bryant, 2007; Liotti et al., 2004; Lanius, 2015; Van der Kolk, 2014), we speculate that unresolved-disorganized attachment and dissociation may be concepts that are not only relevant by themselves in case of loss or trauma, but also part of one dissociation spectrum of more or less (un)conscious awareness of reality (see also Bryant, 2007). However, considering the differential neuroimaging findings in this thesis regarding Ud and a GPF, and the conceptual overlap regarding trauma, dissociation and unresolved-disorganized attachment, simultaneous assessment of posttraumatic stress symptoms, unresolved-disorganized attachment, and dissociation may be a first crucial step to disentangle these concepts in future research and get more insight into the essence of the specific correlations of Ud and GPF to the brain. Measures to perform this research could include a diagnostic interview on PTSD symptoms, for example the CAPS(-CA) (Lahey et al., 2014) a diagnostic interview on dissociation e.g. the DDIS (Ross et al., 1989), attachment-based interviews of the parents e.g. the AAI, WMCI (Working Model of the Child Interview; Zeanah, Benoit , & Barton, 1986; Madigan, Hawkins, Plamondon, Moran, & Benoit, 2015), and parent-child interaction observation e.g. the AMBIANCE (Atkinson, Goldberg, Raval, Pederson, & Leung, 2005; Madigan, Benoit, & Moran, 2007; Madigan, Hawkins, Goldberg, & Benoit, 2006; Madigan et al., 2006).

Conceptual research regarding attachment dimensions of unresolved loss or trauma within a dissociation spectrum should comprise systematic registering of dimensional and categorical aspects of psychiatric disorders according to DSM-5 and ICD-11 criteria (see also Olff, 2015; Olff et al., 2015a), as well as coding of dimensional and categorical aspects of attachment representation according to classical and hostile-helpless coding (Hesse, 2016; Lyons-Ruth, 2003). Also, it would be necessary to assess the existence of any loss or trauma for all participants at baseline using a valid and reliable screening questionnaire as the CRIES-13 (Children and War Foundation, 1998; M. Olff, 2005; Verlinden, Olff, &

Lindauer, 2005) and conducting an additional clinical interview on posttraumatic stress symptoms such as the CAPS-(CA) (Diehle, de Roos, Boer, Lindauer, 2015; Nader et al., 1996; van Meijel, Verlinden, Diehle, & Lindauer, 2014) if loss or trauma is present. In order to capture hidden dimensions that might load onto a GPF, it would be pertinent to compare a strictly non-traumatized depression group with a traumatized depression group alongside anxiety, trauma-naïve, trauma-exposed, PTSD and CPTSD groups, and even inclusion of non-traumatized groups within other diagnostic categories has been recommended (Lanius, 2015; Van der Kolk, 2014; Zald & Lahey, 2018).

The fMRI study on emotional face processing did not yield significant brain results. We expect that in studies with more power, other prospective samples, a design using anger as emotion, emotional face processing will differ between diagnostic and age groups (Wu et al., 2016). Also, using a GPF might reveal correlations of psychopathology to particular emotional face processing. Future studies should use approach-avoidance fMRI tasks when trying to correlate these with attachment status. Finally, Hostile-Helpless coding (Lyons-Ruth, 2003) in addition to the Main and Hesse coding (Hesse, 2016) used in this thesis could reveal additional associations between attachment status and brain functioning and volume.

In general, prospective, longitudinal intervention designs and transgenerational, birth and family cohort studies could elucidate trauma- and attachment-related grey matter, WMI and (resting state) functional (connectivity) changes in the individual and in diagnostic groups over time, taking somatic findings into account. Specifically, other MRI modalities, such as Magnetic Resonance Spectroscopy (MRS) and Magnetisation Transfer Imaging (MTI) would be helpful clarifying trauma- and attachment-related brain changes on the molecular level.

Instead of correlating Ud and GPF to separate MRI modalities of the brain, it would be even more interesting to correlate these variables to a combination of several MRI modalities at once in so called *graph theoretical small world analyses* (Stam, Douw, & de Haan, 2010; Watts, & Strogatz, 1998), *measuring the efficiency of the brain*. Doing so would tap into the concept of 'warm data' i.e. information about the interrelationships that integrate elements of a complex system, in this case brain structure and functioning (Bateson, 2000; Morin, 2008; Ruesch & Bateson, 2009; http://internationalbatesoninstitute.org/warm-data). Graph theoretical small world analyses could illustrate any disturbance of the inner coherence of the brain in case of trauma such as CSA, as graph theory deals with global and local characteristics of networks (Koenis et al. 2015; Petrella, 2011; Puetz et al., 2016). By combining scalefree networks, which are characterized by scalefree grade distribution and networkhubs (Barabási & Albert, 1999; Albert & Barabási, 2002), with small worldliness, which is characterized by high clustering coefficient and short path length

(Watts, & Strogatz, 1998), it is possible to measure the efficiency of the brain networks.

The brain can be considered a network on multiple scales, from synaptic connections between neurons, to corticocortical or cortico-deep gray connections between different cell types and large-scale connections between brain regions in the form of white matter bundles or fascicles (Petrella, 2011; Van den Heuvel, & Sporns, 2013a; Van den Heuvel, & Sporns, 2013b). The brain is organized in a functionally specialized manner, with some areas segregated for certain specialized functions, e.g. vision, motor control, or language. Higher functions depend on integration of information from these regions. Some psychiatric and neurocognitive disorders can be classified as disconnection syndromes, in which there is damage to either white matter connections or association cortices bridging specialized sensorimotor regions (Catani & Ffytche, 2005; Geschwind, 1965a; 1965b). Particular symptoms can theoretically emerge from particular types of damage to large-scale brain networks.

Findings suggest that small-world metrics may be useful imaging-based biomarkers for a number of conditions. In addition, the robustness of a network to particular types of structural damage can be tested with lesion models (Bullmore, & Sporns, 2009). Also, there is evidence that network dysfunction may precede even molecular abnormalities in patients with neurodegenerative disease and that psychiatric disorders may stem from abnormalities in the development of large-scale networks in utero or in early postnatal life. Graph theory network measures may represent endophenotypes of such conditions, and evidence is starting to accumulate that suggests a possible role for graph theory network measures in early diagnosis, and assessment of vulnerability or resilience of these conditions (Bullmore, & Sporns, 2009; Ohashi et al., 2019). Early diagnosis and assessment of vulnerability or resilience of conditions would allow for secondary prevention and better treatment of cognitive brain disorders in the future, since the usefulness of individual conventional imaging tools by themselves is limited (Petrella, 2011; Van den Heuvel, & Sporns, 2013a; Van den Heuvel, & Sporns, 2013b). Applying graph theory to MRI findings to assess the efficiency of the brain may therefore help us better understand the biological underpinnings of behavioural function and dysfunction. Clustering coefficient furthermore has been associated with genetic expression in 50% of cases (Adelstein et al., 2011; Fornito et al., 2011; Van den Heuvel, Kahn, Goñi, & Sporns, 2012; Van den Heuvel, & Sporns, 2013a; Van den Heuvel, & Sporns, 2013b). As we performed analyses of grey and white matter, function and resting state functional connectivity, we have the opportunity to combine several MRI modalities in graph analyses. These could give additional insight into small world properties of the adolescent brain in relation to diagnostic category, as well as in relation to differential associations with Ud and GPF.

Finally, research outside the scope of the research findings in this thesis worth

mentioning is work on the kappa-opioid and endocannabinoid systems, which in relation to attachment besides trauma-related dissociation could reveal pharmacological pathways to treatment of debilitating dissociation symptoms (Lanius et al., 2018). In addition, correlation of registered epigenetic, immunological and hormonal changes over time with assessed trauma and attachment variables, specifically Ud and GPF, could greatly help to gain insight in neurobiological processes and working mechanisms of attachment, trauma and emotion regulation. These in turn might be able to help design tailor-made, personalized and therefore efficacious treatments in the future.

CLINICAL IMPLICATIONS

With regard to implications for child and adolescent clinical practice, our findings suggest that attachment, coherence, and unresolved loss or trauma may be relevant concepts to be taken into account in child psychiatric diagnostic assessment and treatment, especially in adolescents suffering from CSA-related PTSD or clinical depression (Kim, Blashfield, Tyrer, Hwang, & Lee, 2014; Tarren-Sweeney, 2014; Tyrer, 2014).

Specifically, the discussion about the concept of complex PTSD, that has been included in the ICD-11 but not in the DSM-5, may profit from findings in this thesis regarding Ud and psychopathology in diagnostic groups and regarding neural correlates of Ud and GPF. Liotti (2004) already theorized that trauma, unresolved-disorganized attachment and dissociation are interrelated. Unresolved-disorganized attachment is a linguistically analysed reflection of a state of mind in which the coherence of the narrative plays a dominant role, while dissociation and posttraumatic stress reactions are experiential individual findings that only partly can be observed, sometimes better by an outsider than by the individual self (see e.g. Van der Hart, Nijenhuis, & Steele, 2005). As shown in this thesis (Chapters 2-6), one should realize that self-reports of psychopathology, e.g. posttraumatic stress and dissociation, address different aspects and levels of functioning (at rest) and relate to different brain structures, trying to define trauma from different perspectives, than coding of Ud (which includes indices of dissociation in the narrative). A multimodal, multi-informant approach (Van IJzendoorn & Schuengel, 1996) could therefore generate a better picture of which aspects of attachment- and trauma-related dissociation are prevalent in case of loss or trauma, than self-reports as used in clinical practice routine outcome monitoring for example could do alone.

In addition, Lanius suggested a pronounced role for diagnostics and treatment of dissociation in case of trauma (Frewen & Lanius, 2014; Lanius, 2015). She proposed a model that categorizes symptoms of trauma-related psychopathology into (1) those that occur within normal waking consciousness (NWC) and (2) those that are dissociative and

are associated with trauma-related altered states of consciousness (TRASC) along four dimensions: (1) time; (2) thought; (3) body; and (4) emotion, as Thompson and Zahavi outlined (2007). Though some attachment aspects are incorporated in proposed treatment options (Lanius, 2015), proposed psychiatric diagnostics do not include assessment of attachment at all, which we think is worth considering with reference to Liotti's theory and the findings regarding Ud and psychopathology in diagnostic groups and regarding neural correlates of Ud and GPF in this thesis.

For *diagnostics* regarding CSA victims, or for that matter any traumatized individual, our findings emphasize the importance of diagnosing unresolved trauma, but also looking for more general indications of an incoherent autobiographical narrative, which may also be the case in loss or other than victims of sexual abuse. For general clinical application of the AAI, Steele and Steele (2008) already described several applications, which can be implemented in (child)psychiatric practice without transcription or coding of the AAI. However, the effects of these clinical applications need further investigation. In order to structurally implement coded AAIs in clinical practice, the use of advanced voice recognition software, text and data mining, big data analysis and deep learning techniques (see e.g. https://www.forbes.com/sites/bernardmarr/2016/12/08/what-is-the-difference-between-deep-learning-machine-learning-and-ai/#19db351b26cf) could greatly help. In addition, the availability of a larger number of certified transcribers and coders, embedded in a postdoctoral educational system would be a prerequisite.

The clinical implication of our finding that Ud is a trans-diagnostic factor correlating with GMV, WMI of white matter tracts, and RSFC is that systematic categorical as well as dimensional assessment of attachment features and psychiatric symptoms is critical in understanding clinical functioning of adolescents. Systematic diagnostic assessment may also be essential in understanding personality development and how adolescents and young adults deal with (future) pregnancies and/or parenthood.

With regard to clinical applications of knowledge about *attention bias and emotional face processing* anyone, but a clinician in particular, should realize that his or her neutral face might negatively impact upon a traumatized person, even more so than if that person is mentally affected but not traumatized (derived from Chapter 3). A clinician's friendly face and attitude may therefore greatly increase a safe working alliance with anyone seeking help but in particular those traumatized. Attention Bias Modification Treatment (ABMT; Hakamata et al., 2010) or attention control training (ACT; Badura-Brack et al., 2015) are two promising treatments. It may well be that the slower reaction time to fearful and neutral emotional faces in adolescents with CSA-related PTSD interferes with their daily social functioning and prevents them from seeking and accepting help. In that case other strategies, such as a structuring contact with a psychiatric nurse, or perhaps ABMT and ACT, are needed first to engage them coming into psychotherapy.

Finally, as it comes *to treatment* of traumatized individuals, also adolescents, the mentalizing approach and (attachment) attitude of the therapist may be a crucial factor in the success of any therapy applied (Fonagy & Bateman, 2016; Luyten & Fonagy, 2015). Several forms of psychodynamic therapy and mentalization based treatment could provide a solid base to create a safe working alliance with any patient, but especially traumatized individuals who likely are unresolved for loss or trauma or otherwise insecurely attached. Given this safe working alliance, specific therapeutic techniques could be applied, aimed at reducing trauma-related psychiatric and somatic symptoms, thereby enhancing emotional and cognitive functioning (Van der Kolk, 2014).

POLICY IMPLICATIONS

Conducting this study, we noticed various partially non-matching conceptualisations of trauma, attachment and emotion regulation are used in the fields of child psychiatry, child psychology and attachment. This makes speaking in one language everyone will understand, a lingua franca, a challenge. The psychiatric diagnostic classification system (Diagnostic and Statistical Manual of Mental Disorders 4th edition, DSM-IV, used during the study; APA, 2013) is quite different from the Main, Goldwyn, and Hesse system for attachment representation classification (2003; Hesse, 2016) we refer to in this thesis. Definitions of trauma and assessment of the impact of trauma for example differ. This illustrates that the psychiatric perspective and attachment perspective have different observation starting points, different evaluation criteria, and therefore also have different outcomes. This may explain part of the communication problems between psychiatrists and attachment specialists and why (child)psychiatry has not yet incorporated findings from attachment research since John Bowlby and Mary Ainsworth suggested the importance of attachment for emotion regulation about 70-80 years ago.

Additional attachment research since the past four decades has added even more evidence and specifications as to how attachment influences the well-being of humankind and which interventions may help to counteract negative parent-child interactions (e.g. Cyr et al., 2010; Dozier et al., 2014). Therefore, we think it is very unfortunate that (child) psychiatry and attachment research live separate lives and suggest this situation should change quickly: (child)psychiatry and both children and parents could benefit a lot from implementation of attachment research findings. A block chain dynamic, multidisciplinary guideline (Benchoufi, & Ravaud, 2017) on implementation of the concept of attachment in prevention, diagnostics and treatment policies in child and adolescent psychiatry, youth care, and multidisciplinary centres for child abuse and neglect, would be helpful to support clinical practice.

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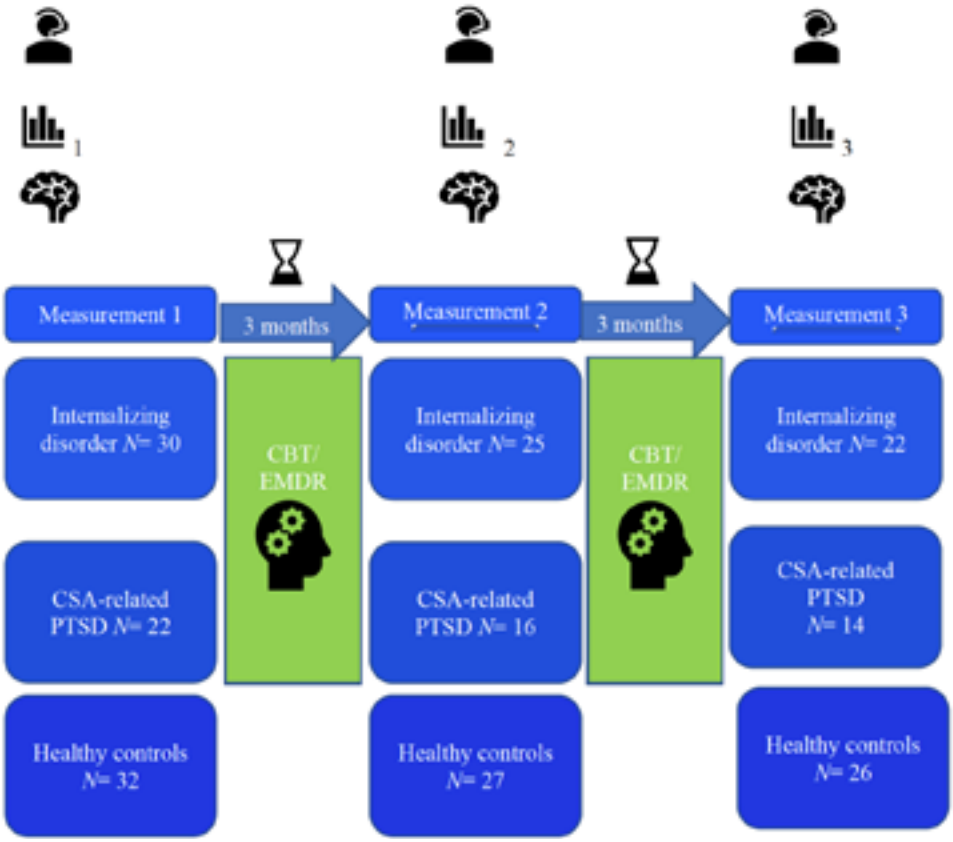
http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml#toc_background)
http://www.FMRIb.ox.ac.uk/fsl ; FSL FMRIB's Software Library

APPENDICES

STUDY DESIGN EPISCA



Graphic representation study design Emotional Pathways' Imaging in Clinical Adolescents (EPISCA) , slight variation presented at Publiekslezing "Hersenspinsels" LIBC, Leiden, May 15th, 2010

Studies presented in this thesis used data from Measurement 1 only

MEASUREMENT

- MRI scan
  - Emotional faces task
  - RSFC, fMRI (task), VBM/DTI/Structural, MTI, MRS
- Questionnaires/testing
  - Psychopathological symptoms, coping, competence feeling, puberty
  - IQ (6 subtests WISC or WAIS)
- Interviews
  - ADIS (Silverman, Saavedra, & Pina, 2001)
  - AAI (Main, Kaplan, & Cassidy, 1985)

EMOTIONAL **F**ACES **T**ASK

Four questions:	Three facial expressions:
How afraid are you?	Afraid
How happy are you?	Happy
How wide is the nose	Neutral
Passive viewing	

- Several conditions
  - Focus on questions
  - Focus on emotions
  - Interaction between questions and emotions
- Behavioural data
  - Reaction times
  - Subjective scores
- fMRI data

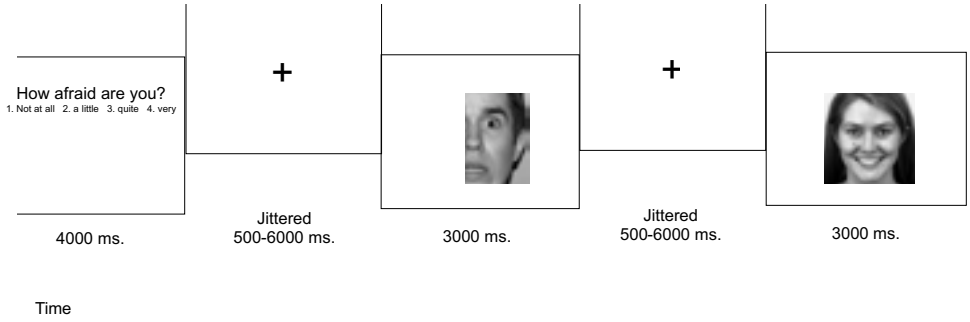


Fig. X. Display of task design. Subjects were presented with one of four states, followed by a centrally located cue, after which one of the emotional faces was shown. Subjects were asked to rate each emotional face on a four-point rating scale ranging from 'not at all' to 'very', based on the presented state. During scanning reaction times and subjective scoring were registered.

SUMMARY IN DUTCH | SAMENVATTING

I have tried not to laugh about human behavior, not to cry or to hate, but to understand.

Baruch Spinoza (1632, Amsterdam-1677, The Hague)

ONVERWERKT-GEDESORGANISEERDE GEHECHTHEID, PSYCHOPATHOLOGIE EN HET ADOLESCENTE BREIN

Een jongere die veel misbaar maakt, in ruzies verzeild raakt, zich verzet tegen autoriteit, of zich juist terugtrekt op zichzelf, zichzelf verwondt, angstig is, alle hulp afwijst en het zelf wil doen. Dit kan zowel met de puberteit of psychische problemen te maken hebben als met onverwerkt trauma of verlies, zich uitend in gehechtheid. Hoe hangen zowel psychopathologie als gehechtheid samen met hoe de hersenen van jongeren gevormd zijn en functioneren? Dat is de vraag die dit proefschrift wil helpen beantwoorden.

Dit proefschrift focust op gehechtheid, trauma en emotieregulatie en hoe deze factoren onderling samenhangen in de adolescentie door het onderzoeken van: 1. gedrags- en geestelijke gezondheid correlaten van gehechtheid en emotieregulatie (bijv. aandachtsbias); 2. neurale correlaten van emotionele gezichtenverwerking (als benadering van emotieregulatie); 3. differentiële neurale correlaten van gehechtheid en psychopathologie. We onderzochten een groep adolescenten met seksueel misbruik-gerelateerde posttraumatische stressstoornis (PTSS), angst- en/of depressieve stoornis (in deze dissertatie genoemd klinische depressie) en niet-klinische controles.

Verheldering van neurobiologische mechanismen die ten grondslag liggen aan gehechtheid, trauma en emotieregulatie zou kunnen helpen om 1) atypische ontwikkeling en gedrag te begrijpen; 2) Het beloop van psychopathologie en neurale plasticiteit te identificeren; 3) de dagelijkse (klinische) praktijk en toekomstig wetenschappelijk onderzoek te informeren. Zowel aan seksueel misbruik gerelateerde posttraumatische stress stoornis, als angst- en depressieve stoornissen zijn ernstige aandoeningen. Er is tijdige, effectieve behandeling voor nodig die echter niet altijd voorhanden is. Onderzoek van onderliggende hersenmechanismen is daarom nodig om unieke en overlappende factoren in beide aandoeningen te identificeren. Deze factoren zouden theoretische concepten en de praktijk die eruit volgt kunnen veranderen.

Eerst geven we achtergrond informatie over gehechtheid. Vervolgens zetten we bevindingen per hoofdstuk op een rij. Daarna bezien we deze bevindingen in samenhang met elkaar en hun betekenis. Ook noemen we beperkingen en klinische implicaties van dit onderzoek. Tot slot bespreken we aanbevelingen voor toekomstig onderzoek en beleid.

Gehechtheid

Gehechtheid is één van de concepten die aan de basis van menselijke interactie ten grondslag liggen. De gehechtheidstheorie beweert dat de interactie met gehechtheidsfiguren, ouders en/of verzorgers, van jongs af aan de basis voor emotieregulatie vormt door intern gevormde concepten van zichzelf en anderen (Bowlby, 1969/1982; 1988). Hoe een kind of adolescent

zich ontwikkelt wordt bepaald door de interactie tussen zijn neurobiologische aanleg en hoe het wordt opgevoed: voorspelbaar en met warmte, kil en afstandelijk of overbeschermd, onder te hoge prestatiedruk of in een geparentificeerde rol. Traumatiserende ervaringen, door kindermishandeling of –verwaarlozing of seksueel misbruik, beïnvloeden een kind negatief. Deze ervaringen kunnen maken dat bepaalde genen aan of juist uit gezet worden en mede zo de lichamelijke gezondheid negatief beïnvloeden. Deze ervaringen kunnen er ook voor zorgen dat de emotieregulatie tekort schiet, er psychiatrische symptomen ontstaan, en als het trauma of verlies onverwerkt blijft, de gehechtheid onveilig of zelfs gedesorganiseerd raakt (Felitti et al., 1998; Gospodarevskaya, 2013; Van der Kolk, 2012; Teicher, Samson, Anderson, & Ohashi, 2016).

Het concept gehechtheid behoeft nog steeds verheldering en meetbare toepasbaarheid in de klinische praktijk. Het bestuderen van hersenmechanismen zou kunnen helpen het concept gehechtheid verder te ontwikkelen. Welke hersenmechanismen zijn essentieel voor gehechtheid? Een belangrijke ontwikkelingstaak in de adolescentie is om autonomie te verwerven en zich los te maken van ouders. Gehechtheid van adolescent aan ouders zou kunnen bepalen hoe een adolescent deze ontwikkelingstaak uitvoert. Hoe is gehechtheid aan hersenvolume en –activiteit te relateren? Verheldering van neurobiologische mechanismen van ontwikkeling en functioneren van kinderen en adolescenten kan helpen om typische en atypische ontwikkeling en gedrag te begrijpen.

Bevindingen per hoofdstuk

In **hoofdstuk 2** beschreven we drie groepen adolescenten, twee klinische groepen (met aan seksueel misbruik gerelateerde PTSS respectievelijk klinische depressie) en een niet-klinische groep qua psychiatrische symptomen en gehechtheidsrepresentaties en vergeleken hen onderling. Ook onderzochten we de associatie tussen psychiatrische symptomen en de dimensionele scores op coherentie van denken en onverwerkt verlies of trauma op het gehechtheidsbiografisch interview (GBI). We onderzochten posttraumatische stress middels een trauma vragenlijst (de Traumatic Symptom Checklist for Children; TSCC), dissociatieve symptomen middels zelfrapportage op de Adolescent-Dissociative Experiences Scale (A-DES) en depressieve klachten middels de Children's Depression Inventory (CDI). Ten eerste vonden we dat de seksueel misbruik groep het meest onverwerkt-gedesorganiseerd gehecht was, vergeleken met zowel de klinische depressie groep als de niet-klinische controle groep. Overrepresentatie van onverwerkt trauma en 'Cannot Classify' classificaties (U/CC) lagen ten grondslag aan deze onverwerkt-gedesorganiseerde gehechtheidsclassificatie. Ten tweede correleerden psychiatrische symptomen met onverwerkt-gedesorganiseerde gehechtheid, maar niet met coherentie van denken. Ten derde scoorde onverwerkt trauma of verlies het hoogst en coherentie van denken het laagst in de seksueel misbruik groep, vergeleken met de klinische depressie en de niet-klinische controle groep. Alleen coherentie van denken onderscheidde de seksueel misbruik groep

van de klinische depressiegroep en niet-klinische controles, gecorrigeerd voor leeftijd, IQ en psychiatrische symptomen. De onverwerkt trauma of verlies schaal onderscheidde beide klinische groepen van controles.

Het was opvallend dat de adolescenten in de seksueel misbruik groep allemaal PTSS hadden. Daarnaast bleken zowel adolescenten met seksueel misbruik als die met angst en/of depressieve klachten hoge scores voor posttraumatische stress, dissociatie en depressieve symptomen te hebben. Ook bleek het seksueel misbruik overwegend ernstig, repetitief en/of langdurig van aard te zijn geweest, was er soms sprake van groepsverkrachting geweest en daarnaast een hoog percentage emotioneel misbruik of verwaarlozing, fysieke mishandeling, verliezen, gepest zijn en andere traumatische ervaringen. Andere traumatische ervaringen bleken overigens ook bij enkele adolescenten uit de klinische depressie groep aanwezig te zijn. De veelheid aan psychiatrische symptomen en traumatische en verlieservaringen naast relationele en zelf-organisatie problemen doet in retrospect vermoeden dat er niet alleen sprake was van PTSS, maar zelfs van de ICD-11 diagnose complexe PTSS (World Health Organization International Classification of Diseases, 11e editie, 2017; o.a. Herman, 1992; Cloitre, 2015; Ford, 2015; Jonkman, Verlinden, Bolle, Boer, & Lindauer, 2013; Karam et al., 2014; Marinova & Maerker; Olff et al., 2015) of in elk geval "PTSS met prominente dissociatieve symptomen" (DSM-5; American Psychiatric Association [APA], 2013). We vermoeden dat óf een al bestaande incoherente manier van denken in samenhang met een insensitieve opvoeding een hoog percentage onverwerkt trauma kan hebben gegenereerd in geval van seksueel misbruik, óf dat de ernst en complexiteit van de traumatische ervaringen en psychiatrische symptomen één van de redenen zou kunnen zijn dat in onze studie onverwerkt-gedesorganiseerde gehechtheid (d.w.z. onverwerkt verlies of trauma) met een overrepresentatie van CC classificaties en lage coherentie van denken onderscheidend waren voor de seksueel misbruik groep. Tevens zou dit kunnen impliceren dat complexe PTSS en onverwerkt-gedesorganiseerde gehechtheid (deels) overlappen of vanuit een ander perspectief hetzelfde klinische fenomeen beschrijven. Dat zou nader onderzocht moeten worden.

Uit onze studie bleek onverwerkt verlies of trauma samen te hangen met posttraumatische stress en depressieve symptomen, maar bleek de mate van dissociatie in de seksueel misbruik groep niet significant te verschillen van die in de klinische depressiegroep. Ook hing dissociatie niet samen met coherentie van denken. Mogelijk komt dit doordat zelfrapportage onvoldoende betrouwbaar is en dat dissociatie een combinatie van interne beoordeling door de adolescent en klinische beoordeling en observatie door de omgeving vergt. Daarnaast is coherentie van denken een evaluatief oordeel van de codeur van het GBI, onafhankelijk van zelfkennis en wat de adolescent over zichzelf vermeldt.

In deze dissertatie zijn zowel categorale als dimensionele variabelen van het GBI gebruikt, voor een discussie hierover verwijzen we naar Roisman, Fraley, & Booth-LaForce, 2014; van IJzendoorn & Bakermans-Kranenburg, 2014. Dit heeft ons inziens

bijgedragen aan meer gedifferentieerd inzicht in de aard van de gehechtheid van de klinisch diagnostische groepen en de statische kracht van de analyses. Zo bleek door gebruik van de categorale variabelen dat de CC classificatie onderscheidend was voor de seksueel misbruik groep, en door gebruik van de continue variabelen dat coherentie van denken met name onderscheidend was in de seksueel misbruik groep, terwijl onverwerkt verlies of trauma geen significant onderscheid maakte tussen de seksueel misbruik en de klinische depressie groep wanneer leeftijd, IQ en psychiatrische symptomen als covariaten in de analyse werden meegenomen.

In **hoofdstuk 3** beschreven we een functionele neuroimaging studie waarbij het zien van angstige, blije en neutrale emotionele gezichten gekoppeld werd aan aandachtsbias en hersenfunctioneren in drie groepen adolescenten: met aan sexueel misbruik gerelateerde posttraumatische stress (PTSS), angstig en/of depressief dan wel gezond. We veronderstelden ten eerste dat adolescenten met aan seksueel misbruik gerelateerde PTSS een aandachtsbias weg van dreiging zouden hebben, en daarom negatieve en neutrale gezichten negatiever zouden interpreteren en langzamer zouden zijn in de interpretatie ervan dan angstig/depressieve adolescenten en niet-klinische controles. Dit bleek ook het geval te zijn, mogelijk door een combinatie van automatische en strategische emotionele gezichtenverwerking waarbij dreiging snel ontdekt wordt enerzijds en men anderzijds moeite heeft met de aandacht van de dreiging af te halen. Ten tweede veronderstelden we dat adolescenten met aan seksueel misbruik gerelateerde PTSS meer activatie in het limbische systeem zoals de amygdala zouden laten zien en minder in de prefrontale hersenen (zoals de dorsolaterale prefrontale cortex, dlPFC) bij het interpreteren van emotionele gezichten als angstig, blij, neutraal, vergeleken met adolescenten met een klinische depressie en niet-klinische controles (Garrett et al., 2012; Masten et al., 2008). Dat bleek niet het geval te zijn in onze onderzoeksgroep. Mogelijk had dat te maken met een snelle amygdala habituatie aan emotionele gezichten in adolescenten met aan seksueel misbruik gerelateerde PTSS, zoals we in latere analyses vonden (Van den Bulk et al., 2016). Het kan ook zo zijn dat het grote aantal covariaten dat we moesten gebruiken voor uitvoeren van de analyses, in combinatie met de beperkte groepsgrootte, het vinden van significante groepsverschillen verhinderde. Mogelijk dat gebruik van een algemene psychopathologie factor ofwel General Psychopathology Factor (GPF) wel significante groepsverschillen zou hebben opgeleverd (Caspi et al., 2014; Lahey et al., 2015; 2017; Zald & Lahey, 2017). Een andere reden dat we geen significante groepsverschillen vonden kan zijn dat er geen significante verschillen tussen de dimensioneel gescoorde psychopathologie symptomen waren, vermoedelijk geassocieerd met in tweede instantie, post-hoc, geconstateerde PTSS in een subgroup van de klinische depressie groep. Ten derde onderzochten we of de ernst van posttraumatische stress, dissociatie en depressieve symptomen in adolescenten met aan seksueel misbruik gerelateerde PTSS en klinische depressie correleerde met verhoogde activatie van de amygdala en insula en verminderde activatie van de dlPFC vergeleken met

niet-klinische controles. Ook hier vonden we geen significante verschillen tussen groepen deelnemers.

In **hoofdstuk 4** beschreven we een gecombineerde structurele en functionele connectiviteit in rust studie waarbij onderzocht werd of onverwerkt-gedesorganiseerde gehechtheid (Ud) aan het volume van de amygdala en/of hippocampus en de functionele connectiviteit in rust gerelateerd was in een groep adolescenten met aan seksueel misbruik gerelateerde PTSS, angst en/of depressieve stoornis of zonder psychiatrische problemen. We gebruikten zowel categorale als dimensionele gehechtheidsvariabele. We veronderstelden dat onverwerkt-gedesorganiseerde gehechtheid versus georganiseerde gehechtheid (Ud/non-Ud) geassocieerd zou zijn met hersenstructuur en met het volume van amygdala en hippocampus, gecontroleerd voor een GPF. Ud/non-Ud bleek (gecorrigeerd voor GPF, leeftijd, IQ en gender) inderdaad gerelateerd aan een kleinere linker hippocampus, maar niet aan de rechter hippocampus of de amygdala beiderzijds. Daarnaast was er een positieve correlatie tussen Ud/non-Ud en de linker hippocampus functionele connectiviteit met de rechter middelste temporale gyrus (MTG) en laterale occipital cortex (LOC), beiden geassocieerd met het verwerken van emotionele informatie. Onze bevindingen komen overeen met onderzoek dat laat zien dat Ud een transdiagnostische factor is die de kwetsbaarheid voor psychopathologie in zijn algemeenheid verhoogt. Deze bevindingen impliceren verder dat eerder gevonden afwijkingen van de hippocampus in mensen met PTSS, angst- of depressieve stoornis geen specifieke biomarker zijn voor individuele psychiatrische stoornissen, maar juist gemeenschappelijk zijn aan verschillende stoornissen, en te maken zouden kunnen hebben met etiologische factoren geworteld in jeugdervaringen met betrekking tot gehechtheid. Stress in de vroege jeugd is gerelateerd aan een ontregelde hormoonhuishouding, waarbij het lichaam bij lichte stress te weinig of juist overmatig reageert. Een beschadigde hippocampus reduceert namelijk het feedback controle mechanisme van de HPA-as die de hormoonhuishouding regelt. Dit leidt tot slechte emotieregulatie en verhoogde kwetsbaarheid voor psychopathologie bij degenen met Ud, onverwerkt-gedesorganiseerde gehechtheid. Ook blijkt Ud gerelateerd te zijn aan atypische hippocampus connectiviteit met het limbisch en default mode netwerk van de hersenen in rust.

In **hoofdstuk 5** beschreven we een Diffusion Tensor Imaging (DTI) studie van de witte stof van de hersenen waarin we onderzochten of Ud en GPF unieke correlaties met de witte stof integriteit van de hersenen, vooral de witte stof banen, hadden in een groep adolescenten met aan seksueel misbruik gerelateerde PTSS, angst en/of depressieve stoornis of zonder psychiatrische problemen. We gebruikten zowel categorale als dimensionele gehechtheidsvariabelen. Het GBI was gebruikt om transdiagnostische risicofactoren te kunnen bepalen. We veronderstelden ten eerste dat Ud en een GPF unieke correlaties zouden hebben met de integriteit van witte stof banen. Ten tweede namen we aan dat, na correctie voor een GPF, Ud geassocieerd was met een reductie van de witte stof integriteit

in regio's die eerder geassocieerd waren met tegenspoed in de kindertijd, zoals cingulum, corpus callosum, superieure longitudinale fasciculus (Daniels, Lamke, Gaebier, Walter, & Scheel, 2013). We vonden dat Ud en een GPF unieke correlaties met de witte stof integriteit van de witte banen in de hersenen vertoonden. Dat is niet verwonderlijk omdat witte stof zich langzaam ontwikkelt in de tijd en zowel psychopathologie als gehechtheid dus veel tijd hebben om invloed op de witte stof integriteit uit te oefenen, maar elk kennelijk op andere plekken van de witte banen en op andere momenten (Andersen, 2003; Ayling, Aghajani. Fouche, & Van der Wee, 2012). Niet iedere regio van het corpus callosum groeit namelijk even hard. Met name het splenium groeit harder dan andere regio's in de kindertijd en is zo kwetsbaarder voor stressoren en daarmee voor Ud, onverwerkt-gedesorganiseerde gehechtheid door trauma of verlies. Onze bevindingen laten zien dat gereduceerde witte stof integriteit in de genu en body van het corpus callosum een transdiagnostische biomarker van uiteenlopende psychopathologie is. Gereduceerde witte stof integriteit van de IFOF en splenium van het corpus callosum daarentegen lijkt gerelateerd te zijn aan de gevolgen van onverwerkt verlies of trauma uit de kindertijd en zou te maken kunnen hebben met de heterogeniteit in diagnostische categorieën.

In **hoofdstuk 6** beschreven we een studie naar de functionele connectiviteit van de hersenen in rust, gefocust op de amygdala en dorsale anterieure cingulate cortex (dACC) in relatie tot de mediale frontale cortex met betrekking tot Ud en een GPF, gecontroleerd voor elkaar, in een groep adolescenten met aan seksueel misbruik gerelateerde PTSS, angst- en/of depressieve stoornis, en zonder psychiatrische klachten. We gebruikten zowel categorale als dimensionele gehechtheidsvariabelen. We vonden dat Ud positief geassocieerd was met grotere functionele connectiviteit tussen de linker amygdala en de linker laterale occipitale cortex, precuneus, en superieure pariëtale lob. Verder was Ud negatief geassocieerd met de connectiviteit tussen de linker amygdala en mediale frontale cortex. Er was geen significante relatie tussen een GPF en de dorsale anterieure cingulate cortex connectiviteit, noch die van de amygdala. Atypische amygdala connectiviteit lijkt dus eerder een kwetsbaarheidsfactor dan een biomarker van psychopathologie te zijn. Deze bevinding onderstreept de toegevoegde waarde van de dimensionele benadering van het gehechtheidsbiografisch interview en het gebruik van een GPF versus de normaliter categorale classificatie van alleen psychopathologie in zowel de klinische praktijk als onderzoek. Het zou ook kunnen betekenen dat het functioneren van een individu in rust afhankelijk is van zijn gehechtheidsrepresentatie, ongeacht psychopathologie. In geval van Ud ontbreekt het het individu vaak aan zelf-reflectie en bewustzijn van eigen psychologisch functioneren. Mogelijk dat door de zwakke verbinding tussen amygdala en frontale hersenschors angst minder bewust wordt beleefd en er vanuit de connectie met de precuneus en superieure parietale lob atypische emotionele informatieverwerking plaatsvindt. Deze hersengebieden zijn eerder geassocieerd met zelfbewustzijn, aandacht in de ruimte, geheugen en dissociatieve symptomen zoals depersonalisatie en

derealisatie. De negatieve connectiviteit tussen amygdala en mediale frontale cortex kan duiden op veranderde amygdala inhibitie. Daardoor kan excessieve angst en amygdala hyperactiviteit ontstaan waarbij niet het verstand maar emoties de overhand zouden kunnen krijgen in geval van onverwerkt-gedesorganiseerde gehechtheid. Veranderingen in de amygdala die eerder gevonden werden bij diverse psychiatrische ziekten blijken geen biomarker te zijn voor individuele psychiatrische ziekten, maar gemeenschappelijk voor overlappende ziektesymptomen. Deze veranderingen in de amygdala lijken dus eerder een kwetsbaarheidsfactor te zijn.

Discussie

Wat betreft het **eerste doel** van deze dissertatie om gedrags- en geestelijke gezondheid correlaten van gehechtheid en emotieregulatie (d.w.z. aandachtsbias) in de adolescentie te onderzoeken, vonden we significante verschillen tussen getraumatiseerde en niet-getraumatiseerde adolescenten wat betreft onverwerkt-gedesorganiseerde gehechtheid, maar slechts deels wat betreft psychopathologische symptomen in de diagnostische groepen (Hoofdstuk 2). Wat betreft gehechtheid bleek er meer overwerkt-gedesorganiseerde gehechtheid, met name 'cannot classify' voor te komen in de groep met aan seksueel misbruik gerelateerde PTSS (Hoofdstuk 2). Door zowel categorale als dimensionele variabelen te gebruiken zagen we dat ook coherentie van gedachten de groep met aan seksueel misbruik gerelateerde PTSS onderscheidde van de klinische depressie groep, terwijl er wat betreft onverwerkt trauma of verlies geen verschil was. Tot slot suggereerden onze bevindingen er onderliggende, onderscheidende hersenmechanismen zijn voor de klachten die je klinisch ziet, afhankelijk of vanuit gehechtheid of psychopathologie perspectief gekeken wordt (Hoofdstuk 4-6).

Deze studie heeft het inzicht in de relatie tussen trauma, dissociatie en gehechtheid vergroot door bevindingen die al bestaande theorieën ondersteunen (Cassidy & Mohr, 2001; Hesse, 2008; Liotti, 2004; Lyons-Ruth et al., 1999, 2006). Mogelijk dat de onderzochte groep adolescenten met aan seksueel misbruik gerelateerde PTSS beter valt te typeren als een groep met complexe PTSS (Herman, 1992; Jonkman, Verlinden, Bolle, Boer, & Lindauer, 2013; Karam et al., 2014) of PTSS met dissociatieve symptomen (DSM-5; American Psychiatric Association [APA], 2013). Dit gezien hun ernstige en/of langdurige fysiek seksueel contact inclusief herhaaldelijke of groepsverkrachtingen en impliciete emotionele mishandeling en verwaarlozing, fysiek mishandeling, verliezen, gepest zijn en andere traumatische gebeurtenissen, gecombineerd met een hoge mate van posttraumatische stress, dissociatieve en depressieve symptomen.

We veronderstellen dat 1) in geval van seksueel misbruik er al sprake zou kunnen zijn geweest van disorganisatie door al eerder bestaande incoherentie van denken ten gevolge van insensitieve opvoeding of atypisch oudergedrag zoals verwaarlozing, of dat 2) seksueel

misbruik of trauma zelf de desorganisatie veroorzaakt heeft. Deze veronderstellingen kunnen slechts getest worden in een longitudinale studie die het diathesis-stress model van trauma (Ingram & Luxton, 2005; Liotti, 2004; Zuckerman, 1999) afzet tegen de differentiële gevoeligheid hypothese (Bakermans-Kranenburg & Van IJzendoorn, 2007; Belsky, 1997a; 1997b). Volgens die laatste hypothese ontwikkelen en groeien kinderen op onder invloed van differentiële omgevingsfactoren en een genetische make-up die meer of minder veerkrachtig of juist gevoelig is, "for better or for worse".

Wat betreft aandachtsbias als benadering (proxy) voor emotieregulatie vonden we dat de groep met aan seksueel misbruik gerelateerde PTSS angstige en neutrale emoties langzamer verwerkte dan de groep met klinische depressie en de gezonde groep (Hoofdstuk 3). We leggen deze negatieve aandachtsbias uit als resultaat van een combinatie van automatische en strategische emotionele gezichtenverwerking, met inbegrip van verhoogde detectie van dreiging en moeite om zich van dreiging los te maken (Cisler and Koster, 2010). Bij mishandelde kinderen is eerder een negatieve aandachtsbias gevonden, maar niet altijd door heterogeniteit in de onderzoeksgroepen, gebruik van andere aandachtsbias componenten en strategieën, een ander paradigma of een andere presentatie van emotionele cues en gestelde vragen.

Wat betreft het **tweede doel** van deze dissertatie, het onderzoeken van neurale correlaties van emotionele gezichtenverwerking (als proxy voor emotieregulatie) in de adolescentie, vonden we geen significante groepsverschillen, geen verschillende amygdala activatie noch een significante relatie tussen zelfgerapporteerde posttraumatische stress, dissociatie of depressieve symptomen en ROI activatie met betrekking tot emotionele gezichtenverwerking. Dit terwijl we wel een geldig en functioneel correct paradigma gebruikten en eerdere bevindingen groepsverschillen suggereerden Nooner et al., 2013; Garrett et al., 2012; Hoofdstuk 3). Een en ander zou te maken kunnen hebben met snelle amygdala habituatie voor emotionele gezichten in adolescenten met aan seksueel misbruik gerelateerde PTSS (Van den Bulk et al., 2016), of gebruik van zoveel covariaten dat het onmogelijk was significantie te bereiken. Mogelijk zouden we andere resultaten gehad hebben bij gebruikmaking van een GPF, zie p. 13; Caspi et al., 2014; Lahey et al., 2015; 2017; Zald & Lahey, 2017). Ook zou overlap in psychopathologie binnen de twee klinische groepen, met post-hoc bevestigde secundaire PTSS in een deel van de klinische depressie groep, reden kunnen zijn dat we geen significante relaties vonden tussen zelfgerapporteerde symptomatologie en hersenactivatie.

Meer kennis over de concepten gehechtheid en emotieregulatie kan klinische en wetenschappelijk toepassing bevorderen. Het is van belang diagnostiek en behandelstrategieën te ontwerpen gebaseerd op zowel gehechtheid als psychopathologie, irrelevante strategieën te verwijderen en nieuwe, holistische, geïntegreerde benaderingen te ontwikkelen die effectiever en haalbaarder zijn dan huidige behandelingen (Nemeroff, 2016; Van der Kolk, 2014). Kennis van werkingsmechanismen zou ook de precisie van

gepersonaliseerde psychotherapie kunnen verbeteren en daarmee de uitkomst kunnen optimaliseren (Nemeroff, 2016; Van der Kolk, 2014).

Wat betreft het **derde doel** van deze dissertatie, differentiële neurale correlaten van gehechtheid en psychopathologie onderzoeken, hebben we vastgesteld dat Ud en een GPF unieke relaties met zowel de grijze stof, de witte stof integriteit van witte stof banen en met functionele connectiviteit van het brein in rust hebben (Hoofdstukken 4-6). Het gaat daarbij om een kleinere linker hippocampus en geassocieerde functionele connectiviteit in rust voor wat betreft de grijze stof, om een associatie van Ud met splenium en IFOF van het corpus callosum en de witte stof integriteit van de witte stof banen daarvan en een associatie van GPF met genu en lichaam van het corpus callosum (Hoofdstuk 5), linker amygdala met geassocieerde functionele connnectivitiet in rust voor Ud en een negatieve associatie met linker amygdala-mediaal frontale hersenschors connectiviteit (Hoofdstuk 6). Wat betreft Ud lijkt er sprake te zijn van lateralisatie van de hersenen naar links met betrekking tot de functionele connectiviteit in rust van de amygdala en het volume van de hippocampus (Hoofdstuk 6 en 4 respectievelijk).

Ondanks de relatief kleine onderzoeksgroep konden we het belang van met name Ud als transdiagnostische factor in relatie tot hersenstructuur, volume en functioneren in rust aantonen, gecorrigeerd voor een GPF en los daarvan. Dit is een interessante bevinding in het licht van de eerdere genetische bevinding van Elliott en collega's (2018) dat GPF een functionele handtekening van transdiagnostisch risico voor psychiatrische ziekte bleek te zijn. Onze studie was de eerste die gehechtheid en psychopathologie in dezelfde (adolescente) onderzoeksgroep vergeleek en de differentiële relaties voor Ud en een GPF in relatie tot de hersenen van adolescenten onderzocht aan de hand van zowel dimensionele als categorale variabelen in gehechtheid en klinisch psychopathologie onderzoek. Omdat Ud is geassocieerd met de functionele connectiviteit van de amygdala in rust betekent dit dat individuele functionele connectiviteit van het brein mogelijk wisselt afhankelijk van de gehechtheidsstatus ongeacht psychopathologie gemeten middels een GPF.

Omdat GPF daarentegen niet significant geassocieerd was met functionele connectiviteit van amygdala of dorsale anterieure cingulate cortex (Hoofdstuk 5; zie Ding et al.. 2018; Peer, Nitzan, Bick Levin, & Arzy, 2017) weten we niet of aanwezigheid van meer of minder psychopathologie, ongeacht gehechtheidstatus, van invloed is op de functionele connectiviteit van een individueel brein. Daarom kunnen we niet stellen dat ook GPF, net als onverwerkt-gedesorganiseerde gehechtheid, een onafhankelijke, predisponerende, transdiagnostische risicofactor is voor het ontwikkelen van stress-gerelateerde en affectieve stoornissen zoals Elliot en collega's (2018) aantoonden omdat ons onderzoek cross-sectioneel was en we niet weten of witte stof signalen beschouwd moeten worden als artefact of als significante activiteit.

Met betrekking tot onverwerkt-gedesorganiseerde gehechtheid vonden we dat er significante associaties waren met structuren in het brein gerelateerd aan: 1. Stress; 2.

Gebieden functioneel verbonden in rust, geassocieerd met het verwerken van emotionele informatie, mentalisatie; 3. Verminderde connectiviteit met mediale (pre)frontale gebieden van de hersenen die cognitieve controle uitoefenen; 4. Verhoogde connectiviteit tussen de amygdala en gebieden van het brein die negatieve moties reguleren.

Deze met onverwerkt-gedesorganiseerde gehechtheid geassocieerde structuren en gebieden in het brein kunnen mogelijk verklaren: 1. grotere kwetsbaarheid voor stressoren in de kindertijd zoals verlies en trauma door: a. reductie van de hippocampale glucocorticoid receptor geassocieerd met toegenomen cortisol en verminderd volume van de hippocampus en b. versnelde proliferatie van oligodendrocyten in het splenium, in reactie op hoge cortisol stress niveau bij chronische blootstelling aan stress waardoor er verstoring van de balans en afwijkingen ontstaan. Deze neurale gevolgen van verlies en trauma zouden de matige emotieregulatie kunnen verklaren met een verminderde drempel om stress te ervaren en een verhoogd risico op psychopathologie. Het zou in andere woorden kunnen verklaren waarom emoties en gedrag cognities domineren in geval van onverwerkt-gedesorganiseerde gehechtheid; 2. minder beheersing van de prefrontale cortex, waarmee verhoogde impulsiviteit, emotionele instabiliteit, gevoeligheid voor stress en risico voor psychopathologie mogelijk verklaard kan worden. 3. atypische emotionele respons en emotionele gezichtenverwerking; 4. algemeen affectieve waarde; 5. atypische verwerking van emotionele stimuli en hoger-niveau visuele verwerking inclusief emotionele scene waarneming; 6. verstoord zelfbewustzijn, geheugen, visuo-spatiële orientatie en mentale bewerking van meningen van anderen, visuele en sensorimotorische input van de hand, depersonalisatie, derealisatie en dissociatie.

Met betrekking tot een GPF vonden we associaties met: 1. toename van radiale, gemiddelde en axiale diffusiviteit, op grond van demyelinisatie en veranderde axonale integriteit van de witte stof integriteit, vooral in het genu en lichaam van het corpus callosum. Deze afwijkingen zouden veroorzaakt kunnen zijn door algemene kwetsbaarheid voor psychopathologie ten gevolge van genetische invloeden of prenatale stress; 2. de functionele connectiviteit van de linker anterieure cingulate cortex met het rechter lichaam van het corpus callosum, de superieure fronto-occipitale fasciculus, en de corticospinale baan.

Concluderend kan gesteld worden dat gehechtheid en psychopathologie unieke relaties met de structuur en het functioneren van de hersenen in rust lijken te hebben, althans, in ons onderzoek. Ook blijkt gehechtheid bij jongeren met ervaringen van seksueel misbruik vaak onverwerkt-gedesorganiseerd te zijn. Onverwerkt-gedesorganiseerde gehechtheid lijkt daarmee niet zozeer een biomarker maar veeleer een kwetsbaarheidsfactor te zijn voor psychopathologie. Ook blijken jongeren met seksueel misbruik een afwijkende aandachtsbias te hebben, maar konden we niet aantonen dat ook de emotionele gezichtenverwerking anders dan normaal verliep. Bovenstaande bevindingen voegen bewijs toe aan de theorie van in het lichaam opgeslagen trauma (Van der Kolk, 2014)

en de theorie van radicaal in het lichaam opgeslagen neurowetenschap van gehechtheid (Beckes, IJzerman, & Tops, 2015) die suggereert dat gehechtheid intrinsiek verweven is het metabolisme en neurobiologisch functioneren.

Beperkingen

Algemene beperkingen van dit onderzoek zijn: 1. Generaliseerbaarheid van de bevindingen door: a. een relatief groot maar voor het doel van het testen van bepaalde hypotheses toch redelijk kleine onderzoeksgroep; b. heterogeniteit in diagnostische groepen; 2. een selectieve en verwezen onderzoeksgroep, gemotiveerd om deel te nemen; 3. beperkte leeftijd, IQ, sexe, diagnostische groep en ethniciteit; 4. dat het een cross-sectionele studie betreft, waardoor conclusies met betrekking tot oorzaak en aspecten in de tijd niet getrokken kunnen worden omdat er derde, niet gemeten, factoren een rol kunnen spelen

Studie-specifieke beperkingen waren dat: 1. coderen van het GBI was beperkt tot de classificaties en schalen volgens Main en Hesse (Hesse, 2016) en niet de complementaire vijandig/hulpeloos codering van Lyons-Ruth (2003) gebruikte; 2. de fMRI taak mogelijk niet sensitief genoeg is om klinische groepsverschillen te detecteren op het niveau van de hersenen. Het originele gezichten aandachts paradigma werd gebruikt in angstige kinderen en gebruikte woede als emotie en de vraag 'hoe vijandig is het gezicht?' in tegenstelling tot de aangepaste fMRI taak. Dit hield een verandering in perspectief in waardoor de verschillen in de mogelijkheid om groepsverschillen te ontdekken mogelijk verklaarbaar zijn; 3. de fMRI taak qua inhoud niet gericht was op gehechtheid of emotieregulatie in klinische groepen. 4. we mogelijk de verkeerde benadering van emotieregulatie hebben gebruikt, aandachtsbias in plaats van aandachtsvariabiliteit, d.w.z. aandacht fluctuaties die afwisselend naar de dreiging en van de dreiging af bewegen; 5. zelfrapportage in plaats van diagnostische interviews gebruikt is en dit de samenstelling van de GPF die in tweede instantie is samengesteld (post-hoc GPF) beïnvloed kan hebben en daarom mogelijk niet geschikt is.

Aanbevelingen voor toekomstig onderzoek

Gecombineerd gebruik van gehechtheids- en psychopathologie variabelen in onderzoek is nodig om te kunnen beoordelen hoe beoordeling van gehechtheid in de (kinder)psychiatrische praktijk kan worden geïmplementeerd.

Wat betreft gebruik van een GPF stelden we die statistisch samen op basis van zelfrapportagelijsten voor gedrags- en emotionele problemen. Zald en Lahey (2018) oordeelden dat gebruik van een GPF in relatie tot neuroimaging nuttig is omdat diagnostische indelingskwesties en tekortkomingen van diagnostische interviews omzeild kunnen worden, terwijl er met een gemeenschappelijke genetische basis wel rekening wordt gehouden. Elliot en collega's (2018) lieten zien dat het transdiagnostische risico

voor veelvoorkomende vormen van psychische ziekte geassocieerd is met wijdverbreide genetische patronen van inefficiënte intrinsieke connectiviteit tussen de visuele associatie hersenschors en netwerken betrokken bij de uitvoerende controle en zelf-refererende processen. Deze netwerken lopen vaak dwars door bestaande categorale stoornissen heen.

De GPF is oorspronkelijk gebaseerd op dimensionele scores verkregen van diagnostische interviews naar posttraumatische stress en dissociatieve symptomen. Voorzichtigheid is daarom geboden bij de interpretatie van een GPF die op zelfbeoordelingslijsten van ouder en kind gebaseerd is. Er moet meer onderzoek gedaan worden naar de betrouwbaarheid en validiteit van een dergelijke GPF. Ook zou men in studies waarin een GPF gebruikt wordt diverse statistische methoden moeten toepassen om statistische verschillen inherent in de gebruikte methode te vergelijken. Ook zou het type ouder-, derde informant-, zelfrapportage en diagnostische interviews die geïncludeerd worden in een GPF zorgvuldig bekeken moeten worden.

Beoordeling van Ud en incoherentie van denken in het GBI is gebaseerd op gedesoriënteerde en gedesorganiseerde (d.w.z. dissociatieve) aanwijzingen (Hesse, 2016), en refereert aan literatuur over dissociatie. We speculeren dat onverwerkt-gedesorganiseerde gehechtheid en dissociatie mogelijk concepten zijn die niet alleen relevant zijn in relatie tot verlies en trauma, maar ook onderdeel zijn van het dissociatie spectrum van meer of minder (on)bewuste gewaarwording van de realiteit (zie ook Bryant, 2007). Gezien de differentiële neurale correlaten van Ud en een GPF in deze dissertatie, gelijktijdige beoordeling van zowel posttraumatische stress symptomen, onverwerkt-gedesorganiseerde gehechtheid en dissociatie zou een eerste cruciale stap kunnen zijn om deze concepten te ontrafelen in toekomstig onderzoek en meer inzicht te krijgen in de essentie van specifieke correlaties van Ud en GPF met de hersenen.

Conceptueel onderzoek met betrekking tot gehechtheid dimensies van onverwerkt verlies of trauma in het dissociatie spectrum dient systematische codering van dimensionele en categorale aspecten van gehechtheidrepresentatie te omvatten volgens zowel de klassieke als de vijandig-hulpeloos codering (Hesse, 2016; Lyons-Ruth, 2003). Het is daarnaast nodig ook het bestaan van verlies of trauma te bepalen voorafgaand aan het onderzoek, met gebruikmaking van een valide en betrouwbaar screeningsinstrument en afname van een aanvullend klinisch interview over postttraumatische stress symptomen als verlies of trauma aanwezig blijkt. Het is daarbij van belang om allerlei diagnostische categorieën met elkaar te vergelijken.

De fMRI studie over emotionele gezichtenverwerking leverde geen significante hersen resultaten op. In studies met meer power, andere prospectieve sample, met gebruikmaking van woede als emotie, hangt emotionele gezichten verwerking af van diagnostische en leeftijdsgroepen (Wu et al., 2016). Ook kan het zijn dat een GPF correlaties van psychopathologie onthult met bepaalde emotionele gezichtenverwerking. Toekomstige studies zouden er goed aan doen toenadering-vermijding fMRI taken te

gebruiken gecorreleerd aan gehechtheidsstatus. De vijandig-hulpeloos codering (Lyons-Ruth, 2003) in aanvulling op de Main en Hesse codering die gebruikt is in deze dissertatie zou aanvullende associaties tussen gehechtheidsstatus en hersenfunctioneren en -volume kunnen onthullen.

In zijn algemeenheid zouden landurige neuroimaging studies waarbij deelnemers in de tijd gevolgd worden vanaf hun geboorte en in relatie tot hun gezin van herkomst nuttig zijn om veranderingen in de tijd die optreden in de hersenen in relatie tot gehechtheid en psychopathologie te kunnen volgen.

Tot slot is het interessant aan te sluiten bij recente bevindingen met betrekking tot medicatie voor dissociatie die gebruik maakt van de kappa-opioid en endocannabinoid systemen. In relatie tot gehechtheid en trauma-gerelateerde dissociatie zou dit soort medicatie naar nieuwe farmacotherapeutische behandelingen van dissociatie kunnen leiden (Lanius et al., 2018).

Klinische implicaties

Onze bevindingen impliceren dat gehechtheid, coherentie van denken [in het gehechtheidsbiografisch interview], en onverwerkt verlies of trauma relevante concepten zijn om rekening mee te houden in de kinderpsychiatrische diagnostiek en behandeling, vooral bij adolescenten met aan seksueel misbruik gerelateerde PTSS of klinische depressie (Kim, Blashfield, Tyrer, Hwang, & Lee, 2014; Tarren-Sweeney, 2014; Tyrer, 2014). Vooral de discussie over complexe PTSS, wel opgenomen in de ICD-11 en niet in de DSM-5 classificatie, zou kunnen profiteren van de bevindingen met betrekking tot onverwerkt-gedesorganiseerde gehechtheid en psychopathologie en hoe deze factoren aan vorm en functioneren van de hersenen gerelateerd zijn. Het lijkt goed het concept van Liotti (2004) dat onverwerkt-gedesorganiseerde gehechtheid, trauma en dissociatie onderling samenhangen nader te bestuderen. Zelfrapportages geven andere bevindingen dan klinische interviews. Een benadering waarbij verschillende informanten bevraagd worden op verschillende manieren zou daarom een beter zicht kunnen geven op welke aspecten van gehechtheid- en trauma-gerelateerde dissociatie voorkomen in geval van trauma of verlies.

Klinische toepassing van het GBI (Steele & Steele, 2008) is goed mogelijk maar behoeft ook meer onderzoek hoe. Gebruik van geavanceerde stemherkenningssoftware, tekst- en data mining, big data analyse en deep learning techniques zouden daarbij behulpzaam kunnen zijn. (see e.g. https://www.forbes.com/sites/bernardmarr/2016/12/08/what-is-the-difference-between-deep-learning-machine-learning-and-ai/#19db351b26cf). Een postdoctorale opleiding voor transciptie en codering van GBIs met voldoende beschikbare getrainde psychologen en pedagogen zou voorwaarde zijn.

De klinische implicatie van de bevinding dat onverwerkt-gedesorganiseerde gehechtheid een transdiagnostische factor is gerelateerd aan de grijze en witte stof

van de hersenen en aan de functionele connectiviteit van de hersenen in rust, is dat systematische beoordeling van zowel categorale als dimensionele gehechtheidskenmerken en psychiatrische symptomen essentieel is om het klinisch functioneren van adolescenten en hun persoonlijkheidsontwikkeling, hoe ze omgaan met (toekomstige) zwangerschappen en/of ouderschap te begrijpen.

Wat betreft de bevindingen rondom aandachtsbias en emotionele gezichtenverwerking is het klinisch interessant zich te realiseren dat een neutraal gezicht een negatieve impact kan hebben op iemand die psychisch kwetsbaar is en zeker als diegene getraumatiseerd is. Attention Bias Modification Treatment (AMBT; Hakamata et al., 2010) en aandachtscontrole training (ACT; Badura-Brack et al., 2015) zijn twee veelbelovende behandelingen. De langzamere reactietijd van adolescenten met aan seksueel misbruik gerelateerde PTSS bij het zien van angstige en neutrale emotionele gezichten interfereert mogelijk met hun dagelijks functioneren, hulp zoeken en accepteren. Mogelijk dat een gestructureerd contact met een psychiatrisch verpleegkundige, of mogelijk AMBT en ACT, eerst nodig zijn alvorens psychotherapie aan te kunnen gaan.

Wat betreft de behandeling van getraumatiseerde individuen, ook adolescenten, zou een mentaliserende benadering en op gehechtheid gerichte attitude van de therapeut een cruciale factor kunnen zijn van welke therapie dan ook (Fonagy & Bateman, 2016; Luyten & Fonagy, 2015). Verschillende vormen van psychodynamische psychotherapie en mentalisatie-bevorderende therapie zouden een basis kunnen bieden om een veilige therapeutische gehechtheidsrelatie te creeëren. Vervolgens kunnen van daaruit specifieke therapeutische technieken gericht op reductie van trauma-gerelateerde psychiatrische en somatische klachten worden toegepast die het emotionele en cognitieve functioneren bevorderen.

Implicaties voor beleid

Trauma, gehechtheid en emotieregulatie worden op uiteenlopende manieren geconceptualiseerd in de kinderpsychiatrie, kinderpsychologie en in gehechtheidsonderzoek. Dat maakt het lastig elkaar goed te begrijpen. Het psychiatrisch classificatiesysteem DSM is anders van opzet en uitwerking, bijvoorbeeld met betrekking tot de definitie van trauma en beoordeling van de impact van trauma, dan het gehechtheidsclassificatiesysteem van Main, Goldwyn, en Hesse (2003; Hesse, 2016) waaraan we in deze dissertatie refereren. Er worden verschillende observatie uitgangspunten en evaluatie criteria gebruikt en daarom zijn er ook verschillende uitkomsten. Dit kan verklaren waarom de gehechtheidstheorie nog niet ingelijfd is in het klinisch denken vanuit de (kinder- en jeugd)psychiatrie. Om dit te veranderen lijkt een (digitale) block chain multidisciplinaire richtlijn over het concept gehechtheid in beleid met betrekking tot preventie, diagnostiek en behandeling van kinderen, jongeren en gezinnen in de (kinder- en jeugd)psychiatrie, jeugdzorg en multidisciplinaire centra voor kindermishandeling en huiselijk geweld aangewezen.

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CURRICULUM VITAE

Marie-José van Hoof was born in Bakel, the Netherlands, on July 16th, 1967. She attended undifferentiated grammar school *St. Willibrord gymnasium* in Deurne from 1979 till 1985, did exams in Latin, Dutch, English, maths, physics, biology and chemistry. At *Helmonds Avondcollege* she did additional VWO exams in German, French and history in 1986 at the Dutch embassy in London, while studying for Cambridge Proficiency and Oxford Higher certificates in English at *Merrion House*, Beaconsfield, UK. From 1986 till 1993 she did masters in medicine and orthopedagogy at *Leiden University* (1988-1993), taking additional courses in law and anthropology, at *Leiden University and the University of Amsterdam*. She earned her medical degree in 1995. She combined her studies with clinical stages at *Soroka Medical Center/Ben-Gurion University of the Negev* in Beersheva, Israel; the *Center for Epilepsy* in Heemstede; the *hospice at St. Peter's Hospital/Albany Medical Center*, Albany, NY, USA; projects for streetchildren in Zaire, Haiti, Uruguay, Argentina, and Paraguay; clinical rotations at *Sinai Hospital & Faculty of Medicine, Long Island Jewish Medical Center/Schneider Children's Hospital/Albert Einstein College of Medicine/Yeshiva University* in NYC, USA; *Chaim Sheba Medical Center/Tel-Aviv University* in TelhaShomer, Israel, and a research project on headache and sleep with professor Egilius L.H. Spierings at *The Faulkner hospital & Brigham and Women's Hospital/Harvard University* in Boston, USA. During her student years she was involved with advancing public health through directorships of the boards of NeMSIC and IFMSA, the Dutch respectively international medical students' associations.

Initially Marie-José worked in paediatrics and neonatology at *Victoria Hospital,* UK, and at *Sophia hospital* in Zwolle. She then continued as a research fellow with (child) psychiatrists David Printz, Daniel Pine, Agnes Whitaker, and David Shaffer at the *New York State Psychiatric Institute/Columbia University* in New York, USA from 1996-1998. After a 6-week interim job at the rehabilitation ward of the *Amsterdam mental hospital* in Santpoort, Marie-José received her training in psychiatry at the *HLOCP consortium* in Leiden/The Hague from 1998-2002. She continued her training in child and adolescent psychiatry at childpsychiatric institutes *Curium and Triversum* till 2006 and helped set up "De Bark" (Parlan), a residential unit for adolescents with orthopsychiatric problems. Working with these adolescents was crucial for the central question underlying this PhD

thesis: how do trauma, attachment and emotion regulation correlate?

From June 2006-January 2017 Marie-José has been working at mental health institute *GGZ Rivierduinen Psychotraumacenter and Department of Child and Adolescent Psychiatry*, combining patient care with policy making and advocacy in the trauma field and research on child abuse and neglect. The latter was carried out in collaboration with *Curium-LUMC, LUMC Department of Psychiatry, Leiden Institute for Brain and Cognition (LIBC), Leiden University Medical Center (LUMC), KJTC Haarlem, and the Department of Child and Family Studies of the Faculty of Social Sciences, Leiden University.*

In 2006 Marie-José initiated and still chairs the expertgroup on trauma and child abuse and neglect at the *Knowledgecenter Child and Adolescent Psychiatry*, nominated for the 2012 Innovation Prize Approach Childmaltreatment by *Stichting VKM (Voorkomen Kindermishandeling)* and *Stichting Kinderpostzegels*. She participated in 'Handreiking meldcode kindermishandeling in de psychiatrie', the reporting code on child abuse and neglect made applicable to psychiatry; the 'artsencoalitie Afwegingskader' (July 2018) by NVvP, the Dutch Association for Psychiatry, in collaboration with the KNMG, the royal Dutch Medical Doctors Organization; and she chairs the committee 'reporting code child abuse and neglect and family violence' at the NVvP. Together with Carlijn de Roos and colleagues Marie-José initiated the start of the Center for Sexual Assault in Leiden, part of the larger national network of Centers for Sexual Assault headed by Iva Bicanic. She also participated in the 'Zorgstandaard' Psychotrauma and stressor-related disorders for children and adolescents. Since 2019 she is a board member for psychotrauma in youth at NtVP, the Dutch Association for Psychotrauma. Since July 2018 Marie-José is involved with international child and adolescent mental health (iCAMH) activities at the International Association for Child and Adolescent Psychiatry and Allied Professionals (IACAPAP).

For the EPISCA research project she studied with David and Deanne Pederson (*Western University*, London, Ontario, Canada; 2009) and with Mary Main and Erik Hesse (*University of California at Berkeley*, Berkeley, USA; 2015) on coding of the Adult Attachment Interview (AAI). Marie-José was awarded the Hilly de Roever-Bonnet fund of the Dutch Female Doctor's Association (VNVA) and WOP Rivierduinen generously awarded part of the necessary funding to carry out this PhD research from 2009-2014.

Besides, Marie-José was involved in the board of women doctors and researchers network of LUMC, called Vitaal, and was nominated for the VNVA essay award 2018. Also,

she participated in organizing the 2014 and 2016 European Conference on Child Abuse and Neglect (EUCCAN) organizing committee. She is a member of the Bohn Stafleu Loghum editorial board for Kind Adolescent Praktijk. In 2006, together with Magda van Wijgerden and Martina Ens-Dokkum, she co-founded the Project On Women Empowerment in Reproductive health (POWER), which sponsored projects for girls and women in Nigeria, Liberia and Uganda (the latter ongoing).

In 2013, together with her sister and brother, Marie-José inherited the family business Hoofzaken. Since March 2017 she chairs the foundation 'Vrienden van het Willibrord' to give back to the school that played such a vital role in her formal education. Since January 2017 Marie-José runs a multidisciplinary private practice in child and adolescent, and adult psychiatry, *iMindU*, in Leiden (www.imindu.nl), aimed at valorization of the findings in this thesis, such as diagnostics in child abuse and neglect, treating trauma and affective disorders and promoting attachment in parent-child interaction and cohesion in families. She has a special interest in refugee and third culture kids and adults with second or third generation problems due to the Sjoa and World War II.

Recently, Marie-José, initiated the *AMOR & PSYCHE* project, https://acties.steunleiden.nl/actie/marie-jose-van-hoof , to raise money for the to be founded *Talent4Research Fund*, facilitated by the *Bontius Foundation* @ LUMC. The Talent4Research Fund wants to raise public awareness of the importance of the concepts attachment, trauma and emotion regulation in childhood and adolescence and stimulate de-stigmatization, societal participation and scientific research in this domain.

PORTFOLIO

Fixed milestones

- Basic Methods and Reasoning in Biostatistics (exemption see Statistiek in Vogelvlucht 14/10/2009 – 22/10/2009)
- BROK course (08/09/2014)
- PhD Introductory Meeting (27/11/2017)

Specific milestones

- participation in diverse meetings related to EPISCA, research and neuroimaging at Curium-LUMC (01/06/2006 - 10/05/2019)
- Peer review (01/07/2006)
- VKJP congress Zaandam (12/10/2006 - 13/10/2006)
- Gehechtheidsbiografisch Interview (01/11/2006 - 08/11/2006)
- teaching activities 2007-now (01/01/2007)
- Workshop by Joany Silberg on traumatized children and dissociation, Leiden (20/03/2007 - 22/03/2007)
- Hoe schadelijk is chronische traumatisering in de kindertijd? Biologische, psychologische en maatschappelijke effecten (23/03/2007)
- Expertmeeting adolescents Brain and Development Lab Leiden (28/05/2007)
- ESCAP Florence 2007. Donald J. Cohen Fellowship fellow (24/08/2007 - 30/08/2007)
- MRI symposium at opening 7 Tesla Facility LUMC (06/09/2007)
- SPSM5 course (01/10/2007 - 03/10/2007)
- PTC minisymposium (01/11/2007)
- Meeting VWS-Inspection Health Care, in particular Child Abuse and Neglect -NVvP on CAN (06/11/2007)
- NtVP congress “Traumazorg in actie”, Zwolle (28/11/2007)
- LIBC symposium (07/02/2008)
- Workshop ‘diagnostiek bij seksueel misbruik’ by Suzanne ter Horst (18/03/2008)
- study visit to Daniel Pine, NIMH, Maryland, USA (28/03/2008 - 01/04/2008)
- ESTD congres 2008 (17/04/2008 - 19/04/2008)
- Najaarsconferentie kindermishandeling 2008 (20/11/2008)

- Publiekslezing. De Anatomische Les. Arieh Shalev lecture. (27/11/2008)
- WOP Rivierduinen (01/01/2009 - 01/01/2015)
- Buddhist brain symposium (20/03/2009)
- Hilly de Roever-Bonnet fonds (01/05/2009 - 01/05/2009)
- Attachment conference with Charles Zeanah/BEAP (14/05/2009)
- KNAW Developmental Neuroimaging congress (18/05/2009 - 20/05/2009)
- Jaap Christoffellezing over behandeling van getraumatiseerde kinderen (19/06/2009)
- Adult Attachment Institute (05/07/2009 - 17/07/2009)
- NWO presenting your research workshop (22/09/2009)
- KNAW symposium prosociaal gedrag (30/09/2009)
- NWO day for women in science, The Hague (02/10/2009)
- Statistiek in vogelvlucht (14/10/2009 - 22/10/2009)
- Cognitive Development and the brain, LUMC, Leiden (26/10/2009)
- PTC minisymposium (19/11/2009)
- Symposium kinder- en jeugdpsychiatrie 'We moeten weer gaan spelen' (26/11/2009)
- NWO talent classes (08/12/2009)
- Pitfalls for Dutch writers (14/01/2010 – 21/01/2010)
- Honorary doctorate Antonio Damasio (08/02/2010)
- The effects of trauma and neglect on the developing brain (17/02/2010)
- International congress Psychotraumacenter. Workshops by Sandra Wieland (17/02/2010)
- Trauma en hechting bij kinderen- herstel in verbinding (18/02/2010)
- Trauma and attachment disorders: diagnostics, attachment-based therapy and prevention. Lectures and workshop by Karl-Heinz Brisch (19/02/2010)
- LIBC junior day (14/05/2010)
- Praktijkcongres kindermishandeling Amsterdam (24/06/2010)
- Veiligheidstraining scanner (23/08/2010)
- Symposium PTSD and stress (01/09/2010)
- RefManager (02/09/2010)
- BROK (01/11/2010 - 05/11/2010)
- Symposium Kinderen, sex en internet (18/01/2011)
- Boerhaave cursus " Trauma en gehechtheid" (09/02/2011)
- Creating Connections congress on EFT (20/04/2011)
- Invitational conference Robert Pynoos (26/05/2011)
- Neuroimaging attachment conference, UCL, London, UK (07/05/2011 - 08/05/2011)

- Reflective Functioning course, Anna Freud Centre, London, UK (09/05/2011 - 11/05/2011)
- Jaap Christoffelslezing 2011 (01/06/2011)
- 12th European Conference on Traumatic Stress, psychotraumatology and human rights, ECOTS/ESTSS Vienna, Austria (05/06/2011)
- AAI training institute by David and Deanne Pederson, Wassenaar (07/07/2011)
- PEO and lectures AMDA research master courses Leiden University (01/09/2011 - 01/06/2012)
- Symposium on Stress, resilience and plasticity (08/09/2011)
- Symposium kinderporno & internet (27/10/2011)
- Studiemiddag werkgroep "Meldcode kindermishandeling" NVvP (12/01/2012)
- Child Abuse and Neglect research master course Leiden University (01/02/2012 - 31/05/2012)
- Ph.D. dag LUMC (02/02/2012)
- Kenniskring child abuse and neglect (05/03/2012)
- Network theory door Kees Stam (29/03/2012)
- Symposium kinderporno op internet " Stop it Now" (02/04/2012)
- Invitational symposium for inauguration Miranda Olff (27/04/2012)
- European Conference on Child Abuse and Neglect (EUCCAN) 2012 (23/05/2012)
- LIBC day (24/05/2012)
- Opening symposium minor child abuse and neglect (12/09/2012)
- FSL course (DTI, VBM), Bristol, UK (18/09/2012 - 21/09/2012)
- Cursus Lab LUMC Ph.D. course (24/09/2012)
- Masterclass Child Abuse and Neglect conference (04/10/2012)
- Conference Child Abuse and Neglect across the lifespan (05/10/2012 - 06/10/2012)
- Dealing with conflicting demands, LUMC (08/10/2012 - 09/10/2012)
- FSL cluster lecture LIBC (30/10/2012)
- Neuroscience of affect and attachment (01/11/2012)
- Boerhaave cursus Van CRF tot Database (14/11/2012)
- Mulock Houwer lecture, Kinderrechtenhuis, Leiden (15/11/2012)
- Publiekslezing "De Anatomische Les" by Terrie Moffitt and Avshalom Caspi (29/11/2012)
- Jelgersmalezing 2013 (08/01/2013)
- TOPGGz visitation participant Psychotraumacenter GGZ Kinderen en Jeugd Rivierduinen (25/04/2013)
- Invitational conference Tim Dalgleish (28/05/2013)

- Jaap Christoffelslezing 2013 (29/05/2013)
- ESCAP, Dublin, Ireland - symposium “child abuse and neglect from international perspective: what works?” (09/07/2013)
- ISPNE Leiden (20/08/2013 - 23/08/2013)
- Workshop on child abuse and neglect by Arnon Bentovim (24/09/2013)
- Visiestuk ‘De Transformatie en gehechtheid- en trauma- geïnformeerde zorg aankinderen en adolescenten’ (01/10/2013 - 01/01/2015)
- Symposium on rape (13/03/2014)
- Experiences Sampling Method (ESM) course (24/04/2014 - 25/04/2014)
- Gordon Harper on child abuse and neglect from public health perspective (20/05/2014)
- congresorganisatie EUCCAN 2014
- EUCCAN 2014 (21/05/2014 - 23/05/2014)
- TNO interview naar praktijk van traumazorg i.v.m. NWO gesubsidieerd onderzoek (01/09/2014)
- Brainstorm session expertgroups on Trauma and CAN and chronic trauma on making the transformation traumaproof (31/10/2014)
- Adult Attachment Institute, Berkeley, USA (05/01/2015 - 16/01/2015)
- CAPS-CA (27/01/2015 - 24/02/2015)
- Inspirerend spreken (20/02/2015)
- Arq Voorjaarssymposium 2015: ‘Complex Trauma???’ (20/03/2015)
- Creating Connections Conference lll - Resilience through Connection (16/04/2015 - 18/04/2015)
- Boerhaave nascholingscursus “Samen slagvaardig handelen voor de veiligheid van het kind: de differential diagnose kindermishandeling en verwaarlozing” (29/05/2015)
- Stepping Stones Bentovim (08/10/2015)
- Wetenschapsmiddag Rivierduinen 2015 (26/11/2015)
- EUCCAN 2016 (25/05/2016 - 27/05/2016)
- Meta-analysis (15/11/2016 - 17/11/2016)
- Van wijk tot wetenschap. Hét kenniscongres voor de jeugdhulp (24/11/2016)
- CAT begeleiding 2017 (01/01/2017 - 01/07/2017)
- Chadwick conference on child abuse and neglect, San Diego, USA (30/01/2017 - 02/02/2017)
- International Attachment Conference, London, UK (29/06/2017 - 01/07/2017)
- ESCAP 2017, Geneva (09/07/2017 - 11/07/2017)

- ISPCAN European regional meeting, Den Haag (01/10/2017 - 04/10/2017)
- CAT begeleiding 2018 (01/01/2018 - 01/07/2018)
- promovendi presentatie LUMC (17/05/2018)
- IACAPAP 2018, Praag (22/07/2018 - 27/07/2018)
- ESTSS 2019, Rotterdam (13/06/2019 - 16/06/2019)
- ESCAP 2019, Vienna (30/06/2019 - 02/07/2019)
- Story Stems workshop, Allison Splaun, Vancouver (16/07/2019 – 17-07-2019)
- 9th International Attachment Conference Vancouver (18/07/2019 - 20/07/2019)
- NtVP lezingen, Assen (25/09/2019)

Publications

International

Van Hoof, MJ, Riem, MME, Garrett, AS, Pannekoek, JN, Van der Wee, NJA, Van IJzendoorn, MH, Vermeiren, RRJM (2019). Unresolved-disorganized attachment associated with smaller hippocampus and increased functional connectivity. *Journal of Traumatic Stress, 32,* 742-752. https://doi.org/10.1002/jts.22432

Van Hoof MJ*, Riem MME*, Garrett AS, van der Wee NJA, van IJzendoorn MH, Vermeiren RRJM (2019). Unresolved-disorganized attachment adjusted for a General Psychopathology Factor associated with atypical amygdala resting-state functional connectivity. *European Journal of Psychotraumatology, 10* (1),1583525. https://doi.org/10.1080/20008198.2019.1583525 [*shared first authorship]

Riem*, MME, van Hoof*, MJ, Garrett, AS, Rombouts, SARB, Van der Wee, NJA, Van IJzendoorn, MH, Vermeiren, RRJM (2019). General psychopathology factor and unresolved-disorganized attachment uniquely correlated to white matter integrity using diffusion tensor imaging. *Behavioural Brain Research 359*, 1-8 https://doi.org/10.1016/j.bbr.2018.10.014. [*shared first authorship]

Rinne-Albers, MAW, Pannekoek, NJ, van Hoof, MJ, van Lang, NDJ, Lamers-Winkelman, F, Rombouts, SARB, van der Wee, NJ, Vermeiren, RRJM (2017). Anterior cingulate cortex grey matter volume abnormalities in adolescents with PTSD after childhood sexual abuse. *European Neuropsychopharmacology, 27*: 1163-1171. https://dx.doi.org/10.1016/j.euroneuro.2017.08.432

Van Hoof, MJ, Van den Bulk, BG, Van Lang, NDJ, Rombouts, SARB, Van der Wee, NJA, Van IJzendoorn, MH, Vermeiren, RRJM (2017). Emotional face processing in adolescents with childhood abuse-related posttraumatic stress disorder, internalizing disorders and healthy controls. *Psychiatry Research: Neuroimaging. 264*, 52-59. http://dx.doi.org/10.1016/j.pscychresns.2017.04.006

Aghajani, M, Veer, IM, van Hoof, MJ, Rombouts, SARB, van der Wee, NJA, & Vermeiren, RRJM (2016). Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. *Human Brain Mapping, 37(*3), 1120-1135. https://doi.org/10.1002/hbm.23093

Rinne-Albers*, MA, Van der Werff*, SJ, Van Hoof, MJ, Van Lang, NDJ, Lamers-Winkelman, F, Rombouts, SARB, Vermeiren, RRJM, Van der Wee, NJA (2016). Abnormalities of white matter

integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study. *European Child and Adolescent Psychiatry 25(*8), 869-78. https://doi.org/10.1007/s00787-015-0805-2 [*shared first authorship]

Van den Bulk, BG, Somerville, LH, Van Hoof, MJ, Van Lang, NDJ, Van der Wee, NJA, Crone, EA, Vermeiren, RRJM (2016). Amygdala habituation to emotional faces in adolescents with affective disorders, adolescents with early childhood trauma and healthy adolescents. *Developmental Cognitive Neuroscience, 21,* 15-25. http://dx.doi.org/10.1016/j.dcn.2016.08.002

Van Hoof, MJ, van Lang, NDJ, Speekenbrink S, van IJzendoorn, MH, Vermeiren, RRJM (2015). Adult Attachment Interview differentiates adolescents with Childhood Sexual Abuse from those with clinical depression and non-clinical controls. *Attachment & Human Development, 17*(4), 354-375. http://dx.doi.org/10.1080/14616734.2015.1050420

Van Hoof, MJ (2011). Child abuse and the child and adolescent psychiatrist: do we need a new approach? *Eur Child Adolesc Psychiatry 20 (suppl 1): S7-S223*; S61. *[abstract]*
Van Hoof, MJ & Lindauer, RJL (2011). Child abuse and the child and adolescent psychiatrist: do we need a new approach? Workshop Landelijk Kenniscentrum Kinder- en Jeugdpsychiatrie. ECOTS/ESTSS Vienna, 4th June. *European Journal of Psychotraumatology vol. 2, Supplement 1, 2011, p. 183.* doi: 10.3402/ejpt.v2i0.7236 *[Abstract]*

Dutch, National

KNMG meldcode kindermishandeling en huiselijk geweld. Online 22 november 2018. Mede-auteur als lid artsencoalitie vanuit NVvP.
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Van Hoof, MJ (2015). Reactie op "meldplicht beter voor kind". *Medisch Contact 70* (50), 22 december online. Ingezonden brief [letter].

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Van Hoof, MJ, Van Kamp IL, Landsmeer-Beker, EA, & Boer, F. (2015). Dbc kindermishandeling moet er snel komen. *Medisch Contact, 45* (5 November), 2158-2160. *Hierover zijn kamervragen gesteld door N. Kooiman (SP) en heeft de minister middels de staatssecretaris gereageerd met een kamerbrief. Op 9 februari 2016 vond een kamerdebat hierover plaats.[discussion in parliament]*

Van Hoof, M.J. (2015). Reactie op "Screenen op problematische gehechtheid is hard nodig". *Medisch Contact 70* (41), 1943. Ingezonden brief [letter].

Van Hoof, MJ, Sepers, JW, Landsmeer EA, & Van de Boon, N. (2015). Samenwerken met ouders als kindermishandeling ontkend wordt. (WD-84). Voorjaarscongres NVvP 31 March 2015, Maastricht. www.nvvp.net.

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Van Hoof, MJ (2014). *Het Gehechtheidsbiografisch interview onderscheidt adolescenten met seksueel misbruik van adolescenten met depressie en controles*. TOPGGz symposium S39.6 " Motivatie van patiënten met een 3e lijns (topklinische) zorgvraag", Voorjaarscongres NVvP 10 April 2014, Maastricht. www.nvvp.net .

Van Hoof, MJ, Van Lang, NDJ, Van den Bulk, BG, & Vermeiren, RRJM (2013). Gehechtheidsrepresentaties en verwerking van emoties in de hersenen. FMRI onderzoek na seksueel misbruik. *Kind en Adolescent Praktijk, 3* (aug), 118-121.

Van Hoof, MJ, Crijnen, AAM, & Vogtländer, L (2012). Naar een Multidisciplinair Centrum kindermishandeling – samenwerking, modellen van communicatie, methodieken. Workshop. *Tijdschrift voor Psychiatrie 54, suppl. 1[abstract].*

Laan, MHCM, Smits, AAM, Van Hoof, MJ, Roose, C, & Uijterwaal, G. (2012). Handreiking Gebruik Meldcode Kindermishandeling in de psychiatrie: hoe verder? *Tijdschrift voor Psychiatrie 54, suppl. 1 [abstract].*

Van Hoof, MJ, Laan, M, Roose, C, Smits, L, & Uijterwaal, G (2011) Handreiking voor psychiaters bij de KNMG meldcode kindermishandeling.*[Uitgave NVvP oktober 2011].*

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Van Hoof, MJ & Zevalkink JD (2011). Attachment, trauma and implementation in psychiatry. Workshop. *Tijdschrift voor Psychiatrie 53, suppl. 1*, S222. *[abstract]*

Van Hoof, MJ (2011). Addendum psychiatrie KNMG meldcode Kindermishandeling: wat moeten we weten? Symposium Kindermishandeling: kennis verplicht tot handelen. *Tijdschrift voor Psychiatrie 53, suppl. 1*, S66. *[abstract]*

Van Hoof, MJ & Vogtländer, L (2011). Voor kind is meldrecht beter dan meldplicht. *Medisch Contact 66(7)*: 394-396. Artikel wordt nu als referentie voor implementatie meldrecht in Suriname gebruikt.

Van Hoof, MJ (2010). M.D. Jordans. Psychosocial intervention in war children. Proefschrift. *Maandblad Geestelijke Volksgezondheid (MGv) 65 (11)*: 926-927 *[boekbespreking]*.

Van Hoof, MJ, Crijnen, AAM, Lindauer, RJL, Schmeets, M, & Vogtländer, L (2010). Diagnostiek bij trauma en kindermishandeling - van preventie tot behandeling. *Tijdschrift voor Psychiatrie 52 (4), suppl. 1, [abstract]*

Van Hoof MJ, & Rinne-Albers M (2010). Gehechtheid, trauma en psychiatrische classificatie. *Tijdschrift voor Psychiatrie 52(4), suppl. 1, [abstract]*

Meens, PHF, Van Lang, NDJ, Vermeiren, RRJM, Van der Wee, NJA, Rinne-Albers, MAW, & Van Hoof MJ (2010). EPISCA-EGT: Een fMRI-pilotstudie naar een aangepast emotiegericht paradigma. *Tijdschrift voor Psychiatrie 52(4), suppl. 1 [abstract]*

Schweizer JJ, Van Elburg AM, Van Hoof MJ, Teeuw AH, & Rodrigues Pereira R (2008). Eetstoornissen bij Nederlandse kinderen: top van de ijsberg? *[Abstract in jaarlijkse conferentie samenvattingenboek Nederlandse Vereniging Kindergeneeskunde - NVK]*

Previous publications (before 2007)

Spierings, ELH & van Hoof, MJ (1997). Fatigue and sleep in chronic headache sufferers: an age- and sex-controlled questionnaire study. *Headache. The Journal of Head and Face Pain, 37*(9), 549-52.

Spierings, ELH, & van Hoof, MJ (1996). Anxiety and depression in chronic headache sufferers. *Headache Quarterly, 7*(3), 235-238.

Van Hoof, MJ, & Aldenkamp, AP (1995). Herkenning van psychosociale problemen in de kindergeneeskundige praktijk; de bruikbaarheid van de Pediatric Symptom Checklist-Nederlandse versie (PSC-NL). *Tijdschrift voor Orthopedagogie, Kinderpsychiatrie en Klinische Kinderpsychologie, 21*, 84-94.

Publications in preparation

Abdulmalik, J, Cat, C, Harper, G, Clemens, V, Fegert, J, van Hoof, MJ, Jud, A, Morgan, W, Prins, C ….(expected 2020). *Child Protection: Prevention, Detection, and Response to Child Abuse and Neglect.* [Chapter in IACAPAP e-textbook by J.M. Rey & A. Martin].

Hein, IM, Oterdoom, van Hoof, MJ, LML, Scheper, FY, Lindauer, RJL (expected 2020). Interventies voor vluchtelingenkinderen met een verhoogd risico op PTSS en de rol van de jeugd GGZ.

Zorgstandaard Psychotrauma en stressorgerelateerde stoornissen bij jeugdigen – authorization expected 2020.

Van de Sande M, van Hoof MJ, van der Wee NJA (expected 2020). Review on atomoxetine compared to methylphenidate and dexamphetamine in children aged 8-18 years old with ADHD.

Gelderblom, CI, Van Hoof, MJ, van Lang, NDJ, Vermeiren, RRJM (expected 2020). Zelfwaardering, gehechtheidrepresentatie en internaliserende symptomen: een longitudinaal onderzoek bij adolescenten met seksueel misbruik of een klinische depressie en niet-klinische controles.

Van Hoof, MJ (expected 2020). The case of the effects and impact of domestic violence. A review.

Posters

International

Aghajani, M, Veer, I, van Hoof, M, Rombouts, S, van der Wee, N, Vermeiren, R (2015). P.7.b.006 Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. *European Neuropsychopharmacology, 25* (Suppl. 2), S637-S638.

Meens PHF, Van Lang NDJ, Van Hoof MJ, Rinne-Albers MAW, Van der Wee NJA, Van Buchem MA, Rombouts SARB, Lamers-Winkelman F, Vermeiren RRJM (2009). EPISCA: Emotional Pathways' Imaging Study in Clinical Adolescents. A pilot study evaluating the first results of our (fMRI) Emotional Faces Task. *[poster ESCAP in Budapest]*

Van Hoof MJ, Van der Wee NJA, De Roos CJAM, Rombouts SARB, Bakermans-Kranenburg MJ, Van IJzendoorn MH, Vermeiren RRJM (2007). Neural correlates of attachment representation and emotional dysregulation in female adolescents with a history of documented childhood sexual abuse; a fMRI study. *[poster ESCAP in Florence]*

<u>*Dutch, national*</u>

Van Hoof, MJ. Unieke neurale correlaten van onverwerkt-gedesorganiseerde gehechtheid en psychopathologie met hersenen van adolescenten. *[poster Voorjaarscongres NVvP, 3-5 April 2019, Maastricht].*

Van Hoof, MJ, Van de Loo, DTM, Van den Bulk, BG, Meens, PHF, Rinne-Albers, MAW, Lamers-Winkelman, F, Van Buchem, MA, Rombouts, SARB, Crone, EA, Van Lang, NDJ, Van der Wee, NJA, Van IJzendoorn, MH, Vermeiren, RRJM (2012). EPISCA: the moderating role of attachment representations on emotion regulation and related activity in brain circuits in childhood sexual abuse: a longitudinal MRI study. Preliminary findings. *[Posterpresentation at Abuse & Neglect conference, 5-6 October 2012, Leiden].*

Van Hoof, MJ, Van den Bulk, BG, Meens, PHF, Rinne-Albers, MAW, Lamers-Winkelman, F, Van Buchem, MA, Rombouts, SARB, Crone, EA, van Lang, NDJ, Van der Wee, NJA, Van IJzendoorn, MH, Vermeiren, RRJM (2012). EPISCA: de modererende rol van gehechtheidsrepresentatie op emotieverwerking en de daaraan gerelateerde activiteit van hersencircuits. *[Posterpresentation at Wetenschapsdag Rivierduinen, 7 June 2012, Oegstgeest].*

Van Hoof, MJ, & Crijnen, AAM (2012). Child sexual abuse and pornography in young children. *[Posterpresentation at EUCCAN, 18-20 May 2012, Amsterdam].*

Meens PHF, Van den Bulk BG, Van Lang NDJ, Van Hoof MJ, Rinne-Albers MAW, Van der Wee NJA, Vermeiren RRJM, & Van Hoof MJ (2010). EPISCA: first results *[poster NVvP Voorjaarscongres in Maastricht]*

Meens PHF, Van den Bulk BG, Van Hoof MJ, Van Lang NDJ, Rinne-Albers MAW, Van Lang NJA, Van der Wee, NJA, Van Buchem MA, Rombouts SARB, Lamers-Winkelman F, & Vermeiren RRJM (2010). EPISCA: Emotional Pathways' Imaging Studies in Clinical Adolescents – Facing the emotions, piloting the results. *[Poster LIBC symposium 20 May 2010, Leiden]*

Van Hoof MJ, Rinne-Albers MAW, Meens PHF, Van Lang NDJ, Van der Wee NJA, Van Buchem MA, Rombouts SARB, Van IJzendoorn MH, Lamers-Winkelman F, & Vermeiren RRJM (2009). Neural motion circuitry in adolescents with sexual abuse: a longitudinal study. *[poster LIBC symposium 14 May 2009, Leiden and Developmental Neuroimaging workshop KNAW 18-20 May, Amsterdam]*

Meens PHF, Van Lang NDJ, Van Hoof MJ, Rinne-Albers MAW, Van der Wee NJA, Rombouts SARB, Van Buchem MA, Lamers-Winkelman F, Vermeiren RRJM (2009). EPISCA: Emotional Pathways' Imaging Study in Clinical Adolescents. A pilot study evaluating the First results of our fMRI Emotional Faces Task. *[poster LIBC symposium 14 May 2009, Leiden and Developmental Neuroimaging workshop KNAW 18-20 May 2009, Amsterdam]*

Presentations

Invited presentations

Van Hoof, MJ. *Neuroimaging van gehechtheid en psychopathologie bij jongeren en hun behandeling.* NtVP lezing, 25 September 2019, Assen.

Van Hoof, MJ, Riem, MME, Garrett, AS, Pannekoek, JN, Rombouts, SARB, Van der Wee, NJA, Van IJzendoorn, MH, & Vermeiren, RRJM. *Unresolved-disorganized attachment and the adolescent brain. Smaller hippocampus and enhanced functional connectivity beyond psychopathology.* ARPH symposium: Early adversity and psychophysiological dysregulation (with M.M.E. Riem, M. Giletta, J. Maas), 25 January 2018, Tilburg [oral presentation].

Van Hoof, MJ. *Stress and the brain: neuroimaging attachment and emotionregulation*. TechTalk, 20-minute-pecha kucha, invitational presentation 1 December 2016, Leiden.

Van Hoof, MJ. *AAI differentiates adolescents with childhood sexual abuse from those with clinical depression and non-clinical controls – 3-minutes pitch.* Invitational presentation, NtvP jaarcongres, 26 May 2016, Lunteren.

Van Hoof, MJ (2014). *Seksueel misbruik en de rol van hechting.* Invited parallelsessie Symposium Kind en Trauma, 11 March 2014, Amsterdam.

Van Hoof, MJ (2013). *Kindermishandeling en de meldcode in de psychiatrie*. Invited opening lecture Symposium GGz Breburg 28 May 2013, Etten-Leur.

Van Hoof, MJ (2013). *De impact van trauma en hechting: invloed van traumatisering op de vroege ontwikkeling en op de latere levensloop*. Invited opening lecture Symposium GGNet over kindermishandeling en gebruik van de meldcode 25 April 2013, Apeldoorn.

International:

Van Hoof, MJ (chair). *Unresolved-disorganized attachment across the lifespan* [symposium] Comprising 1) Whelan, W: Disorganization in the preschool, middle childhood and beyond; 2) Van Hoof, MJ, see below; 3) Unresolved attachment status marks a more than twofold greater risk for Post-Traumatic Stress Disorder and borderline personality disorder – a meta-analysis. IAC, Vancouver, 18-20 July 2019 [oral presentation]

Van Hoof, MJ*, Riem, MME*, Garrett, A.S., Pannekoek, J.N., Rombouts, S.A.R.B., van der Wee, N.J.A., van IJzendoorn, M.H., & Vermeiren, R.R.J.M. *Unresolved-disorganized attachment and psychopathology in the adolescent brain*. IAC, Vancouver, 18-20 July 2019 [oral presentation].

Van Hoof, MJ [1](chair), Riem, MME[2] (co-chair), Rinne-Albers, & MAW[3] Kuipers, GS[4] . Attachment and psychopathology in adolescents, comprising 1) Attachment and emotional face processing in adolescents[1]; 2) Unresolved-disorganized attachment associated with altered amygdala resting-state functional connectivity across psychopathologies[1-2]; 3) Neuroimaging in children, adolescents and young adults with psychological trauma[3]; 4) Attachment and psychopathology in adolescents with eating disorders before psychotherapy to 12 months follow-up[4]. ESCAP, 30 June-2 July 2019, Vienna [symposium].

ESTSS 6-8 June 2019, moderator flashtalks

Prins-Aardema C. & Van Hoof, MJ. *The guideline for family psychiatry in the Netherlands. Diagnostics and treatment in child abuse and neglect but safety first – for each child, each parent, each sibling*. IACAPAP, 25 July 2018, Prague [workshop].

Van Hoof, MJ. *Transition in case of child abuse and neglect: can childpsychiatrists make a difference?* ESCAP, 11 July 2017, Geneva [oral presentation].

Van Hoof, MJ, Crijnen, AAM, & De Ruijter, A. *Ten years advocacy on child abuse and neglect by child and adolescent psychiatrists in the Netherlands*. Chadwick Conference on Child Abuse & Neglect, 31 January 2017, San Diego [workshop].

Van Hoof, MJ. *Attachment, trauma, emotion regulation in child and adolescent psychiatry*. Chadwick Conference on Child Abuse & Neglect, 1 February 2017, San Diego [workshop].

EUCCAN 25-27 May 2016, moderator and member congress organization

Van Hoof, MJ (2014). *The role of attachment in childhood sexual abuse*. EUCCAN 23 May 2014, Amsterdam.

Van Hoof, MJ, Harper, GP, Apter, A, & Herczog, M. *Child abuse and neglect from international perspective: what works?* Symposium chair and presenter ESCAP July 6-9 2013, Dublin.

Van Hoof, MJ. *Child abuse and the child and adolescent psychiatrist: do we need a new approach?* Lezing op symposium Child abuse and neglect. ESCAP 13 June 2011, Helsinki.

Van Hoof, MJ & Lindauer, R.. *Child abuse and the child and adolescent psychiatrist: do we need a new approach?* Chair and presenter workshop Landelijk Kenniscentrum Kinder- en Jeugdpsychiatrie. ECOTS/ESTSS 4 June 2011, Vienna.

Van Hoof, MJ. *The organization of trauma aid* in *the Netherlands*. At symposium "Trauma care in international perspective" with Andreas Krüger, Renate Schepker. IACAPAP Istanbul, 1 May 2008.

<u>*Dutch, National:*</u>
Van Hoof, MJ. *Gehechtheid en psychopathologie bij adolescenten. Uitkomsten van de EPISCA studie*. Promovendi presentatie LUMC, 17 May 2018.

Crijnen, AAM, Hein, I, van Hoof, MJ, Prins, C, Scheper, FY, & Vogtländer, L. *Ouderschap bij verwaarlozing en mishandeling: beoordelen-beslissen-behandelen bij onveiligheid*. Voorjaarscongres NVvP, 12 April 2018, Maastricht [workshop]

Crijnen, AAM, Hein, I, van Hoof, MJ, Scheper FY, & Vogtländer, L. *Veiligheid bij geweld en mishandeling – een praktische en planmatige aanpak*. Presentation at Congres Van Wijk tot Wetenschap, Den Bosch, 23 November 2017.

Crijnen, AAM, van Hoof, MJ, Scheper, FY, & Vogtländer, L.. *Veiligheid bij geweld en mishandeling – een praktische en planmatige aanpak*. Voorjaarscongres NVvP 6 April 2017, Maastricht [workshop].

De Baat, M, van Hoof, MJ, & van Harten, L. *Complex trauma bij kinderen: samen doen wat werkt*. Van Wijk tot Wetenschap conferentie, 24 November 2016, Utrecht.
Van Hoof, MJ. *Het Gehechtheidsbiografisch Interview onderscheidt adolescenten met seksueel*

misbruik van adolescenten met klinische depressie en niet-klinische controles (EPISCA onderzoek). Wetenschapsmiddag Rivierduinen, 26 November 2015, Oegstgeest.

Van Hoof, MJ. *Diagnostiek en meldcode kindermishandeling*. Boerhaave nascholingscursus "Samen slagvaardig handelen voor de veiligheid van het kind: de differentiaaldiagnose kindermishandeling en verwaarlozing", 29 May 2015, Leiden.

Van Hoof, MJ, Sepers, JW, Landsmeer EA, & Van de Boon, N.. *Samenwerken met ouders als kindermishandeling ontkend wordt.* (WD-84). Voorjaarscongres NVvP 31 March 2015, Maastricht [workshop]. www.nvvp.net.

Van Hoof, MJ. *Het Gehechtheidsbiografisch interview onderscheidt adolescenten met seksueel misbruik van adolescenten met depressie en controles.* Spreker TOPGGz symposium "Motivatie van patiënten met een 3e lijns (topklinische) zorgvraag" (chair: A.A. Van Elburg), Voorjaarscongres NVvP 10 April 2014, Maastricht [symposium].

Van Hoof, MJ, Sepers, JW, Landsmeer, N, & Van de Boon, N.. *Kindermishandeling aanpakken en motiveren; twee kanten van dezelfde medaille.* Chair and presenter Voorjaarscongres NVvP 9 April 2014, Maastricht [workshop].

Van Hoof, MJ, Crijnen, AAM, Lindauer, RJL, Schmeets M, & Vogtländer, L.. *Kindermishandeling en het jonge kind – een overzicht van de gevolgen voor psychopathologie en de mogelijkheden van preventie en behandeling.* Chair and presenter Voorjaarscongres NVvP 12 April 2013, Maastricht [symposium].

Laan, MHCM, Smits, AAM, Van Hoof, MJ, Roose, C, & Uijterwaal, G.. *Handelen volgens het stappenplan van de Meldcode kindermishandeling en huiselijk geweld bij vermoedens van kindermishandeling*. Voorjaarscongres NVvP 12 April 2013, Maastricht [workshop].

Van Hoof, MJ. *Trauma en hechting*. KJTC Haarlem, 17 January 2013, Haarlem.

Van Hoof, MJ, Crijnen, AAM, & Vogtländer, L. *Multidisciplinaire, intersectorale overlegstructuur bij kindermishandeling.* Chair and presenter "Naar een Multidisciplinair Centrum kindermishandeling – samenwerking, modellen van communicatie, methodieken" op Voorjaarscongres NVvP 4 April 2012, Maastricht [workshop].

Laan, MHCM, Smits, AAM, Van Hoof, MJ, Roose, C, & Uijterwaal, G.. *Handreiking Gebruik Meldcode Kindermishandeling in de psychiatrie: hoe verder?* Discussion group Voorjaarscongres NVvP 4 April 2012, Maastricht.

Van Hoof, MJ. *Kindermishandeling en verwaarlozing in de kinder- en jeugdpsychiatrische praktijk*. LINC (Leiden Interdisciplinary Network on Child abuse and neglect, 6 February 2012, Leiden.

Werkgroep NVvP. *Studiemiddag Handreiking Meldcode Kindermishandeling in de Psychiatrie*. 26 January 2012, Utrecht.

Van Hoof, MJ & C. Roose. *Handreiking meldcode kindermishandeling in de psychiatrie*. Najaarscongres NVvP 17 November 2011, Utrecht.

Van Hoof, MJ, L. Daenen & J. Zevalkink. *Attachment, trauma and implementation in psychiatry.* Chair and presenter NVvP Voorjaarscongres, 31 March 2011, Amsterdam.

Van Hoof, MJ, Crijnen, AAM, Lindauer, RJL, Schmeets M, & Vogtländer L. *Kennis van trauma en kindermishandeling: vrijblijvend of verplicht?* Chair ; Landelijk Kenniscentrum Kinder- en Jeugdpsychiatrie, NVvP voorjaarscongres, 31 March 2011, Amsterdam [workshop].

Van Hoof, MJ. Meldcode Kindermishandeling. Presentation at symposium CWA, NVvP voorjaarscongres, 30 March 2011, Amsterdam.

Hoof, MJ, Rinne-Albers, MAW & Van Lang, NDJ. *Hersenspinsels. Hoe gaan hersenen om met gevoelens van angst en somberheid?* Kinderkopjes Publiekslezing LIBC junior, 15 May 2010, Leiden.

Hoof, MJ & Rinne-Albers, MAW. *Gehechtheid, trauma en psychiatrische classificatie*. Chair and presenter NVvP voorjaarscongres, 15 April 2010, Maastricht [workshop].
Van Hoof, MJ, Lindauer, RJL, Crijnen, AAM, Vogtländer, L, Schmeets, M. *Diagnostiek bij trauma en kindermishandeling - van preventie tot behandeling.* Chair Landelijk Kenniscentrum Kinder- en Jeugdpsychiatrie, NVvP voorjaarscongres, 14 april 2010, Maastricht [workshop].

Schweizer, JJ, Van Elburg, AA, Van Hoof, MJ, Teeuw, AH, Rodrigues Pereira, R.. *De kinderarts en anorexia nervosa: hoe vaak zien we het en hoe moeten we het behandelen?* Symposium at annual conference of the Dutch Society for Paediatrics | Nederlandse Vereniging Kindergeneeskunde (NVK), 5 November 2008, Veldhoven .

Van Hoof, MJ (2007). *Onderzoek naar seksueel misbruik bij meisjes*. Symposium psychotraumacentrum GGZ Kinderen en Jeugd Rivierduinen,
1 November 2007, Oegstgeest.

In the media

Vlogs m.b.t. kindermishandeling- en verwaarlozing i.v.m. 10-jarig jubileum expertgroep Trauma & Kindermishandeling Kenniscentrum Kinder- en Jeugdpsychiatrie; https://www.kenniscentrum-kjp.nl/nieuws/minister-de-jonge-krijgt-antwoord/

De Psychiater, augustus 2018. Houvast bij gevoelige beslissingen. Afwegingskader meldcode kindermishandeling en huiselijk geweld, pp. 14-15. VNVA website, 27 februari 2018: http://www.vnva.nl/nieuws/item/1467-genomineerden-essayprijs-2018-bekend

ESCAP website October 17, 2017: https://www.escap.eu/research/child-abuse-and-neglect/?utm_medium=email&utm_campaign=Trauma%20and%20child%20abuse&utm_content=Trauma%20and%20child%20abuse+CID_0910821bc8e3a4e4bfa59095f6f0b005&utm_source=HTML%20mailing&utm_term=experts%20in%20trauma%20and%20child%20abuse

VKJP website Tijdschrift De Wetenschap October 17, 2017: https://demo.7u.nl/vkjp.nl/de-wetenschap/expertgroep-trauma-en-kindermishandeling

Kenniscentrum Kinder- en Jeugdpsychiatrie website October 19, 2017: https://www.kenniscentrum-kjp.nl/Nieuws-2017/2017/Tien-jaar-Expertgroep-trauma-en-kindermishandeling#.WehB1a17Fn4

Gehechtheid en seksueel misbruik (2016). InZicht (interview in nieuwsbrief GGD Amsterdam, Steunpunt Seksueel Geweld), *juli 2016*. [oplage: 1000]

Onderzoek naar emotieverwerking bij jongeren is hot item (2009). *R (interview in personeelsblad van GGZ Rivierduinen), december (04)*, p 23-25.

De handreiking vertelt wat onze verantwoordelijkheid is. Handreiking gebruik meldcode kindermishandeling in de psychiatrie (2011). *De Psychiater 8,* 19-21.

Peer Review

Personality Neuroscience
Psychiatry Research
Psychiatry Research: Neuroimaging
Maandblad Geestelijke Volksgezondheid
Nederlands Tijdschrift voor Geneeskunde

Committees, social awareness

Participation de-stigmatization campaigns: MIND (Standing Man), Breaking the stigma for families

Working committee 'Opleiding AIOS psychiatrie ZGP praktijk' - Afdeling ZGP NVvP

Participant in Ministerie van VWS program 'Geweld hoort nergens thuis' (Ronde tafel traumascreening, focusgroepen, locale veld bijeenkomsten)

Board member NtVP 2019- now (portefeuille psychotrauma bij jeugdigen)
iCAMH coordinator IACAPAP juli 2018-heden
Representative NVvP to artsencoalitie KNMG working committee 'ontwikkeling afwegingskader meldcode kindermishandeling' 2017-now

Member NVvP committee "werkgroep meldcode kindermishandeling" since 2016, chair since November 2018

Member 'Zorgstandaard Psychotrauma en stressorgerelateerde stoornissen (bij kinderen en jeugdigen)'

Advisor ZonMW project 'Implementatie Kindcheck in de GGZ', dr. H. Diderich-Lolkes de Beer

Advisor/reader LESA richtlijn kindermishandeling van NHG

Advisor/reader Richtlijn Diagnostiek bij (een vermoeden van) seksueel misbruik bij kinderen van NVK [Guideline diagnostics when suspecting childhood sexual abuse]

2012-2016 co-coordinator/mede kartrekker Centrum Seksueel Geweld, CSG Zuid-Holland (Leiden/Den Haag), with Carlijn de Roos, Tielke Stroeken (assistent)

NVvP Committee "Implementatie meldcode kindermishandeling, handreiking voor psychiaters" - 2010-2011; since then a few times advisor/representation of psychiatrists NVvP to Ministery of Health (Ministerie van VWS) with regard to this theme.

Initiator and chair Expert groep Trauma and Child abuse and neglect (Trauma en Kindermishandeling), Kenniscentrum Kinder- en Jeugdpsychiatrie (http://www.kenniscentrum-kjp.nl/nl/Professionals/themas/trauma_en_kindermishandeling/) - since 2007; Since June 2011 English version website available till 2019; 30.000 unieke bezoekers per maand, 4000 abonnees

nieuwsbrief; O.a. reactie op advies Taskforce Kindermishandeling (oktober 2015, lobby naar politiek; overleg NJI, TNO)

Funding PhD research

Hilly de Roever-Bonnet fonds, Vereniging van Nederlandse Vrouwelijke Artsen (VNVA) (2009); zie www.vnva.nl→ Commissie Hilly de Roever Bonnet Fonds (€ 2.500)

WOP GGZ Rivierduinen (2009-2014) (>€ 300.000)

Previous funding

1997 Obsessive Compulsive Foundation ivm onderzoek naar PANDAS (USD 25.000)
1996 Stichting De Drie Lichten (fl. 25.000)
LUF travel funding to attend IFMSA meetings (board member NeMSIC/SCOPH IFMSA) - '90s

Nomination

Nominated for the VNVA Essayprijs 2018 with essay "De noodzaak de cirkel van intergenerationeel onverwerkt trauma te doorbreken om ikigai te bereiken: een lang, gelukkig en gezond leven voor onze kinderen en toekomstige generaties"; d.d. 27 februari 2018: http://www.vnva.nl/nieuws/item/1467-genomineerden-essayprijs-2018-bekend

The expertgroup 'Trauma en Kindermishandeling' Kenniscentrum Kinder- en Jeugdpsychiatrie was nominated for the Innovatieprijs Aanpak Kindermishandeling 2012.

Teaching

CAT (Critical Appraisal of Topic) coaching third year medical bachelor students (2018):

- Anouk Hopman: "The effectiveness of parent management training in the treatment of children with Attention Deficit and Hyperactivity Disorder"
- Auke Perenboom: "Discerning Post-Traumatic Stress Disorder in abused or neglected children with Autism Spectrum Disorder"
- Nora Wassenburg: "Risk of depressive disorder in young adulthood in victims of childhood bullying".
- Lina de Vries: "Eye movement Desensitization and Reprocessing versus Trauma focused Cognitive Behavioral Therapy in adolescent with posttraumatic stress disorder"

CAT (Critical Appraisal of Topic) coaching third year medical bachelor students (2017):

- Demi Donker: "What is the efficacy in reducing tics and the tolerability of aripiprazole in children with Tourette syndrome?"
- Seline Keijzer: "Is combined medication plus parent management more effective in reducing symptoms than medication alone in children 7-18 years old with ADHD?"
- Margot van de Sande: "Is atomoxetine as efficacious and well tolerated as methylphenidate and dexamphetamine as treatment for ADHD in children 8-18 years old?"

Feedback coaching CAT: good- very good

Workshop presentations for (child and adolescent)psychiatrists, clinical psychologists and other (youth) mental health and youth workers (inter)nationally, see 'Presentations'
CME presentations for general practitioners (2007)

IACAPAP Istanbul 2008. Donald J. Cohen Fellowship mentor together with Luis Rhode.
ESCAP Florence 2007. Donald J. Cohen Fellowship fellow (mentored by Yanki Yazgan & Beate Herpertz-Dahlmann).

Expert witness reporting

Regarding contact with children and custody (grand)children, Indigo advocaten (September 2019, ongoing)
Regarding criminal case domestic violence and emotional abuse, expert witness (November 2018)
Regarding sexual abuse case, Knoops' advocaten (Juni 2017; 2017-2018; appeal ongoing)
Regarding out of home placement under supervision, Jeugdzorg/YesWeCan (juli 2017)

Congress organisation

Boerhaave nascholingscursus voor paramedici en medisch specialisten: "*Samen slagvaardig handelen voor de veiligheid van het kind: de differentiaal diagnose kindermishandeling en verwaarlozing*". LUMC Leiden, 29 mei 2015. [initiator and chair congress committee with dr. E.M. van de Putte and dr. P.T.M. Weijenborg]

European Conference on Child Abuse and Neglect (EUCCAN) 2014, 21-23 May, Amsterdam

European Conference on Child Abuse and Neglect (EUCCAN) 2016, 25-27 May, Amsterdam

As a student co-organizer of several conferences

Audio-visual material

Composition, editing child abuse and neglect film for NVvP (Voorjaarscongres 2019) regarding awareness and enhancement implementation new reporting code child abuse and neglect in mental health care.

Vlogs Kenniscentrum Kinder- en Jeugdpsychiatrie, expertgroup 'Trauma & Kindermishandeling' in collaboration with Team Kim (ervaringsdeskundigen), "Minister de Jonge krijgt antwoord' (October 2018)

Wijk en Wetenschap 2017 (sponsor: Kenniscentrum Kinder- en Jeugdpsychiatrie)

Downpour Resurfacing Dutch subtitling 2017 (sponsor: iMindU)

Brave New World Conference 2016, 48 Hour Brave New World Publieksprijs: Split (participated in the script) https://www.youtube.com/watch?v=ESCknt35yzI&index=3&list=PLlFKL4EUjH17mdi150sCu-yvo2pq1dBw6

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LIST OF ABBREVIATIONS

AAI	Adult Attachment Interview
AAL	Automatic Anatomical Labeling
ABMT	Attention Bias Modification Treatment
ACC	Anterior Cingulate Cortex
ACE	Adverse Childhood Experience
ACT	Attention Control Training
AD	Axial Diffusivity
A-DES	Adolescent Dissociative Experiences Scale
ADIS C/P	Anxiety Disorders Interview Schedule child/parent (version)
AMBIANCE	Atypical Maternal Behaviour Instrument for Assessment and Classification
ANCOVA	Analysis of Co-Variance
ANOVA	Analysis of Variance
APA	American Psychiatric Association
BET	Brain Extraction Tool
CAPS	Child and Adolescent Psychopathology Scale
CAPS-CA	Clinician Administered PTSD Scale for Children and Adolescents
CBCL	Child Behaviour CheckList
CC	Cannot Classify
CDI	Children's Depression Inventory
CERQ	Cognitive Emotion Regulation Questionnaire
CFA	Confirmatory Factor Analysis
CNTR	Controls /Control group [participants EPISCA]
CSA	Childhood Sexual Abuse [group; participants EPISCA]
CSF	Cerebro-Spinal Fluid
dACC	dorsal Anterior Cingulate Cortex
DDIS	Dissociative Disorders Interview Schedule
DEFU	categorical classification system of attachment representation
DEP	anxiety and/or depression group [participants EPISCA]
DIS	Diagnostic Interview Schedule
dlPFC	dorso-lateral Pre-Frontal Cortex
Ds	Dismissive classification
DSM	Diagnostic Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
E	preoccupied classification
EPI	Echo Planar Images
EPISCA	Emotional Pathways' Imaging Study in Clinical Adolescents
F	secure-autonomous classification

FA	Fractional Anisotropy
FC	Functional Connectivity
FDR	False Discovery Rate
FDT	FMRIB's Diffusion Toolbox
FEAT	software tool for high-quality model-based FMRI data analysis
FIRST	FMRIB's Integrated Registration and Segmentation Tool
FLAME	FMRIB's Local Analysis of Mixed Effects
fMRI	functional Magnetic Resonance Imaging
FMRIB	Functional MRI of the Brain [Oxford Centre for FMRIB software library]
FNIRT	FMRIB's Non-linear Image Registration Tool
FSL	FMRIB Software Library
FWE	Family-wise error
g-factor	General intelligence factor
GG corr	Greenhouse-Geisser correction
GGZ	Geestelijke Gezondheidszorg (Mental Health Care)
GLM	General Linear Model
GMV	Gray Matter Volume
GPF	General Psychopathology Factor
HH	Hostile/Helpless [category]
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
HRF	Hemodynamic Response Function
ICD	International Classification of Diseases
IFOF	Inferior Fronto-Occipital Fasciculus
IQ	Intelligence Quotient
JHU	John Hopkins University
KMO	Kaiser Meyer Olkin statistic
LOC	Lateral Occipital Cortex
L/R	Left/Right
LUMC	Leiden University Medical Center
MarsBaR	MARSeille Boîte À Région d'Intérêt
MCFLIRT	Motion Correction FMRIB's Linear Image Registration Tool
MD	Mean Diffusivity
MNI	Montreal Neurological Institute [coordinates]
mPFC	medial Pre-Frontal Cortex
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MTG	Middle Temporal Gyrus
MTI	Magnetisation Transfer Imaging
NAO	Niet Anderszins Omschreven [Not Otherwise Specified]

NIS	National Incidence Study
NWO	Netherlands Organization for Scientific Research
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PCA	Principal Component Analysis
PDS	Pubertal Development Scale
PFC	Pre-Frontal Cortex
PTSD	Post-Traumatic Stress Disorder
RCADS	Revised Child Anxiety and Depression Scale
RD	Radial Diffusivity
RDoC	Research Domain Criteria
ROI	Region Of Interest
RSFC	Resting State Functional Connectivity
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Modeling
SNP	Single Nucleotide Polymorphism
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
TBSS	Tract-Based Spatial Statistics
TFCE	Threshold-Free Cluster Enhancement
TIQ	Total Intelligence Quotient
TRASC	Trauma-Related Altered States of Consciousness
TSCC	Trauma Symptoms Checklist for Children
U	Unresolved loss or trauma (also: Ulosstrauma)
Ud / UD	Unresolved-disorganized attachment
Ud-nonUd	Unresolved-disorganized versus resolved-organized
Uloss	Unresolved loss
Ulosstrauma	Unresolved loss or trauma (also: U)
Utrauma	Unresolved trauma
VAS	Visual Analogue Scale
VBM	Voxel-Based Morphometry
VIF	Variance Inflation Factor
VNVA	Vereniging van Nederlandse Vrouwelijke Artsen [Dutch Society of Female Doctors]
WAIS	Wechsler Adult Intelligence Scales
WBV	Whole Brain Volume
WISC	Wechsler Intelligence Scales for Children

WMCI	Working Model of the Child Interview
WMI	White Matter Integrity
WUSCT	Washington University Sentence Completion Test
YSR	Youth Self Report
ZALC	Zinnen AanvulLijst Curium [Sentence Completion Test for Children and Youth]