Unresolved-disorganized attachment, psychopathology, and the adolescent brain

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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).

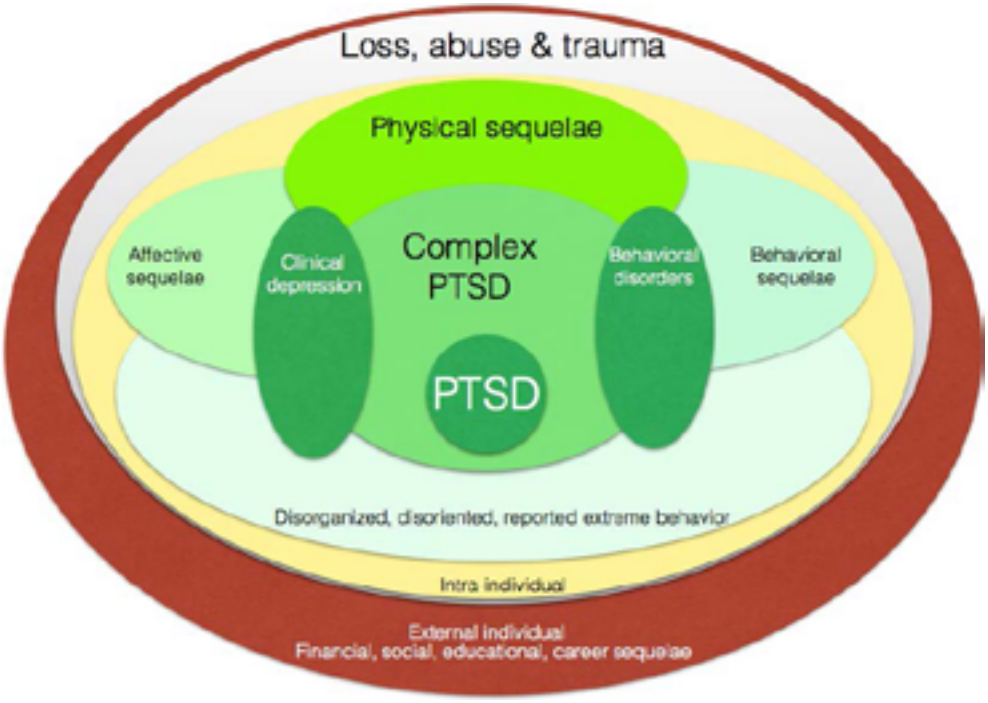

Figure 1. Graphic representation of intra-individual and external sequelae of loss, abuse and trauma and their overlap with psychiatric disorders

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.