Untangling pathways between childhood trauma and psychosis
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Chapter 9.1

Summary and general discussion
Childhood trauma is related to the development of several serious psychiatric disorders, both in childhood and adulthood\(^{94,10}\). The focus of this thesis was on the association between childhood trauma and psychosis. The first aim was to enhance our knowledge with regard to specific associations between different types of trauma, symptom course and psychosocial functioning. The second aim was to investigate possible underlying mechanisms by which childhood trauma influences the development of psychosis.

In this chapter a summary and discussion of the main findings of the previous chapters is presented and recommendations for future research and clinical practice are discussed.

**Summary of the main findings**

Growing evidence indicates that being bullied during childhood should also be considered as childhood trauma. In Chapter 2 we investigated whether being bullied in childhood is related to the development of psychotic symptoms. We summarized all available evidence about the relationship between childhood bullying and the development of psychotic symptoms in non-clinical and clinical samples. Our meta-analysis including all non-clinical studies showed that children who were bullied have a twofold-increased risk of developing subclinical psychotic symptoms compared to children that were never bullied. Moreover, stronger associations were found when bullying was more frequent, severe and persistent.

Only four studies\(^{94,115,123,179}\) reported on the association between childhood bullying and psychotic disorders, which was too sparse to draw definitive conclusions. Moreover, these studies made use of different methodological approaches, complicating direct comparisons. To clarify the direction and strength of this association, future studies should follow bullied and non-bullied children until early adulthood when the first expression of psychosis is most likely to occur.

**Specificity of (different types of) childhood trauma as a risk factor for psychosis**

It has been argued that childhood abuse and neglect have a different effect on neurodevelopmental, social and emotional development\(^{94,120}\) and may therefore be associated with different symptoms\(^{97,98}\). In Chapter 3 we investigated this hypothesis by examining specific associations between abuse and neglect and different symptom domains in patients with psychosis, individuals with genetic risk for psychosis and controls. We found evidence for a dose–response relationship, meaning that more exposure to childhood trauma was associated with more severe psychopathology. With this study, we were able to replicate findings from previous studies by making use of a substantially larger sample of patients, individuals with genetic risk and controls. We found strongest associations between childhood abuse and (sub) clinical symptomatology in all three groups. Furthermore, we explored whether childhood trauma increases the chance of developing psychotic symptoms compared to depressive symptomatology in patients with psychosis. In patients with psychosis and a history of childhood trauma, we found the risk of developing psychotic or depressive symptoms to be comparable. For individuals with genetic risk and controls stronger associations were found between childhood trauma and depressive symptomatology.

In Chapter 4 we examined whether the experience of childhood abuse or neglect was predictive for transitioning to psychosis, by following 125 individuals who met Ultra High Risk (UHR) criteria for psychosis for up to 24 months. Within our sample, childhood trauma was not predictive of transition to psychosis, but UHR patients with a history of childhood trauma did report higher levels of subclinical positive symptoms, general symptoms, depression and lower levels of global functioning at two-year follow-up.

**Childhood trauma and symptom course**

It was already well established that patients with childhood trauma report more severe positive symptoms, suicidal thoughts and depressive symptoms compared to patients without a history of childhood trauma\(^{97,147}\). However, it was still unclear whether childhood trauma was associated with persistence of these symptoms over time. In Chapter 3, we showed that childhood trauma was associated with higher levels of positive, negative and depressive symptoms both at first assessment and at three-year follow-up. However, childhood trauma was unrelated to a differential symptom course; that is, symptoms in the trauma group decreased to a similar extent compared to the non-trauma group.

In the study reported in Chapter 4 we found comparable results for UHR patients. In individuals with higher levels of childhood trauma, attenuated positive symptoms were more severe. Furthermore, childhood trauma was not significantly associated with a differential course of symptoms over time.

**Childhood trauma and cognition**

Childhood trauma has been found to be associated with cognitive deficits in general population studies\(^{20,21,51,77,122,220}\). Both childhood trauma and cognitive deficits are highly prevalent in patients with psychotic disorders\(^{10,173}\) and it has been suggested that childhood trauma may contribute to the cognitive deficits observed in patients with psychotic disorders\(^{220,225,276}\). Furthermore, there is convincing evidence that individuals who later develop a psychotic disorder have lower IQ scores compared to healthy individuals. However it is unknown whether IQ declines (further) after the onset of the disorder. In Chapter 5.1 and 5.2 the association between childhood trauma and cognitive functioning in psychosis was addressed. In Chapter 5.1 we found a similar increase in total IQ score between baseline and three-year follow-up measurement for patients, individuals with genetic risk and controls. Moreover, an increase in IQ was
significantly correlated with improvement in global outcome in patients.

In Chapter 5.2 we investigated the effects of childhood trauma on cognitive functioning in patients, individuals with genetic risk and controls. Childhood trauma differentially impacted IQ across the three groups. Childhood trauma in controls was associated with the largest reduction in IQ, a lesser reduction in siblings and no significant reduction in patients. Overall, the results indicate that although childhood trauma impacts cognitive ability and learning, its additional impact on the already observed cognitive alterations in psychotic disorders may be minor.

**Childhood trauma and structural brain alterations**

There is accumulating evidence suggesting that childhood trauma has lasting effects on brain systems and circuits that mediate the stress response, including the hypothalamic-pituitary-adrenal (HPA) axis. These changes are related to structural alterations in brain regions, such as the hippocampus and amygdala. The hippocampus and the amygdala have an essential role in stress responses since these regions are one of the most important regions in the brain containing glucocorticoid receptors. Glucocorticoids are a type of steroid hormones that play an important role in regulating our stress response. However, in case of prolonged exposure to stress, which coincides with chronic heightened glucocorticoid release, permanent changes in the HPA axis occur.

In Chapter 6, we examined hippocampal and amygdala brain volumes in a large sample of patients with recent onset psychotic disorders, with and without a history of childhood trauma. We found that type II trauma was specifically associated with smaller hippocampal volumes in patients with psychotic disorders compared to patients that experienced type I trauma. Moreover, patients who had been bullied in childhood showed lower hippocampal volume, which is comparable to patients exposed to childhood trauma. We did not find significant differences in amygdala volumes between patients with and without a history of childhood trauma.

**Childhood trauma and attachment**

Psychological models propose that childhood trauma contributes to an increased vulnerability to form negative beliefs about oneself, others and about social interactions. A suggestion put forward in previous studies is that adult attachment may play a role as potential mediating mechanism between childhood trauma and the development of psychosis. Childhood trauma is considered to be one of the most important causes of insecure adult attachment as it increases the vulnerability to form negative beliefs about oneself, others and about social interactions (e.g., negative self-esteem and/or a disruption in the ability to trust others).

In chapter 7 we investigated whether adult attachment mediated the relationship between childhood trauma and positive and negative symptomatology in patients, individuals with genetic risk and controls. The relationship between childhood trauma and positive symptoms appeared to be partially mediated by attachment style in both patients and in individuals with genetic risk. With regards to negative symptoms, only in individuals with genetic risk, attachment style was found to be a mediator.

**Childhood trauma and personality**

Although childhood trauma is related to more social dysfunction in patients with psychosis compared to patients without childhood trauma, this may not count for all patients with childhood traumatic experiences.

In Chapter 8 we examined whether personality characteristics are related to psychosocial functioning and quality of life in patients with psychosis and a history of childhood trauma. Overall, patients with more traumatic experiences showed lower levels of psychological functioning. However, patients with lower neuroticism and higher extraversion, openness, agreeableness, and conscientiousness reported a significantly better quality of life and social functioning compared to other patients with similar traumatic experiences. This indicates that certain personality characteristics may mediate the impact of childhood traumatic experiences on psychosocial functioning and quality of life in patients with psychotic disorders.

**General conclusion**

The aims of the studies described in this thesis were 1) to enhance our knowledge regarding the association between childhood trauma, symptomatology and psychosocial functioning, and 2) to investigate possible underlying mechanisms by which childhood trauma influences the development and course of psychosis.

In summary, the main conclusions of this thesis are:

1. Childhood bullying is related to the development of psychotic symptoms and to a smaller hippocampal volume in patients with psychotic disorders;
2. Different types of childhood trauma have a distinguishable impact on the course of psychotic disorders;
3. Childhood trauma contributes to a shared vulnerability for psychotic and depressive symptoms. Patients that have experienced childhood trauma do not only report psychotic symptoms, but also report to have more depressive symptoms compared to patients without childhood trauma;
4. Chronic childhood trauma leads to alterations in brain areas that are responsible for mediating the stress-response;
5. Although childhood trauma is related to more severe psychopathology and lower levels of functioning, this does not count for all patients with childhood traumatic
experiences; Psychological processes and personality characteristics may buffer against the effects of childhood trauma on the course and outcome of psychotic disorders.

**General discussion**

**An integrated model**

Based on the findings of this thesis and other studies, I present a hypothetical model (visualised in Figure 1). This model integrates different biological and psychological mechanisms through which childhood trauma influences the development and course of psychosis.

Childhood trauma impacts brain areas that mediate our stress-response. As can be seen in Figure 1, prolonged exposure to harm causes stress. Prolonged exposure to stress can result in permanent changes to the hypothalamic–pituitary–adrenal (HPA axis). These changes in the HPA axis are related to structural alterations in brain regions as the hippocampus. In Chapter 6 we found lower hippocampal volume in patients that experienced chronic forms of trauma. The hippocampus plays a vital role in regulating emotional responses to stress and is responsible for dampening HPA axis activity. Arguably, smaller hippocampal volumes may dysregulate this process. It is known that dysregulation of this HPA axis may result in over-activation of dopaminergic circuits, which in turn is associated with psychotic symptoms. The ‘aberrant salience’ model proposes that psychotic symptoms emerge when an increased dopamine release leads to the attention to stimuli that would normally be considered irrelevant. Over-activation of dopaminergic circuits may also cause oversensitivity to stress; this process is called ‘behavioural sensitisation’.

The role of childhood trauma on stress-sensitisation may also in part explain the different effects of abuse and neglect on neurodevelopmental, social and emotional development. Abuse is considered to be highly stressful and is therefore assumed to alter brain systems that are involved in mediating the stress response. Neglect, on the other hand, refers to enduring deprivation from stimulating experiences, which may be less directly related to increased stress-experiences, and hence, may have different consequences on behaviour in individuals vulnerable to developing psychotic disorders.

Psychological processes impact the course and outcome of psychosis as we showed in Chapter 7 and 8. It has been argued that the enduring experience of childhood trauma may increase the change of developing an insecure attachment style, in childhood as well as in adulthood. In adults, a secure attachment style is reflected by a general positive view towards oneself and others, while insecure attachment styles refer to more negative views about oneself and/or others. Arguably, people with negative schemas may become more alert to hostile cues from others which in turn may feed paranoid ideation and ideas of reference. In general, those people are more likely...
to consider ‘neutral’ stimuli as dangerous. The attribution of danger to neutral situations likely decreases the sense of control. A reduced sense of control has been associated with higher levels of distress, which could lead to permanent changes to brain systems that mediate the stress response, similar to the pathway described in the previous paragraph. These alterations may not only result in a direct increased risk for psychotic experiences, it may also lead to dysfunctional interpersonal responses, such as hostility, social withdrawal or lack of assertiveness. Social withdrawal in particular may contribute to the development of psychosis by reducing the possibility of reality testing in social interaction. Although childhood trauma is related to more severe psychopathology and lower levels of functioning, this does not count for all patients with childhood traumatic experiences. Earlier studies found that certain personality characteristics are predictors of psychosocial functioning. For example, it has been found that elevated levels of neuroticism are related to higher levels of emotional distress and more severe symptoms in patients with psychotic disorders.

Interestingly, we found that patients with a more favourable personality profile (lower levels of neuroticism and higher levels of extraversion, openness, agreeableness and conscientiousness) reported higher levels of quality of life and better social functioning in several areas compared to patients with a less favourable personality profile. This may indicate that in some individuals, stressful and traumatic experiences increase the likelihood to develop dysfunctional behaviour, whereas others show adaptation to the same challenges, which is called resilience. Personality factors and attachment style may explain this difference in resilience.

Finally, while the exploration of genetic risk was beyond the scope of this thesis, differences in genetic profiles may interact with childhood trauma inducing psychotic symptomatology (gene-environment interaction). Gene-environment interaction means that the genetic profile of an individual impacts the sensitivity to an environmental factor. Gene-environment interactions may be important in explaining the differences between patients, individuals with genetic risk and controls. In short, it may be that higher levels of genetic vulnerability in the patient group made them more prone to develop psychotic symptoms in reaction to childhood trauma.

If we want to fully disentangle the different mechanisms that play a role in the relationship between childhood trauma and psychosis, it is important to investigate the more complex relationships between biological and different psychological processes. These processes do not exclude one another but likely interact. To make definite inferences about causality and underlying pathways, further prospective and integrative studies are needed, combining neuroscience, results from genome-wide associations and clinical assessments.

### Methodological considerations

Although specific limitations of each study were discussed in the relevant chapters, some overall limitations are worth mentioning here. One major caveat is the use of self-report retrospective questionnaires to measure childhood trauma. The use of a self-report questionnaire increases the chance of reporting and recall bias. The retrospective design of the studies allows us to evaluate associations but does not allow us to make conclusions about causation. Nonetheless, the magnitude of effect sizes, the evidence of a dose-response relationship and the effects found over time in patients, individuals with genetic risk and controls all point to the direction of a causal relationship between childhood trauma and psychosis. However, to make definite inferences about causality and underlying pathways, prospective studies are required.

A second limitation is that the studies in this thesis lack detailed information about experienced trauma such as timing, age of occurrence, the relationship to the perpetrator, severity and duration of the trauma. These factors are important because they are likely to influence the impact of childhood trauma on the vulnerability for developing psychosis, the course of psychopathology and on the outcome of illness. This is considered an important issue for further research.

A third limitation is the strong preponderance of male patients in our studies, therefore we were not able to examine potential gender differences. It is possible that gender is an important factor in differential response to trauma, as well as its impact on psychosis vulnerability and illness course. In addition, there might be gender differences in the response to childhood trauma. Investigating possible gender differences is therefore an important objective for future research.

Taking the limitations into consideration, the studies in this thesis have extended our knowledge concerning the association between childhood trauma and psychosis. The most important strength of the majority of studies in this thesis is that we could investigate the association between childhood trauma and psychosis in large samples of patients, individuals with genetic risk and control subjects. The investigation of psychotic phenomena in individuals with genetic risk for psychosis and control subjects increases our knowledge about the underlying aetiology of psychosis. As mentioned in the introduction of this thesis, psychotic phenomena are not only present in clinical populations, but are also frequently observed in non-clinical groups and it is suggested that mechanisms underlying the development of psychotic symptoms may be similar. Individuals with genetic risk were matched on a range of both genetic and environmental factors, with reduces the chance of residual confounding.

Moreover, including non-clinical groups allows the investigation of risk factors without the confounding effect of illness-related factors and increases knowledge about the underlying aetiology of psychosis. Therefore, we were able to find evidence of a robust association between childhood trauma and psychotic symptoms in subjects with variation in psychosis vulnerability.
Another major strength was that we were able to investigate associations between childhood trauma and various (both biological and psychological) mediating variables and outcome measures, which increases our knowledge about the underlying aetiology of psychosis. We focussed on the mediating role of adult attachment style and personality traits because they are the key components of psychosocial factors described in research concerning childhood trauma.

To the best of our knowledge, we were one of the first to investigate whether the found associations between childhood trauma and psychosis were persistent over time. Investigating childhood trauma in relation to the course of symptoms and functioning over time is required to estimate the long-term impact of childhood trauma.

Finally, our sample size exceeded many previous studies concerning the association between childhood trauma and psychosis. Therefore our findings are more robust and reliable. Moreover, this allowed us to discover relationships, which otherwise would not have been found due to insufficient statistical power.

**Implications for clinical practice**

The present thesis emphasises the importance of integrating the assessment of a trauma history in standard mental health care diagnostic procedures. However, to date clinicians are still somewhat reluctant to discuss and treat trauma in patients with psychosis. Clinicians should be informed about the present state of affairs and should be taught how to open this discussion. It is important that clinicians treating traumatized individuals discuss the presence of psychotic experiences.

There are several ways clinicians could open the discussion and treat trauma in patients with psychosis. First, it might be helpful for patients to receive sufficient information about the prevalence of childhood trauma and about the consequences childhood trauma may have. Second, given that childhood trauma may cause the development of negative cognitions about oneself and others, it is important for clinicians to address dysfunctional interpersonal interaction styles and dysfunctional beliefs and help patients changing them. To increase therapeutic change it may be helpful to target these interventions at the symptoms and problems resulting from different attachment patterns. Third, although for many years clinicians were reluctant to treat trauma of patients with psychosis, recent evidence suggests that it is helpful and necessary to address trauma in treatment itself. Van den Berg and colleagues (2016) showed that trauma-focused therapy (prolonged exposure or eye movement desensitization and reprocessing (EMDR) therapy) is effective and safe in the treatment of trauma in subjects with a psychotic disorder. Treatment reduced symptom levels and revictimization compared to patients without a trauma-focused therapy.

More importantly, our findings also highlight the significance of early (school-based) interventions, designed to prevent and stop bullying. School bullying is a worldwide problem that affects about one-third of children, and approximately eleven per cent are bullied on a regular basis. Negative appraisals about oneself and others may be important subjects for discussion in the classroom to change the existing cognitive schema. Research has suggested that early detection and intervention may have the potential to change the course of early psychopathology.