Childhood Trauma in Psychoses

10

Ruud van Winkel and Aleksandra Lecei

10.1 Introduction

> "I was convinced that we were on the verge of a world war. The public defense sirens were tested every first Monday of the month. To me, those sirens meant that the cruise missiles had already been launched. We had just minutes to do what had to be done: find each other and wait to die. Sometimes I could actually feel the radiation taking effect. I felt nauseous and believed that my hair was falling out. The rest of the world pretended to carry on as normal, but I could see that everyone was afraid. They knew that we were all about to suffer a slow, painful death, but nobody knew how to prepare for it. […] The strange thing is that time did not exist for me in that situation. […] It is a kind of vacuum, no-man's-land. Not in real life, but also not dead. […] Now I no longer see my psychoses as isolated psychopathology. […] My psychoses are my way of reacting to my life history. They are my response to the unpredictable abuse I had to face as a child. I hit my father back when I finally was angry enough, after years of submission. My father left the house after threatening to kill himself, after which the whole family turned against me. […] In the years to follow I lost all my strength and exchanged it for guilt, fear, and incomprehensible psychotic experiences. I became the problem that had to be solved. I don't think that abuse itself is a strong cause for psychosis. […] I think that the threat and the betrayal that come with it feed psychosis. The betrayal of the family that says, "you must have asked for it, " instead of stand-

Author "Aleksandra Lecei" contributed equally to this manuscript.

R. van Winkel (✉)
Dept. of Neurosciences, Research Group Psychiatry, Center for Clinical Psychiatry, KU Leuven, Leuven, Belgium

KU Leuven, University Psychiatric Center KU Leuven, Leuven, Belgium

Dept. of Psychiatry and Psychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands
e-mail: ruud.vanwinkel@upckuleuven.be

A. Lecei
Dept. of Neurosciences, Research Group Psychiatry, Center for Clinical Psychiatry, KU Leuven, Leuven, Belgium
e-mail: aleksandra.lecei@kuleuven.be

G. Spalletta et al. (eds.), *Childhood Trauma in Mental Disorders*,
https://doi.org/10.1007/978-3-030-49414-8_10

> ing up for you. That excuses the offender and accuses the victim. And forces the child to accept the reality of the adults. That forces the child to say that the air is green, while she sees clearly it is not green but blue. That is a distortion of reality that is very hard to deal with when you're a child. You are forced to betray yourself [1]."

This piece is a first person account of a woman with psychosis and a history of childhood trauma. Psychosis is a mental health disturbance that can cause people to perceive and interpret the world differently from those around them. Symptoms can fall into one or more of two categories: positive and negative. Positive symptoms include hallucinations (i.e., seeing, hearing, and feeling things that are not there), delusions (i.e., false beliefs), and disorganized speech and/or behavior. Negative symptoms relate to functions that are diminished or absent in patients with psychosis, such as loss of motivation, flat affect, and apathy. If more than two symptoms are present during at least 6 months and cause functional dysfunction, the psychotic disorder is referred to as schizophrenia (Fig. 10.1).

Evidence accrued in recent years that psychotic experiences are common in the general population with a lifetime prevalence of 7.2% [2]. Psychotic experiences can be fleeting hallucinations, suspiciousness, paranoia, and magical thinking. These are associated with a greater risk for later development of psychotic disorder (or other disorders) and have been reported in young children and adolescents, too [3]. It is, then, important to look into early childhood experiences that may be on the etiological pathway to psychosis. A possible causal role of childhood trauma has been proposed decades ago, not just because a significant proportion of people with psychosis reports a history of adversity [4]. Childhood trauma refers to a broad range of adverse experiences usually before the age of 16, including life events (e.g., death of a parent, environmental catastrophes) or single and/or repeated maltreatment (e.g., sexual abuse, physical abuse, physical neglect, emotional abuse, emotional neglect, peer bullying, i.e., maltreatment with the intention to harm). In this chapter, we will focus on the latter and discuss the different levels through which childhood trauma (which in the literature is sometimes also referred to as "adversity" or "maltreatment") might exert its influence on the development of psychosis.

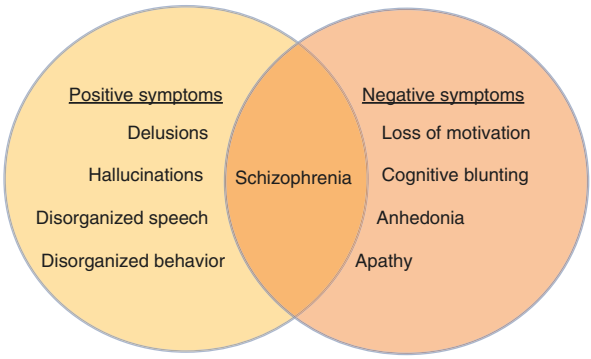

Fig. 10.1 Positive and negative symptoms of schizophrenia

10.2 The Epidemiological Evidence for a Link Between Childhood Trauma and Psychosis

Evidence is amassing that consistently points in the same direction: childhood adversities, specifically with the intention to harm, are associated with an increased risk for psychosis. In a comprehensive meta-analysis, Varese and colleagues identified 36 studies with a combined sample size of 80,000, and concluded that childhood adversities were associated with a two- to fourfold increased risk for later psychosis [5]. The overall association was 2.78 increased odds, irrespective of study design. More specifically, zooming in on different forms of adversity, the odds rations reported were 2.4 for bullying, 3.4 for emotional abuse, 2.9 for neglect, 3.0 for physical abuse, and 2.4 for sexual abuse. Only parental death was non-significantly associated with psychosis (odds 1.7) [5]. There is, furthermore, some evidence for a dose–response relationship [6–10]. Research suggests that for each additional indicator of maltreatment, there would be a modest linear increase in risk for psychosis [11].

Since the review by Varese and colleagues, additional evidence has been published suggesting that a history of childhood trauma is not just common among those with a psychotic disorder, but also among those on the psychosis spectrum, including children and adolescents [7, 12–26]. In a prospective study using a large twin cohort, researchers assessed childhood trauma and psychotic experiences at age 5, 7, 10, and 12 years. They found that maltreatment by an adult, as well as peer victimization with intention to harm were associated with a 3.3 increased risk for psychotic experiences [27]. This is further underlined in a study conducted by Kelleher and colleagues who found that after cessation of trauma in adolescence, psychotic experiences may also stop [7]. Thus, when studying the association between childhood trauma and psychosis, it may be important to move away from categorical diagnoses and consider the whole psychosis spectrum.

10.3 The Question of Causality

It is generally assumed that childhood trauma is a causal risk factor in bringing on later psychosis. However, before such a claim can be substantiated, a number of issues need to be addressed. These include, among others, the question of robustness, temporality and genetic confounding when studies are summarized in a review [7, 28]. As evident from the meta-analysis by Varese and colleagues [5], there seems to be a well-established robust and strong association between childhood trauma and psychosis across different samples along the psychosis continuum. The same meta-analysis also summarized findings that point toward a dose–response relationship [5]. However, these studies were unable to determine the directionality of the association between childhood trauma and psychosis. While the assumption may be that childhood trauma increases the risk for psychosis, other explanations may also need to be considered [28, 29] (Fig. 10.2).

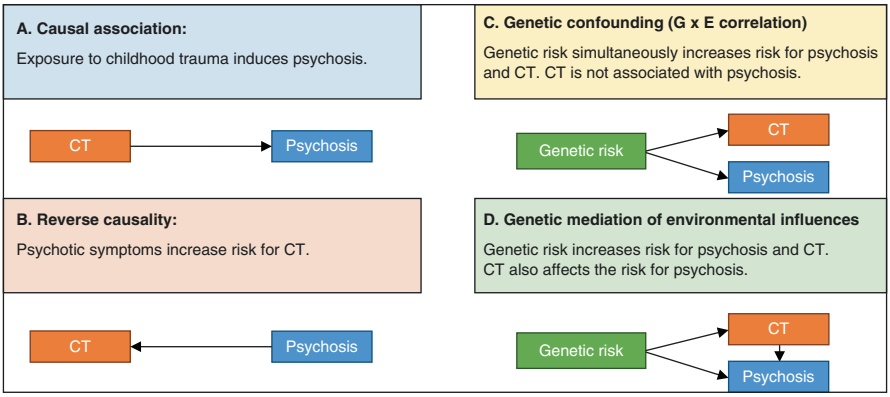

Fig. 10.2 Etiological models explaining the association between childhood trauma (CT) and psychosis [28]

A possible alternative could be the hypothesis of "*reverse causation*." This would be the case if early symptoms of psychosis were to lead to an increased risk of exposure to childhood adversity. Psychotic symptoms would then have to be caused by other factors, and experiences of childhood adversity would only follow later in a person's development [28]. To test this hypothesis, temporality needs to be determined, but obviously, this is very difficult in the context of childhood trauma since prospective studies are ethically difficult. Therefore, only a few studies to date have been able to successfully adopt this approach, and even fewer have assessed whether psychotic experiences were present before the exposure to childhood traumatic events [28]. In one study, researchers found that individuals who were sexually abused before the age of 16 had a twofold increased risk for developing any diagnosis of psychotic disorder, and a 2.6-fold increased risk for schizophrenia, compared to age- and gender-matched non-abused individuals [30]. Similarly, another prospective study found that those maltreated before the age of 12 had a 3.16-fold increased odds to report psychotic symptoms later in life [27]. Neither one of these studies, however, was designed to establish temporality of onset of psychotic symptoms. Recently, two studies have been published that prospectively examined both exposure to childhood trauma and psychotic symptoms. The findings exemplify that, whereas childhood traumatic experiences increased the odds for later psychotic symptoms, psychotic experiences also predicted a greater risk for exposure to traumatic events [7, 31]. The observation of a bidirectional relation calls to consider another, though not necessarily mutually exclusive, explanation.

Before causality, or any relationship can be established, the possibility that both childhood trauma and psychotic symptoms are caused by a third factor needs to be ruled out. It is conceivable that the exposure to early life adversity is not random, but may develop out of a preexisting vulnerability, such as genetic vulnerability. The hypothesis of a "*gene-environment correlation*" postulates that a genetic predisposition would lead to both an increased likelihood of exposure to traumatic events, as well as to the later expression of psychotic symptoms. In this case, individuals with an increased genetic risk for psychosis would be more likely to be exposed to adversity

due to inborn traits associated with psychosis, such as impaired social functioning or cognitive abilities [32–34]. In this case, the association between childhood trauma and psychosis may seem statistically plausible, when in fact this association could be explained by underlying genetic vulnerability. In other words, the relation between childhood trauma and psychosis would be "genetically confounded" [19, 28, 29].

There are different ways of controlling for "genetic confounding." An extensively applied approach is to use family psychiatric history as a proxy for genetic risk. Studies that adopted this approach did not find evidence that family liability confounded the association between childhood trauma and psychosis. Neither did they find evidence that combined family liability and childhood trauma increased the odds for later psychosis beyond the effect of each individually [8, 35], (for a review see [36]). Another method is to use direct measures of genetic vulnerability. A number of studies looked at specific candidate genes (i.e., genes that are thought to be either implicated in psychosis itself, or in possible mechanisms underlying psychosis onset) [37–40]. Again, others computed a polygenic risk score for schizophrenia. A polygenic risk score is a way to combine genome-wide genetic liability into one variable by summing up and weighting all risk alleles carried by one individual [41]. This approach could not confirm (passive) gene–environment correlation either [36]. However, neither of these concepts is currently able to capture all relevant genetic risks [19, 28, 29]. To overcome this limitation, the authors of three recently published studies used a monozygotic twin-differences approach. The idea behind this approach is that if two genetically identical (monozygotic) twins differ in environmental exposure, and that exposure is associated with psychotic symptoms, the association cannot be attributed to underlying genetic risk alone as monozygotic twins share 100% of their genes [19, 29, 31]. In agreement with the other approaches, these studies found that increased levels of exposure to childhood trauma were associated with more symptoms of psychosis, thus showing that the association cannot be solely attributed to genetic confounding.

A last consideration concerns the fact that not all individuals with a history of childhood trauma continue to experience psychotic symptoms. At the same time, whereas a great number of those with a psychotic disorder report having been victimized, not all persons with psychosis have. It is therefore crucial to consider that childhood trauma is neither sufficient nor necessary for the onset of psychosis [8, 28, 42]. Nevertheless, while other genetic and nongenetic factors might play a role in the etiology of psychosis, the current literature suggests that at least part of the association between childhood traumatic experiences and psychosis is genuine, and in agreement with a possible causal explanation [29].

10.4 Differential Sensitivity to Trauma: The Role of Genetic and Epigenetic Variation

While multiple studies have shown that the association between childhood trauma and psychosis persists even after controlling for genetic risk, it is currently unclear how genetic vulnerability plays a role in one's individual risk to develop psychosis following exposure, and which genes are likely to be involved [28, 43, 44]. The

current literature, however limited, points to genes that are not specific to psychosis, but associated with mechanisms such as neuroplasticity and stress regulation. Again, the genetic contribution to the association between childhood trauma and psychosis can be either directly or indirectly examined.

Studies that adopted an indirect approach used family history or a twin-design and focused on heritable traits that are thought to be associated with psychosis. Based on data from a twin sample from the general population, the authors reported that worse cognitive speed, as well as a lifetime diagnosis of depression, moderated the effects of childhood trauma on the development of psychosis [45]. However, other studies, using family psychiatric history by either looking at parental psychiatric history, or at co-twin's symptoms, found no evidence of an interaction between indirect genetic liability and childhood trauma on the emergence of psychotic symptoms [27, 31, 35].

A number of studies have used a direct approach by looking at genetic variation to examine the interaction between childhood trauma and psychosis. Most of these studies examined candidate genes that are involved in regulating neurotransmitters (e.g., serotonin transporter gene SLC6A4/5-HTT/, specifically a functional polymorphism in the promoter region 5-HTTLPR) [46], neuroplasticity and cell survival following stress (brain-derived neurotrophic factor; BDNF) [40, 47], and the stress response system (FKBP5) [37]. For example, there is some evidence that a short-(s-) allele polymorphism in the promoter region of 5-HTTLPR is associated with several psychiatric disorders, possibly through its effects on the stress response system [48, 49]. One study found an interaction between 5-HTTLPR variations and physical neglect and abuse on cognitive functioning in patients with psychosis [46], in line with previous work suggesting that an increased stress response may be associated with cognitive impairments [50]. Another study looked at the moderating effects of the BDNF-Val66Met polymorphism between childhood trauma on positive and negative symptoms of psychosis [51]. Valine (Val) and methionine (Met) are amino acids that are used in the biosynthesis of proteins. The substitution of valine to methionine, by changes in a single base pair of the BDNF gene, may lead to differences in the activity of BDNF. The val/met polymorphism has been linked to changes in intracellular trafficking (i.e., distribution and release of macromolecules throughout and outside of a cell), as well as changes in activity-dependent secretion of BDNF [52]. Met carriers with a history of abuse reported more positive symptoms of psychosis compared to those with a Val/Val genotype [51]. However, others failed to replicate this interaction [40, 47]. A different gene of interest is FKBP5, which is thought to be involved in modulating the feedback loop determining glucocorticoid receptor sensitivity. Collip and colleagues [37] found an interaction between two FKBP5 single nucleotide polymorphisms and childhood trauma on psychotic symptoms and increased stress sensitivity in a twin sample from the general population. In agreement with these findings, a study of two independent samples from the general population found this polymorphism to be related to increased early stress sensitivity and the expression of positive psychotic symptoms [53]. Another replication study found an interaction between childhood trauma and the same polymorphism on schizotypy, psychotic experiences, as well as symptoms of anxiety and depression, in the general population [47]. Green and colleagues

[38], albeit looking at a different polymorphism, found a variation in combination with maltreatment to affect cognition, in those with schizophrenia and healthy controls. For a more extensive overview of relevant gene–environment interaction studies, we also refer to the chapter by Araceli Rosa and colleagues in this handbook.

While the mentioned studies have looked at variations in DNA sequence, it is also possible that childhood trauma exerts its influence through epigenetics [44, 54]. Epigenetics refers to changes in gene expression rather than modifications of the genetic code itself [54]. While this process is not yet fully understood, vigorous scientific attention has been directed to DNA methylation as a mechanism through which early life stress may become "embedded" in the genome [55]. An animal study found that the level of postnatal maternal care in rodents was associated with alterations in the methylation of the glucocorticoid NR3C1 receptor [56]. A human postmortem study [57] reported increased methylation of the NR3C1 promoter and changes in mRNA (i.e., messenger RNA that communicates information from DNA to the ribosome about what amino acid sequence should be read, thereby specifying gene expression) in those with a childhood trauma history, compared to suicide victims and healthy controls. However, a second study failed to replicate these findings [56]. A number of in vivo studies have reported altered DNA methylation as a consequence of childhood trauma (for a review see [42]). To our knowledge, there is only one study that examined methylation in first-episode psychosis patients with a history of childhood trauma within a considerable sample ($n_{\text{first-episode-psychosis}} = 48$; $n_{\text{control}} = 48$) [58]. Researchers found lower DNA methylation of LINE-1 (class I transposable elements in the DNA) sequences in those patients. However, in a recently published article on the E-Risk dataset (n = 1.658) (Environmental Risk longitudinal study), authors found very limited evidence for an association between childhood adversity and changes in epigenetic variation (in peripheral blood) [59]. They also found that methylation associations for adversities overlapped with those of other health behaviors such as tobacco smoking. Another study found similar results in that DNA methylation in whole blood was associated with tobacco smoking, and also BMI and additive genetic effects [60]. This highlights the methodological difficulties of disentangling biological effects of environmental influences from other health-related behaviors associated with a trauma history [59].

The evidence for genetic moderation of the association between childhood trauma and psychosis, thus, is mixed. Nevertheless, these studies exemplify the numerous genetic mechanisms through which childhood trauma could potentially influence the development of psychosis, and other related mental health disorders [54, 59, 61].

10.5 Biological Mechanisms Underlying the Link Between Trauma and Psychosis

The *diathesis-stress model* of mental illness postulates that major life stressors, such as childhood trauma, can be a serious neurodevelopmental insult on the developing brain and contribute to the onset of psychiatric disorders [62]. The idea that

abnormalities in the limbic system could be related to the effects of childhood abuse on brain development dates back to van der Kolk and Greenberg in 1987 [63]. Since then, a number of studies have found structural, functional, and molecular changes in brain structures and persistent associations with childhood trauma, e.g., [64–66]. Below, we will discuss implicated alterations of the brain (more specifically hippocampus, amygdala, and findings from studies on cortical thickness), the stress response system and the immune system. Intact stress response and immune systems are of crucial importance for mental and physical health, behavioral adaptation, and brain development; the dysregulation of these systems may therefore have long-lasting effects on the developing brain and one's mental and physical health [67].

10.5.1 The Brain

10.5.1.1 Hippocampus

The hippocampus may be the most likely place to reflect the effects of childhood trauma [68]. This brain area is densely packed with glucocorticoid receptors, which makes it highly susceptible to early life stress [69]. Structural imaging studies found reduced bilateral hippocampal volume in those with a history of childhood trauma, those with a psychotic disorder, and in individuals with both [67, 68, 70, 71]. Interestingly, volume reductions were also found in nonpsychotic siblings, individuals at risk for schizophrenia, as well as in people with psychotic bipolar disorder (for a review see [72]). Studies found that childhood trauma was associated with reduced hippocampal volume in patients with first-episode psychosis, which may be associated with worse cognitive performance compared to patients with a diagnosis of schizophrenia, but no history of adversity [39, 73, 74]. There is some evidence that the hippocampus is involved in regulating the hypothalamic-pituitary-adrenal (HPA) axis stress response and that smaller hippocampal volume in those with a first-psychotic episode may partially be explained by stress-related processes [39]. In animal models, decreased hippocampal volumes, specifically in dentate gyrus (DG) and cornu ammonis 3 and 1 (CA3;CA1), were found in mice exposed to maternal deprivation (i.e., traumatic event) [75]. This fits well with previous findings from human postmortem studies that suggest that the DG and CA3 subfields appear most affected by molecular and cellular changes when comparing tissue of previously healthy individuals with persons with schizophrenia [76]. Additionally, on a cellular level, it was shown that the hippocampus contains "place cells" and "grid cells" in the entorhinal cortex. These cells are responsible for the spatiotemporal representation of places, routes, and associated experiences [77]. As spatiotemporal disorientation may be a symptom of psychosis in some patients, it may not be farfetched that childhood trauma could exert its effects on the development of psychotic symptoms by affecting hippocampal development [78].

10.5.1.2 Amygdala

The amygdala is a key limbic structure for prioritizing and encoding emotionally salient information, and detecting and responding to facial expressions and potential threats [79, 80]. Given the altered emotional responses observed in patients with schizophrenia, an affective pathway to psychosis has been previously proposed [81–83]. This also makes sense based on the finding that, like the hippocampus, the amygdala is rich of glucocorticoid receptors, which would make it especially vulnerable to early stress, including childhood trauma. Most studies have examined emotional reactivity following childhood trauma on a behavioral level, for example, by examining reactivity to daily life stress [82, 83]. Other studies have examined structural and functional abnormalities of the amygdala in a variety of mental disorders, including psychosis [84–86]. Structural studies report contradicting results. Some found decreased amygdala volumes in those with a first-episode psychosis and a trauma history. Others found increased volumes and argue that this may be due to the stimulating effects of stress on pyramidal cells in this brain structure [87, 88]. The same discrepant findings were found on a functional level, in that some show either patterns of hypo- or hyper-activation during emotional tasks in patients with psychosis [89]. Therefore, Cancel and colleagues [90] suggested to examine functional connectivity between the amygdala and other related brain areas. They found that in patients with schizophrenia and a history of childhood trauma—specifically sexual abuse and physical neglect—connectivity between amygdala and posterior cingulate/precuneus was decreased [90]. These results are similar to previous studies that used a face recognition task and found decreased connectivity in response to fearful faces [91].

10.5.1.3 Findings from Studies on Cortical Thickness

There is some evidence that gray matter density is correlated with childhood trauma in patients with psychosis. Sheffield and colleagues [92] found that overall gray matter differed between psychotic patients with and without a history of trauma, and healthy participants. More specifically, they found that individuals with a history of sexual abuse and a diagnosis of psychosis differed from healthy controls in medial and inferior frontal, inferior and superior temporal, precentral gyri and inferior parietal lobe grey matter density. Yet, psychosis patients without sexual abuse only differed from healthy controls in cerebellar gray matter volume. Furthermore, within the psychosis patients group, those with and without a history of sexual abuse differed in gray matter volume in bilateral anterior cingulate cortices and left inferior frontal gyrus only [92]. In another study, authors reported anterior cingulate volumetric differences (compared to healthy controls) in patients with schizophrenia and antisocial personality disorder after controlling for childhood abuse [93]. Moreover, at least three studies demonstrated that prefrontal cortical deficits can be observed in victims of childhood trauma without mental health problems, too [94–96]. This fits well with cognitive models that propose that childhood trauma is associated with cognitive impairments in those with a psychotic disorder, suggesting that neurocognitive alterations mediate the

development of psychosis following trauma exposure [39, 73, 97]. However, in a large prospective cohort study using the Dunedin dataset (Dunedin Multidisciplinary Health and Development Study, a longitudinal study that started in 1972), Danese and colleagues found that whereas those exposed to victimization had indeed impaired cognitive functions (including general intelligence, executive function, processing speed, memory, perceptual reasoning, and verbal comprehension), these deficits were explained by preexisting cognitive deficits prior to the victimization event(s) [98].

These studies underscore the effect of childhood trauma on brain development and also raise caution when trying to unravel the neurobiological correlates of psychopathology, as some may be specific to the disorder itself, and others may represent alterations associated with exposure to childhood trauma, or may even predate the exposure to trauma [68, 92].

10.5.2 The Stress Response System

One of the most commonly proposed idea is that childhood trauma increases the probability for later psychosis through its impact on the stress response system, which is in growing children, still under development. Early traumatic experiences may cause heightened sensitivity of the HPA-axis to subsequent stress, which eventually could increase the risk for psychosis (and related mental disorders) [99, 100]. Similar results were reported for the association between childhood trauma and subclinical psychotic experiences in a general population sample, through a pathway of heightened subjective stress appraisal [101].

At the behavioral level, studies found that individuals with a history of trauma reacted more strongly, with more negative affect, and more paranoia, to minor daily life stressors [82, 102, 103]. In an experimental study, Valmaggia and colleagues used virtual reality and reported stronger paranoid ideation to a neutral social environment in people at ultra-high risk for psychosis, and a history of bullying [104]. In agreement with these results, another virtual reality study indicated heightened social stress reactivity as a possible link between childhood trauma, psychosis liability, and paranoid ideation. Those with a trauma history were found to report more paranoid ideation and subjective distress, compared to individuals without such experiences [105].

In addition, there is a growing body of literature that links exposure to childhood adversities, and psychosis, to hyper-activation and sensitization of the HPA axis [67, 71, 100]. HPA-axis activity is often measured by examining salivary cortisol levels. There is some evidence for both elevated baseline cortisol secretion and blunted cortisol awakening response in patients with psychosis, including those with childhood trauma [106–109]. Others found that the pituitary gland was enlarged in those with a psychotic disorder [110, 111]. This fits in well with the "*traumagenic neurodevelopmental model*" which assumes that HPA-axis dysregulation may mediate the relationship between childhood trauma and the development of psychosis [97, 112]. However, there is also some evidence that stressful events reduce HPA-axis

activation [113, 114] and that pituitary gland volume in children at risk for psychosis due to adversity is reduced [115]. Irrespective of these discrepancies, there seems to be a correlation between elevated dopaminergic brain response associated with psychosis and salivary cortisol, although the direction is still to be determined [108, 116]. It could be that cortisol exerts its influence on the expression of symptoms through its effects on dopaminergic pathways ("bottom-up" model). It is also plausible that underlying symptoms and corresponding neurotransmitter activity affect HPA-axis activity ("top-down" model) [117].

Childhood trauma may increase the risk for psychosis by affecting the mesolimbic dopamine system through a mechanism of exaggerated dopamine release to subsequent social stressors later in life [99, 118]. There may be a feedback loop at play: prolonged stress, including adversity, may increase glucocorticoid release, which in turn may increase dopamine secretion. This may start a positive feedback loop through which the increased dopaminergic activity elevates HPA activity and glucocorticoid release. Since it has previously been shown that dopaminergic hyperreactivity plays a role in psychosis, this may be a mechanism through which childhood trauma increases the risk for the subsequent development of psychotic symptoms [67]. Yet, most evidence that dopamine release is elevated following exposure to stress still comes mainly from animal models [119], but studies are beginning to emerge which provide some evidence in humans as well [97, 107, 117].

10.5.3 Immune System

There is accumulating evidence that alterations in the innate immune system are associated with psychotic disorders, and that childhood traumatic events are associated with a pro-inflammatory state in adulthood. These alterations include increased chemokines (e.g., CCL-11), acute-phase proteins (e.g., C-reactive protein [CRP]), and cytokines [120]. Some cytokines are pro-inflammatory, such as interleukin IL-6, IL-8, and tumor necrosis factor (TNF-α). Consequently, there are cytokines with a dampening effect as to keep a right balance [121]. A recent meta-analysis reported an association between childhood trauma and inflammatory markers. The biggest effect was found for TNF-α, followed by IL-6 and C-reactive protein [122]. Interestingly, Dennison and colleagues found that increased levels of pro-inflammatory markers were found only in patients with schizophrenia who also had a history of childhood trauma, as compared to patients without [123]. In another study, elevated CRP levels were shown in first-episode psychosis patients with a trauma history, but not in patients without a trauma, or healthy controls [124]. Yet, another study found the same group differences for elevated TNF-α levels [125]. These results have led to speculations that early childhood adversities "*bring about epigenetic changes that lead to a pro-inflammatory phenotype in adulthood*," which has been associated with a range of mental and physical health issues, including psychosis [123]. While this sounds like a plausible interpretation, there is still little direct evidence, to date, supporting this hypothesis.

Interestingly, the association between HPA-axis (dys-)functioning and childhood trauma on the one hand, and the association between childhood trauma and the immune system on the other, has led to the exploration of interactive pathways [126]. It was found that receptors for one or more of the stress hormones are expressed on lymphocytes. Moreover, lymphocytes are also able to synthesize the adrenocorticotropic hormone (ACTH), which is secreted by the pituitary gland and is important in the regulation of the stress response system [127]. While much is still unknown, it may indeed be the case that early life stress is a neurodevelopmental insult on multiple, interacting systems [42, 68].

10.6 Psychological Mechanisms Linking Trauma and Psychosis

In addition to alterations at the biological level, it is likely that the exposure to severe traumatic events in childhood impact on one's psychological development, and that psychological factors may co-determine a person's vulnerability, or resilience, to these events. A number of possible psychological mechanisms linking exposure to psychopathological outcomes have been proposed, including dysfunctional cognitive schemas, affective dysregulation, insecure attachment styles, and dissociative mechanisms.

Cognitive models propose that negative beliefs about the self and others, and increased threat anticipation may mediate the association between childhood trauma and psychosis [128–130]. The *social defeat theory* postulates that it is not the experience of adversity itself, but the enduring feeling of defeat and the subordinate position experienced during adverse events that increase the risk for psychosis. Such feelings may stem from childhood trauma [131–133]. Animal studies report that long-term isolation can lead to reductions in whole-brain volume, hippocampus, or medial prefrontal cortex, and that social defeat can reduce neurogenesis [131]. However, Selten and colleagues note that to date, there are no studies that have examined possible brain changes in humans at psychosis onset in relation to proxy measures of social defeat (for a review see [131]). Preliminary support for the social defeat theory was found by a number of behavioral studies that showed that perceptions of defeat and entrapment were associated with positive symptoms in a clinical group of patients with schizophrenia [134–136]. Results from the NEMESIS-2 study (Netherlands Mental Health Survey and Incidence Study) indicate that self-reported feelings of social defeat may act as a mediator between childhood trauma and the expression of psychosis. This was found for individuals with a psychotic disorder, and also for psychotic experiences in the general population [137]. A virtual reality study found that those at ultra-high risk for psychosis had higher levels of social defeat and entrapment, and were more likely to react with paranoid appraisals to the virtual reality environment than their healthy counterparts [138]. However, there is some debate on the conceptualization of social defeat. The theory is built on observations in animals, in which animals are attacked by others and may actually die from this attack, even if they show subordinate behavior. This

type of "subordination" is likely to be different compared to the subordinate position caused by social exclusion that humans can experience. Other concepts used in the context of social defeat studies in humans are discrimination, negative social evaluation, social adversity, social fragmentation, or social disadvantage [131], which is why the term "social defeat" in relation to human studies has previously been indicated as a "misnomer" (i.e., an inaccurate name or designation) [8]. Karlsen and colleagues looked at the association between (racial) discrimination and psychosis and found it to be strongest for discrimination involving physical assault. It has been proposed that not defeat itself, but hostility, threat, and violence in the context of social disadvantage and discrimination might explain the high rates of psychosis in migrants and minority groups [139].

Some researchers have also pointed to the possible relevance of attachment. Attachment styles are thought to reflect early cognitive-affective representations of the self and others, as well as strategies for regulating distress [140]. Children are dependent on their caregivers and adults around them to keep them safe. In his *attachment theory*, Bowlby [141] proposed that infants internalize experiences of interaction with their caregivers, and that this representation is carried forward into adulthood. Early trauma can affect a child's attachment, which can consequently influence expectations and believes about the self and others in interpersonal interactions later in life [141, 142]. There is some evidence that an insecure attachment style (see Fig. 10.3) might act as mediator between childhood trauma and psychotic experiences in clinical samples and the general population [143–145]. On the other hand, an insecure avoidant attachment style mediated the association between neglect and paranoia in data from the US National Comorbidity Survey [146]. Overall, it looks like that an anxious and avoidant attachment style might mediate the relationship between childhood trauma and positive symptoms of psychosis [144–149]. Interestingly, this association was not found for negative symptoms [42].

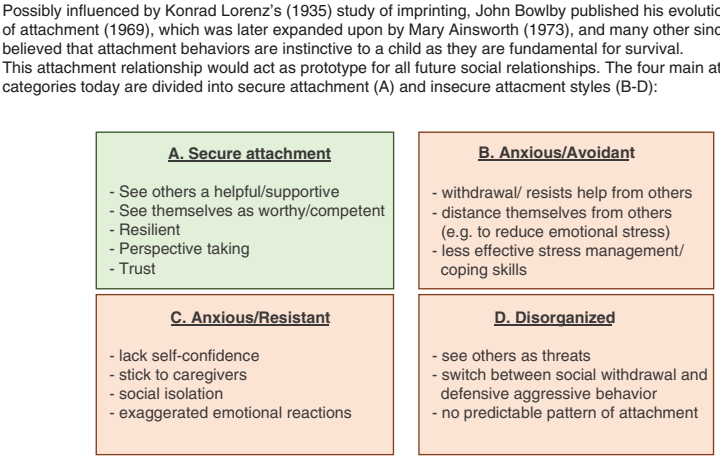

Fig. 10.3 Attachment styles

Finally, it may be that a dissociative response to childhood trauma paves the way to psychosis. Dissociation can be defined as "*a disruption in the usually integrated functions of consciousness, memory, identity or perception of the environment*" [112, 150]. Research showed that individuals who apply a dissociative coping style following trauma are more likely to have impaired reality testing and may develop subsequent psychotic experiences [151]. In a clinical sample of psychotic patients, it was shown that those with a positive history of trauma had increased dissociative tendencies compared to patients without a trauma history [152, 153]. Moreover, it was found that the risk for psychosis through a history of physical neglect could be explained by increased dissociation in patients with psychosis [154]. Lastly, both in nonclinical and clinical groups, the association between childhood trauma and hallucination proneness was mediated by dissociative tendencies [23, 153].

10.7 Specificity of the Association Between Types of Trauma and Distinct Psychotic Symptoms

When moving away from broad diagnostic categories to a symptom-specific level, there is a discussion in the literature whether there are associations between specific forms of childhood trauma and specific symptoms of psychosis (e.g., 154). It has, for example, been proposed that different forms of adversities may exert differential influences upon affective and cognitive processes [6, 23, 155]. However, empirical findings have provided mixed support for this hypothesis. A number of studies found an association between sexual abuse and hallucinations and delusions in that the content may be related to patients' past traumatic experiences [10, 16]. Other studies found emotional abuse and neglect to be most strongly associated with dissociative symptoms [152, 156–158]. Another study, however, found sexual abuse to be most strongly associated with dissociative symptoms [159], while other studies found no evidence for specificity at all [160, 161]. Previous work had some statistical limitations in that they merely relied on the presence or absence of a statistically significant associations between a given form of adversity and a specific symptom of psychosis, but did not formally test whether this association was significantly stronger than the association with another form of adversity, or another specific symptom. Van Nierop and colleagues formally tested specific associations and showed that no form of trauma had a statistically stronger association than the other with specific symptoms [162]. Only experiences with an intention to harm were more strongly associated with psychosis compared to experiences without such component. Authors concluded that, besides the presence of "intention to harm," no other "specificity" exists [162]. In agreement with this finding, a study that looked at children's risk of reporting psychotic symptoms found that the outcome was similar when the perpetrator was an adult or a peer, as long as there was an intention to harm (in agreement with the social defeat hypothesis) [132]. This suggests that the only specific predictor is an element of threat intentionally induced by others [162].

Moreover, it was found that about 45% of the general population's attributable risk for childhood onset psychiatric disorders is accounted for by early maltreatment [163]. As convincingly outlined in this handbook, individuals with a history of early adverse experiences do not only have a higher risk for psychosis, but also show a higher prevalence of a number of disorders, including depression, anxiety, substance abuse, eating disorders, suicidal symptomatology, personality disorder, dissociative disorders, and posttraumatic stress disorder [4, 164–168]. Thus, childhood trauma seems to be characterized by an admixture of affective, anxious, and psychotic symptoms [17, 169, 170]. Investigating symptoms across these different, but related disorders (i.e., internalizing, externalizing, thought disorders) led to suggest that maltreatment was associated with greater "general psychopathology" (i.e., p-factor), but not with any specific endophenotype (i.e., measurable biomarkers that are correlated with a disorder, partly because of a shared genetic disposition) [171].

10.8 Treatment Considerations for Patients with a Trauma History

A history of childhood trauma is associated with a greater risk for psychiatric disorders, more comorbidity, worse social functioning, lower remission rates, and less favorable treatment outcomes in general [168, 169, 172–175]. There is some evidence, albeit limited, that greater (supportive) networks act as protective factors, but that social skills in those with trauma and/or psychosis are impaired, which may reduce the likelihood of having such networks [33, 176]. Therefore, social skills, as well as underlying mechanisms related to childhood trauma, such as stress sensitivity and cognitive biases, may be viable targets for psychotherapeutic interventions. Research on possible therapeutic outcomes in clinical groups converges to the necessity of distinguishing between patients with and without a history of childhood trauma [42]. It is not surprising, then, that treatments based on cognitive-behavioral therapy and exposure therapy, and focusing on reducing sensitivity to stress, readjusting cognitive biases, teaching social skills, psychoeducation, stabilization, and development of safe coping skills may be effective for those with a trauma history [177–179].

10.9 Conclusion

In this chapter, we have reviewed a body of research on the association between childhood traumatic experiences and psychoses. Evidence suggests that, at least in some people, exposure to childhood trauma with the intention to harm contributes to the onset of psychotic experiences and psychotic disorders. There is, however, also evidence suggesting that underlying traits, such as genetic predisposition, lower cognitive and social skills, may increase the risk for exposure to adversity. Whereas childhood trauma may be neither sufficient nor necessary to explain the onset of psychosis, at least part of that association seems to be causal. Nevertheless,

it is important to note that this relationship is not restricted to psychosis only, but holds for a whole myriad of psychiatric disorders. Yet, findings that neurobiological changes can also be observed in individuals with a history of maltreatment, but no psychiatric disorder is perplexing. It may be that there are certain alterations that early life stress brings about, and also that there are compensatory mechanisms in resilient individuals, which enables them to balance out such neurodevelopmental insults [68, 92–96]. To make things more complex, the different pathways from childhood trauma to psychosis discussed in this chapter may act at different and complementary conceptual levels of examination (i.e., neurobiological, psychological), which, when taken together, might converge into an integrated model of psychosis [155, 180, 181].

References

1. Boevink WA. From being a disorder to dealing with life: an experiential exploration of the association between trauma and psychosis. Schizophr Bull. 2006;32(1):17–9.
2. Linscott RJ, Van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med. 2013;43(6):1133–49.
3. Fisher HL, Caspi A, Poulton A, Meier MH, Houts R, Harrington H, et al. Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. Psychol Med. 2013;6(8):2077–86.
4. Bendall S, Jackson HJ, Hulbert CA, McGorry PD. Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. Schizophr Bull. 2008;34(3):568–79.
5. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the Risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull. 2012;38(4):661–71.
6. Heins M, Simons C, Lataster T, Pfeifer S, Versmissen D, Lardinois M, et al. Childhood trauma and psychosis: a case-control and case-sibling comparison across different levels of genetic liability, psychopathology, and type of trauma. Am J Psychiatry. 2011;168(12):1286–94.
7. Kelleher I, Keeley H, Corcoran P, Ramsay H, Wasserman C, Carli V, et al. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. Am J Psychiatry. 2013;170(7):734–41.
8. Morgan C, Gayer-Anderson C. Childhood adversities and psychosis: evidence, challenges, implications. World Psychiatry. 2016;6:93–102.
9. Rössler W, Hengartner MP, Ajdacic-Gross V, Haker H, Angst J. Impact of childhood adversity on the onset and course of subclinical psychosis symptoms—results from a 30-year prospective community study. Schizophr Res. 2014;153(1–3):189–95. https://doi.org/10.1016/j.schres.2014.01.040.
10. Shevlin M, Murphy J, Read J, Mallett J, Adamson G, Houston JE. Childhood adversity and hallucinations: a community-based study using the National Comorbidity Survey Replication. Soc Psychiatry Psychiatr Epidemiol. 2011;46:1203–10.
11. Wicks S, Sc B, Hjern A, Ph D, Gunnell D, Lewis G, et al. Social adversity in childhood and the Risk of developing psychosis: a National Cohort Study. Am J Psychiatry. 2005;(September):1652–7.
12. Addington J, Stowkowy J, Cadenhead KS, Cornblatt BA, Mcglashan TH, Perkins DO, et al. Early traumatic experiences in those at Clinica high Risk for psychosis. Early Interv Psychiatry. 2013;7(3):300–5.

13. Holshausen K, Bowie CR, Harkness KL, Holshausen K, Bowie CR, Harkness KL, et al. The relation of childhood maltreatment to psychotic symptoms in adolescents and young adults with depression the relation of childhood maltreatment to psychotic symptoms in adolescents and young adults with depression. 2016;4416
14. Paksarian D, Eaton WW, Mortensen PB, Merikangas KR, Pedersen CB. A population-based study of the risk of schizophrenia and bipolar disorder associated with parent – child separation during development. 2015;2018:2825–37.
15. Shevlin M, Mcanee G, Bentall RP, Murphy J. Specificity of association between adversities and the occurrence and co-occurrence paranoia and hallucinations : evaluating the stability of childhood risk in an adverse adult environment. Psychosis [internet]. Routledge. 2015;7(3):206–16. https://doi.org/10.1080/17522439.2014.980308.
16. Thompson A, Nelson B, Mcnab C, Simmons M, Leicester S, Mcgorry PD, et al. Psychotic symptoms with sexual content in the " ultra high risk " for psychosis population : frequency and association with sexual trauma. Psychiatry Res. 2010;177(1–2):84–91. https://doi.org/10.1016/j.psychres.2010.02.011.
17. van Nierop M, Viechtbauer W, Gunther N, van Zelst C, de Graaf R, ten Have M, et al. Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. Psychol Med. 2015;45(06):1277–88.
18. Wolke D, Lereya ST, Fisher HL, Lewis G, Zammit S. Bullying in elementary school and psychotic experiences at 18 years : a longitudinal , population-based cohort study. Psychol Med. 2014;44:2199–211.
19. Alemany S, Goldberg X, van Winkel R, Gastó C, Peralta V, Fañanás L. Childhood adversity and psychosis: examining whether the association is due to genetic confounding using a monozygotic twin differences approach. Eur Psychiatry. 2013;28(4):207–12.
20. Alemany S, Ayesa-Arriola R, Arias B, Fatjó-Vilas M, Ibáñez MI, Ortet G, et al. Childhood abuse in the etiological continuum underlying psychosis from first-episode psychosis to psychotic experiences. Eur Psychiatry. 2015;30(1):38–42.
21. Barrigon ML, DIas FJ, Gurpegui M, Ferrin M, SM D, Moreno-Granados J, et al. Childhood trauma as a risk factor for psychosis : a sib-pair study. J Psychiatr Res. 2015;70:130–6.
22. Bartels-Velthuis AA, Van De Willige G, Jenner JA, Wiersma D, Van Os J. Auditory hallucinations in childhood: associations with adversity and delusional ideation. Psychol Med. 2012;42(3):583–93.
23. Bentall RP, Wickham S, Shevlin M, Varese F. Do specific early-life adversities lead to specific symptoms of psychosis? A study from the 2007 the adult psychiatric morbidity survey. Schizophr Bull. 2012;38(4):734–40.
24. Bratlien U, Øie M, Haug E, Møller P, Andreassen OA, Lien L, et al. Environmental factors during adolescence associated with later development of psychotic disorders - a nested case-control study. Psychiatry Res. 2014;215(3):579–85. https://doi.org/10.1016/j.psychres.2013.12.048.
25. Daalman K, Diederen KMJ, Derks EM, Van Lutterveld R, Kahn RS, Sommer IEC. Childhood trauma and auditory verbal hallucinations. Psychol Med. 2012;42(12):2475–84.
26. DeRosse P, Nitzburg GC, Kompancaril B, Malhotra AK. The relation between childhood maltreatment and psychosis in patients with schizophrenia and non-psychiatric controls Pamela. Schizophr Res. 2014;155:66–71.
27. Arseneault L, Cannon M, Fisher HL, Guilherme D, Polanczyk G, Moffit TE, et al. Childhood trauma and Children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study Louise. Magn Reson Imaging. 2011;31(3):477–9.
28. Van Winkel R, Van Nierop M, Myin-Germeys I, Van Os J. Childhood trauma as a cause of psychosis: linking genes, psychology, and biology. Can J Psychiatr. 2013;58(1):44–51.
29. Lecei A, Decoster J, Hert M, De Derom C, Jacobs N, Menne-lothmann C, et al. Evidence that the association of childhood trauma with psychosis and related psychopathology is not explained by gene-environment correlation : a monozygotic twin differences approach. Schizophr Res. 2018; https://doi.org/10.1016/j.schres.2018.05.025.

30. Cutajar MC, Mullen PE, Ogloff JRP, Thomas SD, Wells DL, Spataro J. Schizophrenia and other psychotic disorders in a cohort of sexually abused children. Arch Gen Psychiatry. 2010;67(11):1114–9.
31. Schaefer JD, Moffitt TE, Arseneault L, Danese A, Fisher HL, Houts R, et al. Adolescent victimization and early-adult psychopathology: approaching causal inference using a longitudinal twin study to rule out noncausal explanations. Clin Psychol Sci. 2017;6(3):352–71.
32. Danese A, Moffitt TE, Arseneault L, Ben A, Dinardo PB, Gandelman SB, et al. The origins of cognitive deficits in victimized children: implications for neuroscientists and clinicians. Am J Psychiatry. 2018;174(4):349–61.
33. Velthorst E, Ph D, Fett AJ, Ph D, Reichenberg A, Ph D, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. Soc Funct psychotic Disord. 2017;(November):1075–85.
34. Velthorst E, Fett AKJ, Reichenberg A, Perlman G, Van Os J, Bromet EJ, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. Am J Psychiatry. 2017;174(11):1075–85.
35. Trotta A, Di Forti M, Iyegbe C, Green P, Dazzan P, Mondelli V, et al. Familial risk and childhood adversity interplay in the onset of psychosis. Bi Psych Open. 2015:6–13.
36. Trotta A, Iyegbe C, Di Forti M, Sham PC, Campbell DD, Cherny SS, et al. Interplay between schizophrenia polygenic risk score and childhood adversity in first-presentation psychotic disorder: a pilot study. PLoS One. 2016;11(9):1–14.
37. Collip D, Myin-germeys I, Wichers M, Jacobs N, Derom C, Thiery E, et al. FKBP5 as a possible moderator of the psychosis-inducing effects of childhood trauma. 2013;261–268.
38. Green MJ, Chia T, Cairns MJ, Wu J, Tooney PA, Scott RJ, et al. Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. J Psychiatr Res. 2014;49:43–50. https://doi.org/10.1016/j.jpsychires.2013.10.018.
39. Mondelli V, Cattaneo A, Murri MB, Papadopoulos AS, Aitchison KJ. Stress and inflammation reduce BDNF expression in first- episode psychosis : a pathway to smaller hippocampal volume. J Clin Psychiatry. 2011;72(12):1677–84.
40. Ramsay H, Kelleher I, Flannery P, Clarke MC, Lynch F, Harley M, et al. Relationship between the COMT-Val158Met and BDNF- Val66Met polymorphisms, childhood trauma and psychotic experiences in an adolescent general population sample. 2013;8(11):1–10.
41. Lewis CM, Vassos E. Prospects for using risk scores in polygenic medicine. Genome Med. 2017:9–11.
42. Misiak B, Krefft M, Bielawski T, Ahmed AM, Sasiadek MM, Frydecka D. Toward a unified theory of childhood trauma and psychosis: a comprehensive review of epidemiological , clinical , neuropsychological and biological findings. Neurosci Biobehav Rev. 2017;75:393–406.
43. Van Os J, Kenis G, BPF R. The environment and schizophrenia. Nature. 2010;468(7321):203–12. https://doi.org/10.1038/nature09563.
44. Van Winkel R. Aetiological stratification as a conceptual framework for gene-by-environment interaction research in psychiatry. Epidemiol Psychiatr Sci. 2010;616(2015):6–11.
45. Pfeifer S, Krabbendam L, Germeys IM, Wichers M, Jacobs N, Thiery EW, et al. A cognitive intermediate phenotype study confirming possible gene – early adversity interaction in psychosis outcome: a general population twin study. 2010;2439
46. Aas M, Djurovic S, Athanasiu L, Steen NE, Agartz I, Lorentzen S, et al. Serotonin transporter gene polymorphism, childhood trauma, and cognition in patients with psychotic disorders. Schizophr Bull. 2012;38(1):15–22.
47. De Castro-catala M, Van Nierop M, Barrantes-vidal N, Sheinbaum T, Kwapil TR, Pe E, et al. Childhood trauma, BDNF Val66Met and subclinical psychotic experiences. Attempt at replication in two independent samples. 2016;83:121–9.
48. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt RE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. 2010;167(10):509–27.

49. Mueller A, Brocke B, Fries E, Lesch KP, Kirschbaum C. The role of the serotonin transporter polymorphism for the endocrine stress response in newborns. Psychoneuroendocrinology. 2010;35(2):289–96.
50. Lupien SJ. The effects of stress and stress hormones on human cognition : implications for the field of brain and cognition. 2007;65:209–37.
51. Alemany S, Arias B, Aguilera M, Villa H, Moya J, Ibáñez MI, et al. Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. Br J Psychiatry. 2011;199(1):38–42.
52. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003;112:257–69.
53. Alemany S, Moya J, Ibanez MI, Villa H, Mezqita L, Ortet G, et al. Research letter: childhood trauma and the rs1360780 SNP of FKBP5 gene in psychosis: a replication in two general population samples. 2016, 2016;46:221–3.
54. Rutten BPF, Mill J. Epigenetic mediation of environmental influences in major psychotic disorders. Schizophr Bull. 2009;35(6):1045–56.
55. Szyf M, Bick J. DNA methylation: a mechanism for embedding early life experiences in the genome. Child Dev. 2013;84(1):49–57.
56. Weaver ICG, Cervoni N, Champagne FA, Alessio ACD, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. 2004;7(8):847–54.
57. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009;12(3):342–8.
58. Misiak B, Szmida E, Karpiński P, Loska O, Sąsiadek MM, Frydecka D. Lower LINE-1 methylation in first-episode schizophrenia patients with the history of childhood trauma. Epigenomics. 2015;7(8):1275–85. https://doi.org/10.2217/epi.15.68.
59. Marzi SJ, Ph D, Sugden K, Ph D, Arseneault L, Ph D, et al. Analysis of DNA methylation in Young people: limited evidence for an association between victimization stress and epigenetic variation in blood. Am J Psychiatry. 2018;175(13):1–13.
60. Hannon E, Knox O, Sugden K, Burrage J, Wong CCY, Belsky W, et al. Characterizing genetic and environmental influences on variable DNA methylation using monozygotic and dizygotic twins. 2018;1–27.
61. Van Winkel R, Esquivel G, Kenis G, Wichers M, Collip D, Peerbooms O, et al. Genome-wide findings in schizophrenia and the role of gene – environment interplay. 2010;16:185–92.
62. Bebbington P. Misery and beyond: the pursuit of disease theories of depression. 1987;13–20.
63. van der Kolk B, Greenberg MS. The psychobiology of the trauma response: hyperarousal, constriction, and addiction to traumatic reexposure. Psychological trauma. Washington, DC: American Psychiatry Press; 1987. p. 63–87.
64. Teicher MH, Samson JA, Polcari A, McGreenery CE. Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. Am J Psychiatry. 2006;163(11):993–1000.
65. Teicher MH, Parigger A. The 'maltreatment and abuse chronology of exposure' (MACE) scale for the retrospective assessment of abuse and neglect during development. PLoS One. 2015:1–37.
66. Teicher MH, Vitaliano GD. Witnessing violence toward siblings: an understudied but potent form of early adversity. PLoS One. 2011;6(12).
67. Ruby E, Polito S, McMahon K, Gorovitz M, Corcoran C, Malaspina D. Pathways associating childhood trauma to the neurobiology of schizophrenia. Front Psychol Behav Sci. 2014;3(1):1–23.
68. Teicher MH, Samson JA. Annual research review : enduring neurobiological effects of childhood abuse and neglect. J Child Psychol Psychiatry. 2016;3:241–66.
69. Uematsu A, Matsui M, Tanaka C, Takahashi T, Noguchi K, Suzuki M, et al. Developmental trajectories of amygdala and Hippocampus from infancy to early adulthood in healthy individuals. PLoS One. 2012;7(10)

70. Adriano F, Caltagirone C, Spalletta G. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. Prog Clin Neurosci. 2012;18(2):180–200.
71. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev. 2003;27:33–44.
72. Tamminga CA, Stan AD, Wagner AD. The hippocampal formation in schizophrenia. Am J Psychiatry. 2010;10(167):1178–93.
73. Aas M, Dazzan P, Fisher HL, Morgan C, Morgan K, Reichenberg A, et al. Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. Schizophr Res. 2011;129(1):12–9. https://doi.org/10.1016/j.schres.2011.03.017.
74. Shannon C, Douse K, Mccusker C, Feeney L, Barrett S. The association between childhood trauma and memory functioning in schizophrenia. 2011;37(3):531–7.
75. Scott D, Tamminga CA. Effects of genetic and environmental risk for schizophrenia on hippocampal activity and psychosis-like behavior in mice. Behav Brain Res. 2018;339(October 2017):114–23. https://doi.org/10.1016/j.bbr.2017.10.039.
76. Li W, Ghose S, Gleason K, Begovic A, Perez MS. Bartko J, et al, Synaptic proteins in schizophrenia hippocampus indicate increased neuronal activity in CA3. 2015;172(4):373–82.
77. Moser EI, Kropff E, Moser M. Place cells, grid cells, and the brain' s spatial representation system. 2008.
78. Geuze E, Vermetten E, Bremner JD. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Mol Psychiatry. 2005;10(2):160–84.
79. Derntl B, Habel U, Windischberger C, Robinson S, Kryspin-Exner I, Gur RC, et al. General and specific responsiveness of the amygdala during explicit emotion recognition in females and males. BMC Neurosci. 2009;10:1–14.
80. Zheng J, Anderson KL, Leal SL, Shestyuk A, Gulsen G, Mnatsakanyan L, et al. Amygdala-hippocampal dynamics during salient information processing. Nat Commun. 2017;8:1–11. https://doi.org/10.1038/ncomms14413.
81. Isvoranu A-M, Van Borkulo CD, Boyette L-L, Wigman JTW, Vinkers CH, Borsboom D, et al. A network approach to psychosis : pathways between childhood trauma and psychotic symptoms. Schizophr Bull. 2017;43(1):187–96.
82. Lardinois M, Lataster T, Mengelers R, Van Os J, Myin-Germeys I. Childhood trauma and increased stress sensitivity in psychosis. Acta Psychiatr Scand. 2011;123(1):28–35.
83. Lataster J, Myin-Germeys I, Lieb R, Wittchen HU, van Os J. Adversity and psychosis: a 10-year prospective study investigating synergism between early and recent adversity in psychosis. Acta Psychiatr Scand. 2012;125(5):388–99.
84. Aas M, Navari S, Gibbs A, Mondelli V, Fisher HL, Morgan C, et al. Is there a link between childhood trauma, cognition, and amygdala and hippocampus volume in first-episode psychosis? Schizophr Res. 2012;137(1–3):73–9. https://doi.org/10.1016/j.schres.2012.01.035.
85. Hoy K, Barrett S, Shannon C, Campbell C, Watson D, Rushe T, et al. Childhood trauma and hippocampal and amygdalar volumes in first-episode psychosis. Schizophr Bull. 2012;38(6):1162–9.
86. Suslow T, Lindner C, Dannlowski U, Walhöfer K, Rödiger M, Maisch B, et al. Automatic amygdala response to facial expression in schizophrenia : initial hyperresponsivity followed by hyporesponsivity. BMC Neurosci. 2013;14(140)
87. Mitra R, Jadhav S, McEwen BS, Vyas A, Chattarji S. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci. 2005;102(26):9371–6. https://doi.org/10.1073/pnas.0504011102.
88. Vyas A, Jadhav S, Chattarji S. Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. 2006;143:387–93.
89. Anticevic A, Van Snellenberg JX, Cohen RE, Repovs G, Dowd EC, Barch DM. Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. Schizophr Bull. 2010;38(3):608–21.
90. Cancel A, Comte M, Boutet C, Schneider FC, Rousseau P, Boukezzi S, et al. Childhood trauma and emotional processing circuits in schizophrenia : a functional connectivity study. Schizophr Res. 2017;184:69–72. https://doi.org/10.1016/j.schres.2016.12.003.

91. Mukherjee P, Sabharwal A, Kotov R, Szekely A, Parsey R, Barch DM, et al. Disconnection between amygdala and medial prefrontal cortex in psychotic disorders. Schizophr Bull. 2016;42(4):1056–67.
92. Sheffield JM, Williams LE, Woodwads ND, Heckers S. Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. Schizophr Res. 2013;143(1):185–91.
93. Kumari V, Uddin S, Premkumar P, Young S, Gudjonsson GH, Raghuvanshi S, et al. Lower anterior cingulate volume in seriously violent men with antisocial personality disorder or schizophrenia and a history of childhood abuse. Aust N Z J Psychiatry. 2014;48(2):153–61.
94. Carballedo A, Lisiecka D, Fagan A, Saleh K, Ferguson Y, Connolly G, et al. Early life adversity is associated with brain changes in subjects at family risk for depression. World J Biol Psychiatry. 2012;13(8):569–78.
95. Edmiston EE, Wang F, Mazure CM, Guiney J, Sinha R, Mayes LC, et al. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Arch Pediatr Adolesc Med. 2011;165(12):1069–77.
96. Gerritsen L, Tendolkar I, Franke B, Vasquez AA, Kooijman S, Buitelaar J, et al. BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. Mol Psychiatry. 2012;17(6):597–603.
97. Read J, Fosse R, Moskowitz A, Perry B. The traumagenic neurodevelopmental model of psychosis revisited. Neuropsychiatry. 2014;4(1):65–79.
98. Danese A, Baldwin JR. Hidden wounds? Inflammatory links between childhood trauma and psychopathology. Annu Rev Psychol. 2017;68:517–44.
99. Collip D, Myin-Germeys I, Van Os J. Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? Schizophr Bull. 2008;34(2):220–5.
100. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49(12):1023–39.
101. Rössler W, Ajdacic-Gross V, Rodgers S, Haker H, Müller M. Childhood trauma as a risk factor for the onset of subclinical psychotic experiences: exploring the mediating effect of stress sensitivity in a cross-sectional epidemiological community study. Schizophr Res. 2016;172(1–3):46–53. https://doi.org/10.1016/j.schres.2016.02.006.
102. Collip D, Oorschot M, Thewissen V, Van Os J, Bentall R, Myin-Germeys I. Social world interactions: how company connects to paranoia. Psychol Med. 2011;41(5):911–21.
103. Reininghaus U, Kempton MJ, Valmaggia L, Craig TKJ, Garety P, Onyejiaka A, et al. Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. Schizophr Bull. 2016;42(3):712–22.
104. Valmaggia LR, Day FL, Kroll J, Laing J, Byrne M, Fusar-poli P, et al. Bullying victimisation and paranoid ideation in people at ultra high risk for psychosis. Schizophr Res. 2015;168(1–2):68–73. https://doi.org/10.1016/j.schres.2015.08.029.
105. Veling W, Counotte J, Pot-Kolder R, Van Os J, Van Der Gaag M. Childhood trauma, psychosis liability and social stress reactivity: a virtual reality study. Psychol Med. 2016;46(16):3339–48. http://www.ncbi.nlm.nih.gov/pubmed/27619196
106. Gallagher P, Watson S, Smith MS, Young AH, Ferrier IN. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. 2007;90:258–65.
107. Mondelli V, Dazzan P, Hepgul N, Di Forti M, Aas M, D'Albenzio A, et al. Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment. Schizophr Res. 2010;116(2–3):234–42. https://doi.org/10.1016/j.schres.2009.08.013.
108. Pruessner JC, Champagne F, Meaney MJ, Dagher A. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11 C] Raclopride. 2004;24(11):2825–31.

109. Ritsner M, Gibel A, Maayan R, Ratner Y, Ram E, Modai I, et al. State and trait related predictors of serum cortisol to DHEA(S) molar ratios and hormone concentrations in schizophrenia patients. Eur Neuropsychopharmacol. 2007;17(4):257–64.
110. Pariante CM, Dazzan P, Danese A, Morgan KD, Brudaglio F, Morgan C, et al. Increased pituitary volume in antipsychotic-free and antipsychotic-treated patients of the Æsop first-onset psychosis study. Neuropsychopharmacology. 2005;30(10):1923–31.
111. Pariante CM. Pituitary volume in psychosis: the first review of the evidence. J Psychopharmacol. 2008;22(2 Suppl.):76–81.
112. Read J, Mental A, Board H, Connolly J, Zealand N. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. Psychiatry: Interpers Biol Process. 2001;64(4)
113. Mondelli V, Dazzan P, Hepgul N, Di Forti M, Aas M, Albenzio D, et al. Europe PMC funders group abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment. Schizophrenia Res. 2012;116:234–42.
114. Yehunda R. Biology of posttraumatic stress disorder. J Clin Psychiatry. 2001;62(2001):2018.
115. Cullen AE, Day FL, Roberts RE, Pariante CM, Laurens KR. Pituitary gland volume and psychosocial stress among children at elevated risk for schizophrenia. Psychol Med. 2015;45(15):3281–92.
116. Pruessner M, Cullen AE, Aas M, Walker EF. Neuroscience and biobehavioral reviews the neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci Biobehav Rev. 2017;73:191–218. https://doi.org/10.1016/j.neubiorev.2016.12.013.
117. Belvederi Murri M, Pariante CM, Dazzan P, Hepgul N, Papadopoulos AS, Zunszain P, et al. Hypothalamic-pituitary-adrenal axis and clinical symptoms in first-episode psychosis. Psychoneuroendocrinology. 2012;37(5):629–44. https://doi.org/10.1016/j.psyneuen.2011.08.013.
118. Van Winkel R, Stefanis NC, Myin-Germeys I. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. Schizophr Bull. 2008;34(6):1095–105.
119. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci. 2005;7(2):103–23.
120. Strous RD, Shoenfeld Y. Schizophrenia, autoimmunity and immune system dysregulation: a comprehensive model updated and revisited. J Autoimmunity. 2006;27:71–80.
121. Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. J Allergy Clin Immunol. 2010;125(2 Suppl. 2):S53–72. https://doi.org/10.1016/j.jaci.2009.07.008.
122. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry. 2016;21(5):642–9. https://doi.org/10.1038/mp.2015.67.
123. Dennison U, McKernan D, Cryan J, Dinan T. Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype. Psychol Med. 2012;42(9):1865–71.
124. Hepgul N, Pariante CM, Dipasquale S, Diforti M, Taylor H, Marques TR, et al. Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. Psychol Med. 2012;42(9):1893–901.
125. Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, et al. Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav Immun. 2013;31:90–5.
126. Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr Scand. 2014;129(3):180–92.
127. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol. 2002;20(1):125–63.
128. Gracie A, Freeman D, Green S, Garety PA, Kuipers E, Hardy A, et al. The association between traumatic experience, paranoia and hallucinations: a test of the predictions of psychological models. Acta Psychiatr Scand. 2007;116(4):280–9.

129. Morrison AP. A cognitive behavioural perspective on the relationship between childhood trauma and psychosis. Epidemiol Psychiatr Sci. 2009;18(2009):2018.
130. Smith B, Fowler DG, Freeman D, Bebbington P, Bashforth H, Garety P, et al. Emotion and psychosis : links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. 2006;86:181–8.
131. Selten J, Booij J, Buwalda B, Meyer-lindenberg A. Biological mechanisms whereby social exclusion may contribute to the etiology of psychosis: a narrative review. 2017;43(2):287–92.
132. Selten J, Van Der Ven E, Rutten BPF, Cantor-graae E. The social defeat hypothesis of schizophrenia : an update. 2013;39(6):1180–6.
133. Selten J, Cantor-Graae E. Social defeat: risk factor for schizophrenia? Brit J Psychiatry. 2005;1–2.
134. Birchwood M, Gilbert P, Gilbert J, Trower P, Meaden A, Hay J. Interpersonal and role related scheme influence the relationship with the dominant "voice" in schizophrenia: a comparison of three models. Psychol Med. 2004;34(8):1571–80.
135. Birchwood M, Meaden A, Trower P, Gilbert P, Plaistow J. The power and omnipotence of voices: subordination and entrapment by voices and significant others. Psychol Med. 2000;30(2):337–44.
136. Taylor PJ, Gooding PA, Wood AM, Johnson J, Pratt D, Tarrier N. Defeat and entrapment in schizophrenia : the relationship with suicidal ideation and positive psychotic symptoms. Psychiatry Res. 2010;178(2):244–8. https://doi.org/10.1016/j.psychres.2009.10.015.
137. van Nierop M, van Os J, Gunther N, van Zelst C, de Graaf R, ten Have M, et al. Does social defeat mediate the association between childhood trauma and psychosis? Evidence from the NEMESIS-2 study. Acta Psychiatr Scand. 2014;129(6):467–76.
138. Valmaggia LR, Day F, Garety P, Freeman D, Antley A, Slater M, et al. Social defeat predicts paranoid appraisals in people at high risk for psychosis. Schizophr Res. 2015;168(1–2):16–22. https://doi.org/10.1016/j.schres.2015.07.050.
139. Karlsen S, Nazroo JY, McKenzie K, Bhui K, Weich S. Racism, psychosis and common mental disorder among ethnic minority groups in England SAFFRON. Psychol Med. 2005;35:1795–803.
140. Bartholomew K, Horowitz LM. Attachment styles among young adults: a test of four-category model. J Pers Soc Psychol. 1991;40:30–40.
141. Bowlby J. Attachment and loss, vol. II. Separation: anxiety and anger. London: Penguin Books; 1973.
142. Howard JA. Attachment and trauma. In: Distress or deliberately defiant? Managing challenging student behaviour due to trauma and disorganised attachment. Toowong, QLD: Australian Academic Press; 2013.
143. Korver-Nieberg N, Berry K, Meijer CJ, De Haan L. Adult attachment and psychotic phenomenology in clinical and non-clinical samples: a systematic review. Psychol Psychother Theory Res Pract. 2014;87(2):127–54.
144. Sheinbaum T, Bifulco A, Ballespi S, Mitjavila M, Kwapil TR, Barrentes-Vidal N. Interview investigation of insecure attachment styles as mediators between poor childhood care and Schizophrenia—spectrum phenomenology. PLoS One. 2015;1–12.
145. Sheinbaum T, Kwapil TR, Barrantes-vidal N. Fearful attachment mediates the association of childhood trauma with schizotypy and psychotic-like experiences. Psychiatry Res. 2014;220(1–2):691–3. https://doi.org/10.1016/j.psychres.2014.07.030.
146. Sitko K, Bentall RP, Shevlin M, Sullivan NO, Sellwood W. Associations between speci fi c psychotic symptoms and speci fi c childhood adversities are mediated by attachment styles : an analysis of the National Comorbidity Survey. 2014;217:202–9.
147. Van Dam DS, Velthorst E, Meijer CJ, De Haan L, Risk FG. Childhood maltreatment , adult attachment and psychotic symptomatology : a study in patients , siblings and controls. Soc Psychiatry Psychiatr Epidemiol. 2014:1759–67.
148. Goodall K, Rush R, Grünwald L, Darling S, Tiliopoulos N. Attachment as a partial mediator of the relationship between emotional abuse and schizotypy. Psychiatry Res. 2015;230(2):531–6. https://doi.org/10.1016/j.psychres.2015.09.050.

149. Pearce J, Simpson J, Berry K, Bucci S, Moskowitz A, Varese F. Attachment and dissociation as mediators of the link between childhood trauma and psychotic experiences. Clin Psychol Psychother. 2017;24(6):1304–12.
150. Anketell C, Dorahy MJ, Shannon M, Elder R, Hamilton G, Corry M, et al. An exploratory analysis of voice hearing in chronic PTSD: potential associated mechanisms. J Trauma Dissociation. 2010;11(1):93–107.
151. Kilcommons AM, Morrison AP. Relationships between trauma and psychosis: an exploration of cognitive and dissociative factors. Acta Psychiatr Scand. 2005;112(5):351–9.
152. Holowka DW, King S, Saheb D, Pukall M, Brunet A. Childhood abuse and dissociative symptoms in adult schizophrenia. Schizophr Res. 2003;60(1):87–90.
153. Perona-Garcelán S, García-Montes JM, Francisco J, López-Jiménez AM, Ruiz-Veguilla M, Ductor-Recuerda MJ, et al. Relationship between childhood trauma , mindfulness , and dissociation in subjects with and without hallucination proneness relationship between childhood trauma , mindfulness , and dissociation in subjects with. J Trauma Dissociation. 2014;9732
154. Evans GJ, Reid G, Preston P, Palmier-Claus J, Sellwood W. Trauma and psychosis : the mediating role of self-concept clarity and dissociation. Psychiatry Res. 2015;228:626–32.
155. Bentall RP, De Sousa P, Varese F, Wickham S, Sitko K, Haarmans M, et al. From adversity to psychosis: pathways and mechanisms from specific adversities to specific symptoms. Soc Psychiatry Psychiatr Epidemiol. 2014;49(7):1011–22.
156. Schäfer I, Harfst T, Aderhold V, Briken P, Lehmann M, Moritz S, et al. Childhood trauma and dissociation in female patients. J Nerv Ment Dis. 2006;194(2):135–8.
157. Schäfer I, Fisher HL, Aderhold V, Huber B, Hoffmann-Langer L, Golks D, et al. Dissociative symptoms in patients with schizophrenia: relationships with childhood trauma and psychotic symptoms. Compr Psychiatry. 2012;53(4):364–71. https://doi.org/10.1016/j.comppsych.2011.05.010.
158. Vogel M, Spitzer C, Kuwert P, Möller B, Freyberger HJ, Jörgen H. Association of Childhood Neglect with adult dissociation in schizophrenic inpatients. 2009;124–130.
159. Sar V, Taycan O, Bolat N, Oezmen M, Duran A, Ozturk E, et al. Childhood trauma and dissociation in schizophrenia. Psychopathology. 2010;43:33–40.
160. Longden E, Sampson M, Read J. Childhood adversity and psychosis: generalised or specific effects? Epidemiol Psychiatr Sci. 2016;25(4):349–59.
161. Van Nierop M, Lataster T, Smeets F, Gunther N, Van Zelst C, De Graaf R, et al. Psychopathological mechanisms linking childhood traumatic experiences to risk of psychotic symptoms: analysis of a large, representative population-based sample. Schizophr Bull. 2014;40(Suppl. 2):123–30.
162. Van Nierop M, Lataster T, Smeets F, Gunther N, Van Zelst C, De Graaf R, et al. Psychopathological mechanisms linking childhood traumatic experiences to risk of psychotic symptoms: analysis of a large, representative population-based sample. Schizophr Bull. 2014;40(Suppl. 2):123–30.
163. Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, et al. Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) I: associations with first onset of DSM-IV disorders. Arch Genet Psychiatry. 2010;67(2):1–21.
164. Ball JS, Links PS. Borderline personality disorder and childhood trauma: evidence for a causal relationship. 2009.
165. Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E, Pedersen CB. Full Spectrum of psychiatric outcomes among offspring with parental history of Mental disorder, August 2010. Dean et al. 2010;67(8):822–9.
166. Mortensen PB, Pedersen MG, Pedersen CB. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? 2018;(2010):201–210.
167. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med. 2012;9(11)

168. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am J Psychiatry. 2013;170(10):1114–33.
169. Van Nierop M, Bak M, De Graaf R, Ten Have M, Van Dorsselaer S, Van Winkel R, et al. The functional and clinical relevance of childhood trauma-related admixture of affective, anxious and psychosis symptoms. 2016;91–101.
170. Wigman JTW, Van Winkel R, Ormel J, Verhulst FC, van Os J, Vollebergh WAM. Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence. 2012;266–273.
171. Caspi A, Houts RM, Belsky DW, Goldman-mellor SJ. The p factor: one general psychopathology factor in the. Clin Psychol Sci. 2015;2(2):119–37.
172. Álvarez M-J, Roura P, Osés A, Foguet Q, Solà J, Arrufat F-X. Prevalence and clinical impact of childhood trauma in patients with severe Mental disorders. J Nerv Ment Dis. 2011;199(3):156–61.
173. Conus P, Cotton S, Bg S, Berk M, Daglas R. Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. Bipolar Disord. 2010;1:244–52.
174. Gil A, Gama CS, de Jesus DR, Lobato MI, Zimmer M, Belmonte-de-Abreu P. The association of child abuse and neglect with adult disability in schizophrenia and the prominent role of physical neglect. Child Abus Negl. 2009;33(9):618–24.
175. Hodgins S, Lincoln T, Mak T. Experiences of victimisation and depression are associated with community functioning among men with schizophrenia. Soc Psychiatry Psychiatr Epidemiol. 2009;44(6):448–57.
176. Gayer-Anderson C, Fisher HL, Fearon P, Hutchinson G, Morgan K, Dazzan P, et al. Gender differences in the association between childhood physical and sexual abuse, social support and psychosis. Soc Psychiatry Psychiatr Epidemiol. 2015;50(10):1489–500. https://doi.org/10.1007/s00127-015-1058-6.
177. Frueh BC, Grubaugh AL, Cusack KJ, Kimble MO, Elhai JD, Knapp RG. Exposure-based cognitive behavioral treatment of PTSD in adults with schizophrenia or schizoaffective disorder: a pilot study. J Anxiety Disord. 2010;23(5):665–75.
178. Morgan C, Fisher H. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma—a critical review. Schizophr Bull. 2007;33(1):3–10.
179. Trappler B, Newville ÆH. Trauma healing via cognitive behavior therapy in chronically hospitalized patients. 2007;317–325.
180. Garety PA, Bebbington P, Fowler D, Freeman D, Kuipers E. Implications for neurobiological research of cognitive models of psychosis: a theoretical paper. Psychol Med. 2007;37(10):1377–91.
181. Howes OD, Mcdonald C, Cannon M, Arseneault L, Boydell J, Murray RM. Pathways to schizophrenia : the impact of environmental factors. 2004;7(August)