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Review article

Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings

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ABSTRACT

There is a growing body of research focused on the relationship between childhood trauma and the risk of developing psychosis. Numerous studies, including many large-scale population-based studies, controlling for possible mediating variables, provide persuasive evidence of a dose-response association and are indicative of a causal relationship. Existing evidence supports the specificity model, showing differential associations between particular adversities and clinical symptoms, with cumulative adversity causing less favorable clinical and functional outcomes in psychotic patients. To date, several psychological and biological models have been proposed to search for underlying developmental trajectories leading to the onset of psychosis, influencing psychopathological manifestation and negative functional outcomes due to a history of childhood trauma. In this article, we provide a unified review on the relationship between childhood trauma and psychosis by integrating results of epidemiological, clinical, neuropsychological and biological studies. The question whether psychosis with a positive history of childhood trauma should be considered as a new psychotic phenotype, requiring specific therapeutic interventions, warrants further investigation.

Contents

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1. Introduction

Childhood trauma is defined as harm, potential of harm or threat of a harm resulting from commission or omission by child's caregiver (Sideli et al., 2012). This definition captures a range of severe adverse experiences, such as physical, sexual and emotional abuse, neglect, parental death and bullying, which according to latest research, may affect about one- third of the general population (Kessler et al., 2010). The most common forms of trauma, reported by both men and women, are physical abuse, physical neglect, and emotional abuse, all of which are likely to co-occur (Scher et al., 2004). Accumulating body of evidence suggests the association between childhood adverse experiences and increased risk of a range of negative social outcomes including mental illnesses, next to lower educational level or higher criminality (Sarchiapone et al., 2009; Scher et al., 2004).

Recent studies have focused on establishing the biopsychosocial model of psychosis. Both biological vulnerability and environmental exposure impact the onset and outcome of schizophrenia, spectrum disorders. In the recent years, some models focused on the central role of stressful life events that may influence critical windows of brain development, triggering the onset of psychosis, as well as act in the course of psychosis worsening long-term outcomes (Misiak et al., 2014b). In addition, it has been demonstrated that psychosocial stress, especially childhood traumatic events, may interact with genetic vulnerability or shape gene expression via epigenetic mechanisms, contributing to the development of psychiatric disorders (Babenko et al., 2015; Brietzke et al., 2012).

Several lines of evidence indicate that a history of childhood adversities is highly prevalent in patients with psychosis, influences psychotic psychopathology and correlates with biological alterations underlying the pathophysiology of psychosis. In this article, we discuss results of epidemiological studies addressing the association between childhood trauma and psychosis. In subsequent sections, we describe correlates of childhood adversities in clinical manifestation and outcome of psychosis. We also provide an overview of studies investigating biological consequences of childhood trauma. Finally, we present an integrated summary of findings with critical point of view for current evidence and research gaps in the field that need to be addressed in future studies. We raise the discussion as to whether positive history of childhood trauma might provide new insight into psychological mechanisms of psychosis development together with specific epidemiological, biological and clinical correlates that are present in patients with psychotic disorders exposed to adverse childhood events. A simplified overview of an integrated and unified theory behind the relationship between childhood trauma and psychosis was presented in Fig. 1.

2. Epidemiological findings

The meta-analysis performed by Varese et al. (2012b) revealed that patients with psychosis are almost 3 times more likely to report having been exposed to childhood trauma in comparison with healthy controls. These findings have been reported regardless of study design and type of traumatic events with exception of parental death, which had not been associated with increased psychosis risk. In agreement with these findings, a recent meta-analysis by Bonoldi et al. (2013) estimated the prevalence of childhood sexual, physical and emotional abuse at 26%, 39% and 34%, respectively. Some studies have also reported that childhood adversities may increase psychosis risk in a dose-dependent manner (Schafer and Fisher, 2011). Interestingly, in the study by Lataster et al. (2012), early and recent adversities have been associated with each other without an additive effect at the highest level of exposure to recent stressors. These findings might suggest that early childhood adversities may lead to psychosis development either by increasing exposure to later adversity or by making individuals more sensitive to later adversity if it is severe. In one study, the magnification effect of latest traumatic experiences on the ones from childhood was observed (Bebbington et al., 2011). Importantly, a history of childhood trauma has been associated with psychotic experiences in healthy people (Sommer et al., 2010). Additionally, it has been shown that a history of childhood adversities might be related to a persistent trajectory of these symptoms (Wigman et al., 2011a,b). Finally, childhood traumatic events have been found to predict transition from ultra-high risk for psychosis (UHR) states to overt psychosis (Thompson et al., 2014; Yung et al., 2015). In one of these studies (Yung et al., 2015), transition to psychosis predicted poor long-term functioning, suggesting that the UHR conceptualization may detect a subgroup of individuals, who are at risk of schizophrenia development. Importantly, it should be noted that cessation of traumatic experiences may reduce the incidence of psychosis (Kelleher et al., 2013). The above mentioned meta-analysis by Varese et al. (2012b) revealed that the removal of childhood adversities would result in a 33%-reduction in the number of psychosis cases.

Since a number of environmental insults have been associated with a risk of psychosis, epidemiological studies have also focused the interest on the interactions of childhood adversities with other risk factors in order to provide broader insight into social trajectories leading to psychosis onset. Indeed, there are studies addressing interactions between socioeconomic status, cannabis use, urbanicity and childhood adversities on the development of psychosis. The second Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) provided evidence that social defeat may serve as a mediating variable in the association between childhood trauma and psychosis (van Nierop et al., 2014). In addition, both NEMESIS-1 and NEMESIS-2 indicated that a history of childhood trauma mediates the relationship between sexual minority status and psychosis risk (Gevonden et al., 2014; van Nierop et al., 2014). However, it has not been confirmed that familial history of psychosis (a proxy genetic risk) accounts for association between childhood physical abuse and psychosis risk (Fisher et al., 2014). Other studies revealed an additive effect of urbanicity, cannabis use and childhood trauma on the risk of subthreshold psychotic experiences (Guloksuz et al., 2015). Similarly, there are studies showing interactions between cannabis use and childhood traumatic events (Harley et al., 2010; Houston et al., 2008; Houston et al., 2011; Konings et al., 2012; Murphy et al., 2013). Interestingly, in the study by Houston et al. (2008), the effect of sexual trauma on psychosis development was significant only for those, who used cannabis under the age of 16 years.

It should be noted that the majority of epidemiological studies in this field are based on retrospective self-reports of childhood trauma. This controversial issue appears also in other studies inves-

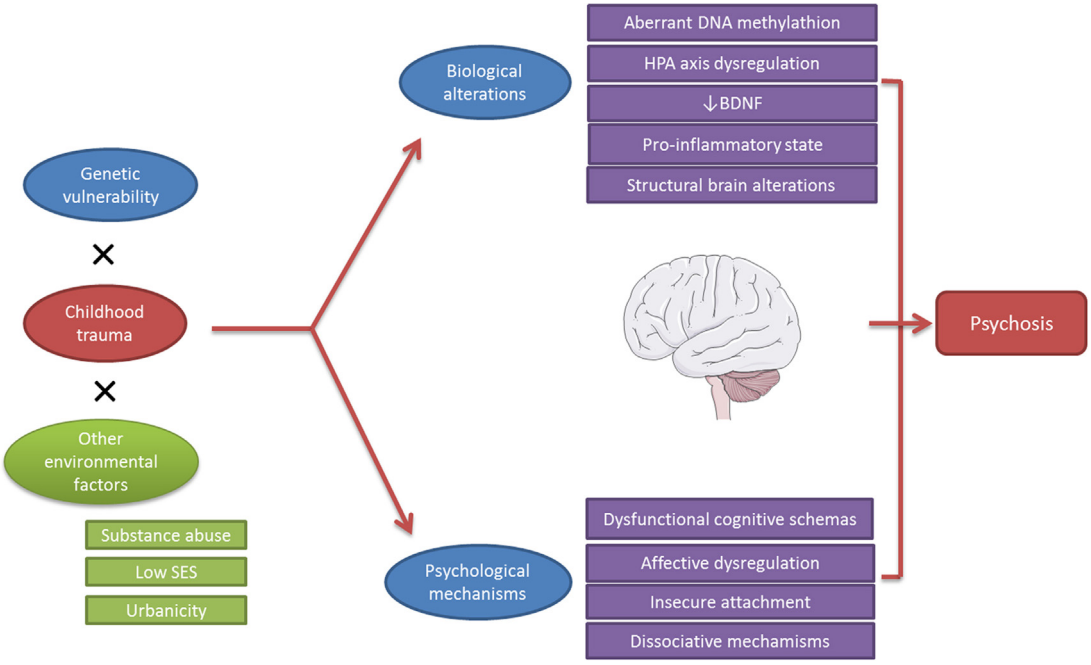

Fig. 1. A simplified overview of trajectories leading from childhood trauma to psychosis. Childhood adversities may interact with genetic vulnerability to psychosis and other environmental factors including i.e. substance abuse, low socioeconomic status (SES) or high urbanicity. It may lead to psychosis via distinct biological alterations, including aberrant DNA methylation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, decreased levels of brain-derived neurotrophic factor (BDNF) or subclinical pro-inflammatory that are observed in parallel to structural brain changes, especially in the hippocampus and amygdala. Childhood adversities might also increase a risk of psychosis through several psychological mechanisms, such as dysfunctional cognitive schemas, affective dysregulation, insecure attachment and dissociation.

tigating clinical and biological correlates of childhood adversities. This caveat should be taken into account especially in studies on patients experiencing acute psychotic symptoms. On the other hand, the inclusion of reports from other third parties also remains controversial since they might have been involved in the abuse. The study by Hardt and Rutter (2004) addressed this limitation evaluating the validity of self-reports by means of comparisons with contemporaneous, prospectively obtained, court or clinic or research records and by collecting retrospective reports of two siblings. Authors found that self-reports of childhood trauma are rather under- than overestimated. In addition, it has been demonstrated that self-reports are stable over time and unaffected by current psychopathological symptoms (Fisher et al., 2011).

3. Clinical manifestation and outcome

3.1. Psychopathological manifestation

There are numerous studies suggesting differential associations between particular childhood adversities and psychotic symptoms (Bentall et al., 2012; Ruby et al., 2015; Shevlin et al., 2008; Sitko et al., 2014), while other support this view only partially (Longden et al., 2015). Most consistently, it has been reported that a history of childhood trauma increases the severity of positive symptoms of psychosis including auditory verbal hallucinations and delusions (Duhig et al., 2015; Read et al., 2005). In one study, it has been demonstrated that childhood adversities may influence the severity of delusions and hallucinations in a dose-response relationship (Muenzenmaier et al., 2015). While effects of childhood trauma on psychotic experiences have been clearly demonstrated, childhood adversities have not been associated with negative symptoms of schizophrenia in some studies (Ruby et al., 2015; Ucok and Bikmaz, 2007).

Some studies have also looked beyond the relationship between childhood trauma and psychotic symptoms. It has been reported that patients with psychosis and childhood trauma tend to present higher levels of current and lifetime substance abuse (Conus et al., 2010), dysthymic, depressive and anxiety symptoms (Duhig et al., 2015; Lysaker and Salyers, 2007; Ruby et al., 2015; Schenkel et al., 2005), as well as dissociative symptoms (Braehler et al., 2013; Muenzenmaier et al., 2015; Sar et al., 2010; Schafer et al., 2012). In the study on data from the NEMESIS-2 study and the Genetic Risk and Outcome of Psychosis (GROUP) study, a history of childhood trauma was related to a specific admixture of affective, anxiety and psychosis symptoms that extends traditional diagnostic boundaries (van Nierop et al., 2015b). In the ALSPAC birth cohort, depressive and anxiety symptoms appeared to mediate a relationship between childhood trauma and psychotic-like experiences (Fisher et al., 2013).

A number of studies have addressed a specific impact of various types of childhood trauma on psychopathological symptoms of psychosis. Specifically, sexual abuse has been linked to auditory hallucinations in first-episode schizophrenia (FES) females (Misiak et al., 2016). In the Adult Psychiatric Morbidity Survey, childhood rape was related to higher odds of hallucinations (Bentall et al., 2012; Shevlin et al., 2011). In one study, hallucinations, but not delusions, were predicted by a history of physical and sexual abuse (Read et al., 2003). Similarly, in the study by Salokangas et al. (2015) depression, obsessive-compulsive disorders, anxiety and sexual abuse appeared to be one of the major clinical factors predicting persistence of paranoid symptoms in subjects at risk of psychosis. Another study looking at the association between types of childhood trauma and symptomatic manifestation revealed that only sexual abuse, but not other types of childhood adversities predicted the risk of violence in patients with psychotic disorders (Bosqui et al., 2014).

Along these lines, a number of studies have addressed whether childhood adversities are related to the content of psychotic symptoms. In the study by Hardy et al. (2005), nearly half of reported hallucinations were related to subjects similar to experienced trauma. Read and Argyle (1999) provided evidence that even the content of a broader spectrum of psychotic symptoms, including hallucinations, delusions and thought disorder might be associated with childhood abuse. Furthermore, in the study on UHR individuals, psychotic experiences with sexual content were associated with childhood sexual abuse (Thompson et al., 2010). Similarly, our group demonstrated that childhood trauma might be especially related to abusive, accusatory and persecutory voices in FES females (Misiak et al., 2016). On the contrary to these findings, Daalman et al. (2012) revealed that childhood trauma might be related to auditory hallucinations but the valence of voices might be either positive or negative. Taking into account these results, it has been proposed that hallucinations may constitute dissociative memories of traumatic events (Mauritz et al., 2013). Another explanation was proposed by Birchwood et al. (2000), who revealed that measures of power and rank between auditory hallucinations and the subject experiencing them correspond with self-perceived measures of power and rank in social environment. These findings suggest that hallucinations with negative content might reflect lower social self-appraisal being the consequence of childhood adversities.

Interestingly, it has been demonstrated that even the severity of subclinical psychotic experiences might be related to a history of childhood trauma (Boyda and McFeeters, 2015; Sommer et al., 2010). Similarly, in the study by Kraan et al. (2015), higher levels of childhood trauma were associated with more severe attenuated and more persistent positive symptoms. This is consistent with the study by Daalman et al. (2012) showing that sexual and emotional trauma during childhood serve as a rendering factor for subjects more vulnerable to experience auditory verbal hallucinations in general – both psychotic and non-psychotic individuals.

Post-traumatic stress disorder (PTSD) has been suggested to be a pathway linking childhood trauma with later psychopathology. It should be noted that schizophrenia and PTSD share overlapping symptoms, including dissociation or psychosis. This overlap makes it difficult to recognize trauma in disorders related to adverse experiences, such as PTSD and other psychiatric disorders (Mauritz et al., 2013). Epidemiological studies have demonstrated that approximately every fourth person who was a victim of childhood abuse develops PTSD (Green, 1994). The study performed by Choi et al. (2015) presented PTSD as a partial mediator between childhood abuse and symptoms of psychosis, linking the experience of chronic posttraumatic stress with increased likelihood of developing psychotic manifestation.

3.2. Cognitive performance

It has been shown that there is a negative impact of childhood trauma on cognitive functions in healthy individuals as well as in patients with psychosis and their high-risk offspring, especially with respect to general cognitive abilities, memory, and executive functions (Aas et al., 2011a; Aas et al., 2014a; Berthelot et al., 2015; Bucker et al., 2012; Lysaker et al., 2001; Perez and Widom, 1994; Schenkel et al., 2005; Shannon et al., 2011; Vasilevski and Tucker, 2015).

There are few studies investigating early trauma in people with psychotic disorders, both in first- episode psychosis patients as well as in chronic patients. It has been shown that male schizophrenia patients with sexual abuse have impaired processing speed, working memory, and executive functioning in comparison with non-abused patients (Lysaker et al., 2001). Similarly, patients with schizophrenia-spectrum disorders with a history of childhood trauma showed decreased learning and visual context processing compared to patients without trauma (Schenkel et al., 2005). Shannon et al. (2011) demonstrated the association between childhood trauma and reduced verbal memory and working memory performance, even after controlling for pre-morbid IQ and depressive symptoms in patients with chronic schizophrenia. In the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, it was found that childhood trauma is associated with reduced performance on attention, concentration, language, mental speed tasks as well as with reduced verbal intelligence in FEP patients, especially in males with affective psychosis (Aas et al., 2011a). Similar results were found in the study by Aas et al. (2012c), showing a reduction in cognitive functioning among patients with schizophrenia-spectrum and bipolar disorders, in particular with regard to working memory and executive functions. There are studies showing inconclusive or negative findings between childhood trauma and cognitive functioning in FEP patients (Aas et al., 2011b; Sideli et al., 2014) and in chronic schizophrenia-spectrum disorder patients (Green et al., 2014; Hernaus et al., 2014; Ruby et al., 2015). Moreover, a non-clinical group of individuals experiencing auditory verbal hallucinations (Sommer et al., 2010) with similar rates of childhood trauma as the patients with psychotic disorders (Daalman et al., 2012) showed reduced performance in various cognitive domains, such as executive functioning, working memory and language abilities (Daalman et al., 2011). Detailed analysis showed that childhood trauma fully explained the association between psychotic experiences and reduced executive functioning, as well as working memory (Begemann et al., 2015). Additionally, the level of childhood trauma was associated with reduced verbal inhibition in the domain of executive functioning (Begemann et al., 2015). Surprisingly, there is also one study showing that early trauma predicts better cognition in female patients with schizophrenia-spectrum disorders (Ruby et al., 2015). This association is most probably mediated by better vigilance and attention due to increased stress-based arousal.

Interestingly, it has been shown that there is an interaction between genetic markers and childhood trauma on cognitive dysfunction in patients with psychotic disorders (Aas et al., 2012a; Aas et al., 2013; Green et al., 2014). For example, Aas et al. (2012a) observed that the *5-HTTLPR* short allele carriers who experienced high levels of childhood trauma show more cognitive dysfunction in comparison with all other groups, most probably due to larger increases in the levels of stress hormones compared with long allele carriers. Similarly, the *Met* allele carriers of the *BDNF* Val66Met polymorphism with high level of childhood abuse showed more profound cognitive impairments than all other groups, as well as had smaller hippocampus and larger ventricles (Aas et al., 2013). However, one study failed to show an interaction between the *BDNF* gene polymorphism and traumatic events in childhood on cognition in later life (Hernaus et al., 2014). Consistent with previous findings, the *COMT* Val/Val homozygotes performed worse on cognitive measures in the absence of childhood adversity; however, a significant interaction between the *COMT* genotype and physical abuse was associated with better executive functions in the *COMT* Val/Val homozygotes, relative to those of the same genotype with no history of abuse (Green et al., 2014). These results suggest possible epigenetic modulation of gene polymorphisms expression due to childhood traumatic events that influence cognition in schizophrenia.

3.3. Psychosis outcome

Although it is now increasingly being recognized that a history of childhood trauma is related to clinical manifestation of psychosis, less is known about the way childhood adversities may influence response to treatment. In the study by Mondelli et al. (2015), which was focused on immune-inflammatory predictors of early

response to antipsychotic treatment in FEP patients, those who did not respond to treatment more frequently reported childhood adversities. However, the authors did not present as to whether a specific type of childhood trauma might be more closely related to early non-response to treatment. More specifically, our group revealed that a history of childhood trauma, especially emotional abuse, might be related to early non-response to antipsychotic treatment in patients with FES (Misiak and Frydecka, 2016). It has been also reported that treatment-resistant schizophrenia patients might experience emotional abuse and neglect, as well as sexual abuse more frequently than the patients responding to antipsychotic treatment (Hassan and De Luca, 2015). Finally, in one study patients with severe mental illness and a higher number of childhood adversities received higher doses of antipsychotics and mood stabilizers (Schneeberger et al., 2014). These findings would suggest that more severe biological dysregulation observed in patients with psychosis and self-reported history of stressful childhood experiences might underlie less favorable treatment outcomes. However, a scarcity of studies addressing this issue does not allow us to draw unequivocal conclusions.

More studies have investigated the effects of childhood traumatic events on functional outcomes in patients with psychosis. A recent systematic review with meta-analysis revealed the impact of childhood adversity on the persistence of psychotic experiences and clinically relevant psychotic symptoms (Trotta et al., 2015b). In the study by Alameda et al. (2015), patients in the early course of psychosis reporting a history of sexual and physical abuse, especially those experiencing childhood adversities before the age of 12 years, had more severe functional impairment. Similarly, in the NEMESIS-2 and the GROUP studies, patients with psychotic disorders and the admixture of affective, anxious and psychosis symptoms related to a history of childhood trauma had lower quality of life, higher prevalence of substance use disorders and lower global functioning (van Nierop et al., 2015a). In one study, physical abuse has been associated with not being in a relationship in a 1-year follow-up of patients with FEP (Trotta et al., 2015a). In the same study, parental separation in childhood has been related to longer admissions to psychiatric wards and non-compliance with medication. Poorer functioning has been also reported in the premorbid period of FEP patients (Stain et al., 2014) and individuals with subclinical psychotic symptoms (Boyda and McFeeters, 2015), who have experienced childhood trauma. On the contrary, Trauelsen et al. (2016), who studied FEP patients revealed that childhood adversities have been associated with worse global functioning after the onset of psychosis but not in the premorbid period. In the study by Gil et al. (2009), authors investigated whether there is a difference between particular categories of childhood adversities with respect to their effect on functional capacity in schizophrenia. They found that disability in schizophrenia is related to physical neglect as well as emotional abuse and neglect but not to other types of childhood traumatic events.

4. Psychological mechanisms linking childhood trauma and psychosis

Findings from longitudinal studies and a dose-dependent relationship suggest a causal association between childhood trauma and the development of psychosis (Bentall et al., 2012; Longden et al., 2015; Shevlin et al., 2008). Several studies have been conducted to search for a potential model explaining the correlation between traumatic events and psychotic symptoms and some psychological explanatory mechanisms have been proposed, such as dysfunctional cognitive schemas, affective dysregulation, insecure attachment styles, and dissociative mechanisms.

Cognitive models propose that the emergence of feeling of threat and paranoia that give raise to persecutory delusions, is based on pre-existing negative beliefs about the self together with threatening appraisals of others (Fowler et al., 2006; Freeman et al., 2002; Garety et al., 2001; Gracie et al., 2007; Morrison, 2009). The association between negative beliefs about self and others with paranoia has been shown in both non-clinical (Fowler et al., 2006) and clinical samples (Smith et al., 2006). Following this line of research, the study on a non-clinical sample revealed that negative beliefs about self and others may serve as key mediators in the relationship between trauma and psychosis (Gracie et al., 2007). Similar results have been obtained in clinical samples, including schizophrenia patients (Kilcommons and Morrison, 2005).

Based on the social defeat theory form animal studies (Anstrom et al., 2009; Cao et al., 2010), it has been suggested that it is not the experience of an adverse childhood event itself but the enduring exposure to a subordinate position that is a common denominator of various environmental factors, including traumatic events, to risk of developing psychosis (Selten and Cantor-Graae, 2005, 2007; Selten et al., 2013). Preliminary support for this theory was shown in the study on individuals with clinical high risk for psychosis (Stowkowy and Addington, 2012). In this study, feelings of losing rank or failed struggle were associated with attenuated psychotic symptoms (Stowkowy and Addington, 2012). Similarly, early memories of shame due to traumatic events have been associated with paranoia in the general population (Matos et al., 2013). Additionally, in a sample of schizophrenia patients, it has been found that perceptions of defeat and entrapment are associated with positive symptoms, such as auditory hallucinations (Birchwood et al., 2004; Taylor et al., 2010) and suspiciousness (Taylor et al., 2010), while results from the NEMESIS-2 study show that social defeat is an important mediator in the link between childhood adverse experiences and later expression of psychosis, both at the level of psychotic experiences in the population and at the level of psychotic disorder (van Nierop et al., 2014). Interestingly, it has been shown that prolonged exposure to aversive environments can lead to the sensitization of the dopaminergic system with social defeat stress selectively altering mesocorticolimbic dopamine release (Tidey and Miczek, 1996).

Some authors point to the relevance of the affective pathway between trauma and psychosis. Affective dysregulation is strongly associated with reality distortion (Kramer et al., 2014), as well as it directly exacerbates psychotic phenomena (Wigman et al., 2012) and increases the risk of psychotic disorder (van Rossum et al., 2011). Schizophrenia patients with delusions are more likely to assign a negative meaning to neutral stimuli compared to patients without delusional thinking and this effect is correlated with the severity of delusions. This mechanism of negative valuation results in highly maladaptive evaluation of reality that leads to increased risk of psychotic experiences among vulnerable individuals (van Rossum et al., 2011). Moreover, it has been shown that a history of adverse events in early life is associated with increased sensitivity to stress in patients with psychosis (Lardinois et al., 2011), while individuals with high genetic risk of psychosis and psychotic patients react with increased negative emotions to normal, daily stressors (Lataster et al., 2010; Myin-Germeys and van Os, 2007). A 10-year prospective cohort study found that traumatic childhood events together with recent life events act together to induce psychotic symptoms (Lataster et al., 2012). Childhood trauma has been shown to increase the likelihood of admixture of affective, anxiety and psychotic symptoms that may be present already in the earliest stages of psychopathology (van Nierop et al., 2015b). Moreover, it has been shown that a psychosocial stress task causes a significant release of dopamine, especially in individuals who had experienced low maternal care, suggesting a sensitization effect (Pruessner et al., 2004).

Some researchers explore the relevance of attachment styles on the relationship between adverse experiences in the childhood and psychotic symptoms in the adulthood. Attachment style reflects habitual cognitive-affective representations of the self and others as well as strategies for regulating distress. The majority of studies refer to four basic attachment styles – one secure and three insecure, such as preoccupied, dismissing/avoidant and fearful/anxious (Bartholomew and Horowitz, 1991). Previous work has demonstrated associations of insecure attachment with psychotic phenomena in clinical and non-clinical samples [for review see (Korver-Nieberg et al., 2014)]. In recent years, empirical studies have been conducted on insecure attachment styles as mediators of the association between childhood adversities and psychotic symptoms. In the non-clinical study on Spanish population, it was found that an insecure fearful attachment style mediated the association of physical/emotional trauma with schizotypy, suspiciousness and psychotic-like experiences, further implicating attachment disruptions in the pathway from childhood trauma to psychosis (Sheinbaum et al., 2014). Data from the US National Comorbidity Survey have shown that insecure attachment partially explained the relationship between rape and hallucinations, while insecure avoidant attachment style was fully mediating the association between neglect and paranoia (Sitko et al., 2014). In a clinical sample of people with psychotic disorders together with their siblings, the association between childhood maltreatment and positive symptoms was partially mediated by attachment style (van Dam et al., 2014).

The relationship between childhood trauma and psychosis may be also mediated by dissociation, defined as a disruption in the usually integrated functions of consciousness, memory, identity, or perception of environment (Anketell et al., 2010). The pathway to adult psychopathology may begin with a dissociative response to childhood trauma (Read et al., 2001). Individuals who cope with trauma via dissociation are more likely to have impaired reality testing and subsequently experience psychosis (Kilcommons and Morrison, 2005). Moreover, psychotic patients exposed to traumatic childhood experiences score higher on measures of dissociative tendencies compared to patients with no history of trauma (Holowka et al., 2003; Perona-Garcelan et al., 2010). It has been shown that a relationship between childhood trauma and hallucination proneness is positively mediated by dissociative tendencies in non-clinical (Perona-Garcelan et al., 2014) and clinical samples (Varese et al., 2012a). Additionally, the impact of physical neglect on the likelihood of experiencing psychosis was explicable through the effects of increased dissociation in psychotic patients (Evans et al., 2015).

5. Biological correlates of childhood adversities

5.1. Hypothalamic-pituitary-adrenal (HPA) axis response

Overwhelming evidence indicates the HPA axis dysregulation in schizophrenia-spectrum patients. Walker et al. (2008) suggested a synergistic relation between activation of the HPA axis and activation of dopaminergic circuits in the developmental course of schizophrenia, with glucocorticoid secretion increasing dopamine activity, particularly in the mesolimbic system (Walker et al., 2008). It has been reported that patients with psychosis or at-risk individuals are characterized by elevated morning cortisol levels (Girshkin et al., 2014), higher diurnal cortisol levels (Mondelli et al., 2010b), blunted cortisol awakening response (CAR) (Day et al., 2014) and attenuated cortisol response to stress (Ciufolini et al., 2014). A recent *meta*-analysis demonstrated higher pituitary gland volume in subjects at risk of psychosis and FEP patients in comparison with healthy controls at the trend level significance. The authors also observed a significant positive correlation between antipsychotic treatment and pituitary gland volume in schizophrenia patients (Nordholm et al., 2013). It should be noted that some of these abnormalities seem to be specific to psychosis patients. For instance, PTSD patients have been found to present with blunted CAR and lower diurnal cortisol levels, whereas increased CAR together with increased diurnal cortisol levels might be more specific for patients with depression. Furthermore, on the basis of a meta-analysis, Ciufolini et al. (2014) revealed that patients with depression might display a pattern of cortisol response to stress that is similar to that observed in healthy controls. Interestingly, some HPA axis abnormalities have been found to precede the onset of psychosis. Indeed, blunted CAR has been observed in subjects at risk of psychosis (Cullen et al., 2014; Day et al., 2014). Finally, higher CAR has been found to predict higher severity of positive symptoms in patients with FEP from schizophrenia-spectrum disorders (Belvederi Murri et al., 2012).

It has been proposed that the HPA axis dysregulation may mediate the relationship between childhood trauma and psychosis. Indeed, the traumagenic neurodevelopmental model suggests that long-term exposure to stressors may result in elevated release of glucocorticoids, which can stimulate striatal dopaminergic activity, making individuals more prone to develop psychosis (Read et al., 2001; Walker and Diforio, 1997). Interestingly, studies including the measures of childhood trauma have demonstrated that early-life stress has an opposite effect on the HPA axis disturbances observed in psychosis patients. For instance, Cullen et al. (2015) showed that exposure to physical punishment has a negative impact on pituitary gland volume in children at risk of schizophrenia. Similarly, a history of childhood sexual abuse was positively correlated with CAR in FEP patients in the study by Mondelli et al. (2010a). In addition, the authors revealed a non-significant negative correlation between childhood trauma and diurnal cortisol levels in FEP patients, whereas this correlation was positive in healthy controls at the non-significant level. They noticed that a similar correlation can be observed in PTSD patients (Yehuda, 2001), suggesting that extremely stressful events may reduce HPA axis activation.

5.2. Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) promotes growth and differentiation of neurons, as well as influences synaptic plasticity and connectivity. BDNF modulates cognitive processes and its deficiency might be associated with increased risk of schizophrenia. It has been shown that psychotic disorders are associated with reduced BDNF levels in the brain (Durany et al., 2001), serum and plasma (Cui et al., 2012). Moreover, it has been suggested that BDNF may be involved in the onset of psychosis in individuals exposed to early trauma and serve as a potential clinical biomarker associated with detrimental effects of childhood trauma on brain plasticity (Theleritis et al., 2014).

A number of polymorphisms have been detected in the *BDNF* gene; however, the Val66Met polymorphic variant has been most widely studied in various mental disorders, including psychosis-spectrum disorders. It has been shown that the Met variant is associated with lower *BDNF* expression. Several studies have reported reduced levels of BDNF in patients with schizophrenia-spectrum disorders, including drug-naïve FEP patients (Green et al., 2011). It has been shown that childhood trauma is correlated with reduced leukocytes BDNF mRNA levels (Aas et al., 2014b; Mondelli et al., 2011) and plasma BDNF levels in psychotic disorders (Theleritis et al., 2014). Moreover, it has also been shown that high levels of childhood trauma and the Met variant show an additive association with reduced BDNF mRNA expression (Aas et al., 2014b). More specifically, in the study investigating FEP cases, it

was found that lower BDNF plasma levels were associated with separation, physical and sexual abuse among individuals who experienced traumatic events compared to those who did not (Theleritis et al., 2014).

Additionally, it was also shown that the *BDNF* Val66Met genotype moderates the effect of childhood abuse on the positive dimension of psychotic-like experiences in healthy college students (Alemany et al., 2011); however, this finding was not replicated in adolescents (Ramsay et al., 2013). Interestingly, interactions between traumatic events, immune system and stress hormones have been described in the development of psychosis due to traumatic experiences. In the study on FEP patients, it was shown that childhood trauma and high levels of recent stressors predict lower BNDF expression through an inflammation–mediated pathway (Mondelli et al., 2011). In turn, lower BNDF expression has been associated with increase in interleukin (IL)-6 expression and cortisol levels (Mondelli et al., 2011).

In addition, one study revealed that the *BDNF* 66Met allele carriers highly exposed to childhood adversities had reduced volumes of hippocampal subfields (CA2/3 and CA4 dentate gyrus regions) compared to other subgroups of patients (Aas et al., 2014b). The same group demonstrated that the *BDNF* 66Met allele carriers highly exposed to childhood trauma had worse cognitive performance (Aas et al., 2013). An interaction between the *BDNF* Val66Met polymorphism and childhood trauma on hippocampal volumes and cognition was not confirmed by Hernaus et al. (2014) in patients with various psychotic disorders.

5.3. Immune-inflammatory mechanisms

It has been suggested that childhood traumatic events impact the immune system, leading to a pro-inflammatory state in the adulthood that in turn is conferring vulnerability to develop psychotic disorders. A recent meta-analysis has shown a significant association between childhood trauma and inflammatory markers in the adulthood, with the highest effect size for tumor necrosis factor-α (TNF-α), followed by IL-6 and then C-reactive protein (CRP) (Baumeister et al., 2015). Interestingly, this study revealed that various types of traumatic events might have a differential impact on inflammatory markers. Physical and sexual abuse was related to increased TNF-alpha and IL-6 levels, while CRP levels were primarily associated with parental absence in the early life (Baumeister et al., 2015). In schizophrenia patients, increased levels of pro-inflammatory markers, including IL-6 and TNF-α were found only in patients with a positive history of childhood trauma, while there were no differences with respect to IL-1β and IL-8 (Dennison et al., 2012). In FEP patients, it has been shown that childhood sexual abuse has been associated with higher body-mass index (BMI) and CRP in comparison with controls and patients without a history of sexual abuse (Hepgul et al., 2012). In turn, another study demonstrated that FEP patients with childhood trauma had significantly higher serum levels of TNF-α and monocyte chemoattractant protein-1 compared to patients without childhood trauma; however, there were no significant associations with other cytokines (serum or mRNA levels), such as IL-1α, IL-1β, IL-2, IL-4, IL-8, IL-10 or interferon-γ (Di Nicola et al., 2013).

5.4. Metabolic dysregulation

Several studies indicate that patients with schizophrenia and related disorders have higher prevalence rates of metabolic syndrome (MetS) in comparison with the general population (Mitchell et al., 2013). High prevalence of MetS in this group of patients has been primarily associated with the effects of pharmacological treatment (Hasnain et al., 2010), unhealthy life style characteristics (Vancampfort et al., 2011) and the severity of negative symptoms (Sicras-Mainar et al., 2015) as well as cognitive impairment (Lindenmayer et al., 2012). However, it is also increasingly apparent that FEP patients are characterized by subthreshold metabolic dysregulation that cannot be attributed to medication effects (Chen et al., 2013; Misiak et al., 2014a; Petrikis et al., 2015). These findings suggest the existence of common genetic underpinnings of MetS and psychotic disorders or the influence of environmental factors acting before the onset of psychosis.

Studies in the general population have demonstrated that psychosocial stress contributes to the development of obesity and related disorders. It has been shown that prolonged stress may promote the consumption of highly palatable food despite the sensation of satiety and induce binge eating behaviors (Hebebrand et al., 2014; Morris et al., 2014). In addition, stress may increase the HPA axis activity and alter the secretion hypothalamic neuropeptides with orexigenic and anorexigenic activities (Morris et al., 2014). These mechanisms explain results of studies in non-psychiatric populations that have shown higher risk of obesity (Li et al., 2015), diabetes (Gilbert et al., 2015) and hypertension (Parrish et al., 2013) in adult individuals exposed to childhood adversities. However, to date only three studies have addressed the contribution of childhood trauma to cardiometabolic risk in schizophrenia-spectrum patients. In the study by Hepgul et al. (2012), a history of childhood sexual abuse was associated with significantly higher BMI in FEP patients. Similarly, Rajkumar (2015) found an association between childhood trauma and higher BMI and systolic blood pressure in schizophrenia patients. In turn, our group revealed that a history of childhood adversities, especially sexual and emotional abuse, might be associated with higher systolic and diastolic blood pressure as well as the levels of low-density lipoproteins (LDL) in FES patients (Misiak et al., 2015a). Given that a history of childhood trauma is highly prevalent among schizophrenia-spectrum patients, it should be stressed that early-life stress might be also perceived as an important factor contributing to high prevalence of MetS in patients with psychotic disorders.

5.5. Gene × environment interactions and epigenetics

Although a causal relationship between a history of childhood trauma and psychosis exists, childhood adversities are neither necessary nor sufficient to trigger the onset of psychosis (Collip et al., 2013; van Winkel et al., 2008). This observation together with evidence for substantial heritability of schizophrenia-spectrum disorders has initiated the emergence of studies looking at gene × environment (G × E) interactions as a putative missing link between psychosocial stress during childhood and the development of psychosis.

Several studies addressing this issue have focused on the effects of single nucleotide polymorphisms (SNPs) in the FK506 binding protein 5 (*FKBP5*) gene. This gene encodes a *cis*-trans prolyl isomerase, which acts as a co-chaperone and regulates glucocorticoid receptor (GR) sensitivity (Binder, 2009). It has been shown that the A allele at two SNPs in the *FKBP5* gene (rs4713916 and rs9296158) serves as a risk factor psychosis in subjects exposed to childhood traumatic events (Collip et al., 2013). These alleles were also associated with lower cortisol levels suggesting that GR hypersensitivity might be a risk factor for psychosis in subjects exposed to childhood trauma. Another study by Alemany et al. (2015) investigated the role of the *FKBP5* rs1360780 polymorphism with respect to the risk of psychotic experiences in the Spanish general population sample. The authors found that TT homozygotes with a history of childhood trauma presented higher levels of positive psychotic experiences compared to the CC homozygotes. Interestingly, in the study by Green et al. (2015), schizophrenia patients

and healthy controls with a history of childhood trauma and the CC genotype for the *FKBP5* rs1360780 polymorphism performed worse on measures of attention. In addition, schizophrenia patients with the TT genotype had worse global neuropsychological performance regardless of exposure to childhood trauma. It is important to note that the interaction between the *FKBP5* genotype and childhood trauma is not specific for psychosis since it has been also demonstrated in subjects with depression (Appel et al., 2011) or depressive symptoms (Velders et al., 2011). Similarly, it has been demonstrated that the *FKBP5* gene polymorphisms interact with traumatic events on the risk of PTSD (Binder et al., 2008; Xie et al., 2010).

To our knowledge, two studies addressed the interaction between catechol-*O*-methyltransferase (*COMT*) gene polymorphism (Val158Met) and childhood trauma on the risk of psychotic experiences in the general population (Ramsay et al., 2013; Vinkers et al., 2013). In one study (Vinkers et al., 2013), Val/Val homozygotes had significantly higher levels of psychotic experiences after exposure to both childhood trauma and cannabis use. In the second study (Ramsay et al., 2013), Val/Val homozygotes exposed to childhood adversities were more likely to report psychotic experiences at the borderline significance. The authors (Ramsay et al., 2013) also included the analysis of the *BDNF* Val66Met polymorphism; however, no significant interaction was found. Finally, one study addressed the moderating effects of genetic factors on the relationship between childhood trauma and clinical manifestation of psychosis (Green et al., 2014). The severity of positive symptoms was greater in the *COMT* Met carriers who had experienced physical abuse, and the severity of negative symptoms in the *COMT* Met carriers was greater in the presence of emotional neglect. A significant interaction was also observed between genotype and emotional neglect in increasing the severity of negative symptoms for the *COMT* Met/Met homozygotes.

It is now increasingly being recognized that patients with schizophrenia-spectrum disorders are characterized by epigenetic dysregulation [for review see (Dempster et al., 2013; Misiak et al., 2013; Nishioka et al., 2012)]. Although this observation is based mainly on studies investigating DNA methylation in peripheral tissues, concordant patterns of aberrant DNA methylation in some genes between the brain and peripheral blood leukocytes have been reported (Auta et al., 2013; Murphy et al., 2005; Walton et al., 2015). Importantly, some studies addressing epigenetic alterations in schizophrenia revealed differential DNA methylation of genes encoding proteins involved in stress response pathways including GR (Auta et al., 2013), BDNF (Auta et al., 2013; Dong et al., 2015a; Dong et al., 2015b; Ikegame et al., 2013) and genes involved in immune-inflammatory processes (Frydecka et al., 2014; Kordi-Tamandani et al., 2013; Liu et al., 2013). To date, there is only one study, performed by our group, which investigated epigenetic consequences of childhood trauma in FES patients (Misiak et al., 2015b). We found lower DNA methylation of LINE-1 sequences in FES patients with self-reported history of childhood trauma. However, we observed no significant differences between FES patients and healthy controls in terms of LINE-1 methylation. These sequences are relics of previous retrotransposition events and serve as surrogate measures of global DNA methylation (Darby and Sabunciyan, 2014; Ehrlich, 2002). This field is worth of studying since several studies have reported altered DNA methylation of stress response genes as a consequence of exposition to childhood adversities [for review see: (Vinkers et al., 2015)]. The far goal for future studies will be to disentangle epigenetic marks of childhood trauma that are specific for distinct phenotypes and thus related to causality.

6. Neural substrates

Comprehensive models linking stress and psychosis vulnerability imply that major life stressors may exert sustained and deleterious effects on brain development trajectories triggering the onset of psychosis. In this vein, the majority of studies investigating neural substrates of childhood trauma in psychosis have focused on hippocampal and amygdalar brain regions. Both structures have been implicated in the regulation of HPA axis (Myers et al., 2014) and thus it is conceivable that they mediate the association between childhood adversities and psychosis. Additionally, the amygdala complex has been recognized as a neural substrate for emotional reactivity and learning, whereby cues acquire significance through conditioning with rewarding or aversive events (Gallagher and Chiba, 1996). These lines of fundamental knowledge have provided grounds for studies investigating these structures as putative neural substrates of childhood traumatic events.

It has been found that a history of childhood trauma may predict lower amygdala and/or hippocampus volume in FEP patients (Aas et al., 2012b; Hoy et al., 2012) as well as reduced whole-brain volumes in chronic patients (Ruby et al., 2015). Interestingly, evening cortisol levels accompanied larger brain volume reductions (Ruby et al., 2015). More complex relationships have been also reported in patients with psychotic disorders. For instance, in the study by Aas et al. (2013), psychosis patients with the *BDNF* 66Met allele and a history of sexual abuse had lower right hippocampal volume and larger left and right ventricles. In turn, the study by Mondelli et al. (2011) revealed lower BDNF and higher IL-6 levels in FEP patients. These alterations together with higher cortisol levels predicted a lower left hippocampus volume, while a history of childhood trauma was associated with lower BDNF levels through elevated IL-6 levels. In one study (Sheffield et al., 2013), sexual abuse, but not other types of childhood adversities, was associated with lower total volume of gray matter. These results corroborate previous findings indicating that higher levels of stress hormones might be related to lower brain volumes in abused individuals (De Bellis et al., 1999).

7. Effects of sex differences in studies on childhood trauma

Studies addressing effects of sex in the relationship between childhood trauma and psychosis have provided mixed results. For instance, MacMillan et al. (2001) reported that a history of childhood trauma increases the likelihood of lifetime psychopathology in females, but not in males. In two studies a history of physical and sexual abuse has been associated with psychosis only in females (Fisher et al., 2009; Gayer-Anderson et al., 2015). Similarly, the association between childhood trauma and higher levels of anomalous self-experiences has been reported in females but not in males (Haug et al., 2015). Our study on FES patients also revealed that the association between sexual abuse and auditory verbal hallucinations might be specific for females (Misiak et al., 2016).

However, results suggesting that males might be more vulnerable to the consequences of childhood adversities have been also reported. In one study, males with psychosis and a history of childhood trauma appeared to report more psychosomatic concerns, including cardiovascular comorbidities, migraines and anhedonia, while the corresponding group of females was more likely to report a lifetime history of elevated mood and being in a relationship (Sweeney et al., 2015). In the National Comorbidity Survey (Shevlin et al., 2007), childhood rape had higher predictive value for psychosis in males. It has been also demonstrated that healthy males, but not females, with subclinical psychotic experiences are characterized by reduced hippocampal volume (Samplin et al., 2013).

In one study, sex differences were demonstrated in association between early trauma and cognition, with better cognition in traumatized women but not men (Ruby et al., 2015).

Fisher et al. (2009) concluded that effects of sex in studies investigating the association between childhood trauma and psychosis might be explained by psychological mechanisms. Indeed, it has been demonstrated that women tend to internalize emotional burden related to traumatic experiences, while men rather externalize traumatic events in the way of engaging in maladaptive behaviors (Eisenberg et al., 1994; Sigurdardottir et al., 2014). Sex differences might be also explained by different emotional processing and coping strategies employed by male and female patients. It has been shown that males tend to react to trauma with hyperarousal, while females typically respond with dissociation (Read et al., 2001). Moreover, women rely more heavily on more adaptive coping styles when exposed to stress, as opposed to fight-flight response that is more often used by men (Klein and Corwin, 2002; Taylor et al., 2000). From the biological perspective, a more rapid HPA axis response with a greater output of steroid hormones is observed in females (Goel et al., 2014).

It should be noted that there are several methodological issues that should be considered in the analysis of effects of sex on the impact of childhood trauma. First of all, usually a smaller number of men than women reach criteria for both psychosis and sexual abuse, so studies may be underpowered to detect significant associations in males. Moreover, it has been shown that childhood trauma is related to suicide and aggressive behaviors, thus male subjects might be underrepresented in the studied populations due to either death or imprisonment (Barker-Collo and Read, 2011).

8. Future directions and conclusions

Although a history of childhood trauma has been associated with higher risk of psychosis, it is neither sufficient nor necessary to trigger the onset of psychosis. This observation points to an important question about factors contributing to stress resiliency. It should be noted that neither of studies have investigated, which attachment styles and stress coping strategies are being adopted by patients with psychosis and a history of childhood trauma. Another point limiting our understanding of the relationship between early-life stress and psychosis originates from observations that childhood adversities might contribute to the development of a broader spectrum of mental disorders (MacMillan et al., 2001). To make things more complex, biological consequences of childhood trauma are not specific for psychosis and have been reported in other mental disorders. It has been demonstrated that genetic factors may interact with childhood adversities influencing the risk of psychosis. Given that G × E interactions are increasingly being recognized as a putative explanation of the relationship between childhood trauma and psychosis, future studies should disentangle whether epigenetic dysregulation observed in psychosis might be attributed to early-life stress. Taking into account non-specific biological consequences of childhood adversities in psychosis, differentiating trajectories leading from childhood trauma to distinct lifetime psychopathologies still remains a far research goal in the field. Emerging studies have tried to address this point by investigating childhood trauma in a broader context of environmental insults, such as low socioeconomic status, substance use disorders and urbanicity. This approach has initiated more integrated insight that aimed to develop biopsychosocial models of childhood trauma and a unified theory behind the link between childhood adversities and psychosis (Barker et al., 2015).

Apart from etiological considerations, psychosis with positive history of childhood trauma is being increasingly recognized as the clinical construct crossing traditional diagnostic boundaries that might be perceived as a distinct psychiatric phenotype. Indeed, above mentioned studies have provided evidence that patients with psychosis and childhood trauma might be characterized by more severe clinical manifestation, especially in terms of psychotic symptoms, and biological alterations. In addition, several studies have suggested that patients exposed to childhood adversities might have poor prognosis in terms of functional outcomes. However, it remains unknown whether a positive history of childhood trauma might impact the efficacy of pharmacological treatment in psychosis. Therefore, future studies should focus on the relevance of childhood trauma with respect to clinical outcomes.

A history of childhood trauma in patients with psychosis might be also important to tailor treatment strategies aimed at reducing sensitivity to stress in daily life. Therefore, future studies should evaluate the efficacy of stress reduction strategies including i.e. self-relaxation techniques (Hodel et al., 1998), adaptation of cognitive behavioral therapy to remediate stress sensitivity (Birchwood and Trower, 2006) or mindfulness-based interventions (Shonin et al., 2014) as add-on therapeutic approaches in psychosis. Moreover, it should be noted that coercive measures that are frequently used in compulsory hospitalizations, may cause further trauma in sensitized patients and thus contribute to less favorable treatment response and outcome.

Conflict of interest

None to declare.

Contributors

Introduction: B.M., M.K., epidemiological findings: B.M., clinical manifestation and outcome: B.M., D.F., psychological mechanisms linking childhood trauma and psychosis: D.F., T.B., A.A.M., biological correlates of childhood trauma: B.M., D.F., M.M.S., neural substrates: B.M., effects of sex differences in studies on childhood trauma: B.M., future directions and conclusions B.M., D.F., manuscript editing: A.A.M.

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