R E V I E W

The Impact of Childhood Trauma on Developing Bipolar Disorder: Current Understanding and Ensuring Continued Progress

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Abstract: Childhood trauma (CT) has been repeatedly linked to earlier onset and greater severity of bipolar disorder (BD) in adulthood. However, such knowledge is mostly based on retrospective and cross-sectional studies in adults with BD. The first objective of this selective review is to characterize the short-term effects of CT in the development of BD by focusing on studies in young people. The second objective is to describe the longer-term consequences of CT by considering studies with adult participants. This review first outlines the most prominent hypotheses linking CT exposure and the onset of BD. Then, it summarizes the psychological and biological risk factors implicated in the development of BD, followed by a discussion of original studies that investigated the role of CT in young people with early-onset BD, youths at increased risk of developing BD, or young people with BD with a focus on subclinical and clinical outcome measures. The review considers additional biological and psychological factors associated with a negative impact of CT on the long-term course of BD in later adulthood. Finally, we discuss how the integration of information of CT can improve ongoing early identification of BD and mitigate severe clinical expression in later adulthood.

Keywords: bipolar disorder, childhood trauma, vulnerability, early onset, peripheral blood marker, brain

Introduction
Bipolar Disorder

Bipolar disorder (BD) is a mood disorder associated with unusual shifts in mood, activity levels, concentration and the ability to carry out day-to-day tasks.[1] These changes in mood include manic and depressive episodes, interspersed between euthymic periods. Manic episodes are characterized by elevated irritability and goal-directed impulsivity, while euphoric behaviors can resemble psychotic symptoms, such as delusions and hallucinations.[2] Delusions can also occur in around a third of individuals in acute bipolar manic episodes.[3] In contrast to manic episodes, depressive symptoms include exacerbated negativity and sadness, and periods of hopelessness. BD affects approximately 1% of the global population and can lead to long-term psychological, cognitive and physical impairments. This results in high economic and social burdens on the community.[4] Consistent with mental health conditions on the mood-psychosis spectrum, the development of BD is thought to largely result from the interactions between genetic and environmental risk factors, in particular exposure to childhood trauma (CT).[5]

Prevalence of Childhood Trauma in Bipolar Disorder

CT is a form of chronic stress usually in the form of emotional or physical abuse, neglect or sexual abuse (https://apps.who.int/violence-info/child-maltreatment); abusive behaviors can also include bullying or familial dysfunctions. Prevalence of CT exposure is often under-reported but is likely to lie between 25% (as reported in the UK)[6] and 40% (as reported in the USA)[7] or even 50% in individuals with psychotic disorders.[8,9] Other studies proposed that individuals with BD are 2.63 times more likely to report CT compared to healthy individuals (approximately 2.72 times for individuals with psychosis[10,11]). Additionally, individuals with BD exposed to CT are 1.85 times more likely to experience their first episode earlier,[12–14] show increased rapid cycling[15–18] and more severe forms of the disorder[10,19–23] compared to those who did not experience CT.

Childhood Trauma and Co-Existing Health Conditions

Exposure to CT has been associated with an increased risk of developing mental and physical health conditions later in life. A recent systematic review of meta-analyses concluded that exposure to childhood sexual abuse was associated with a wide range of psychosocial and health outcomes.[24] Similar findings have been reported for exposure to other traumatic events.[25]

Mental Health Conditions

CT is associated with increased odds of developing any stress-sensitive psychiatric disorder, including mood, anxiety and addiction disorders.[25–27] Interestingly, this association holds whether it is assessed retrospectively or prospectively.[26] Other meta-analyses have shown a high prevalence of CT among individuals with psychotic disorders,[10,28] with CT also being linked to the occurrence, as well as persistence, of subclinical psychotic experiences in healthy people.[29–31] CT has also been found to predict transition from ultra-high risk for psychosis to overt psychosis.[32,33] Even though some studies have shown that different subtypes of CT could increase the risk of developing different types of psychiatric conditions (eg-[34,35]), these findings remain mixed and other factors of frequency, severity, or timing of CT may rather be playing a role in this regard.[36] In addition, a recent meta-analysis of 13 independent studies suggests that exposure to CT is associated with an increased risk of suicidal behavior in individuals with BD[37]. In particular, individuals with BD who attempted suicide reported being exposed to CT more frequently than those who were not exposed, in particular when exposed to emotional abuse or sexual abuse (both Hedges' g = −0.39).

Physical Health Conditions

Exposure to CT can have detrimental effects on physical health in adulthood. Convergent evidence shows that CT is associated with higher risk of developing several chronic medical conditions, including chronic obstructive pulmonary disease, frequent headaches, autoimmune disorders, obesity, smoking, cardiac disease and sleep disturbance.[38] The strength of this association varies depending on the disease[27]; it is weak or modest for physical inactivity, overweight or obesity, and diabetes (odd ratios < 2); moderate for smoking, heavy alcohol use, poor self-rated health, cancer, heart disease, and respiratory disease (odd ratios 2–3).[27] These findings have been replicated across the world[39–42] and a causal link between these outcomes and CT has been established.[43]

Difficulties of Current Prediction Efforts at the Onset of Psychosis

The phenotypic heterogeneity observed in BD makes any prediction of the long-term outcomes following the first episode of BD very difficult. This has important implications for the choice of the most effective treatments and strategies to adopt. A recent review provided evidence for more reliable tools for optimized identification, including novel machine learning methods (eg, neural networks and support vector machine), imaging methods (eg, new radio-ligands), and biological markers (eg, genetics and other "omics" approaches).[44] Most studies have investigated these modalities separately, but the emergence of big data-sets and new methodological advances allow multimodal investigation of finer phenotypic features with better power to detect smaller effects and capture complex inter-actions. To ease the economic and time burden associated with the recruitment and management of new studies, large-scale consortia have emerged and provide disorder-specific frameworks, such as the BD working group of the Enhanced NeuroImaging Genetics through Meta-analysis (ENIGMA) consortium[45] and the Psychiatric Genomics Consortium (PGC).[46] These consortia are still in their early stages, but represent promising avenues to increase our understanding of the development of severe psychiatric disorders, such as BD.

The present narrative review aims to summarize the current understanding of the short-term impact of CT exposure on the development of BD as well as the long-term clinical, cognitive and neurobiological consequences of CT on individuals with BD. The relevant literature was reviewed until August 1st, 2020, using the search terms [("child* abuse" OR "child* neglect" OR "child* trauma" OR "early abuse" OR "early trauma" OR "early neglect" OR "sexual abuse" OR "physical abuse" OR "emotional abuse" OR "family conflict" OR "childhood adversity" OR "early life stress") AND ("bipolar" OR "mania" OR "manic" OR "hypomania" OR "hypomanic" OR "cyclothymia" OR "cyclothymic" OR "manic depress*")] in Pubmed.

Childhood Trauma and Development of Bipolar Disorder

The onset of BD typically occurs in adolescence or early adulthood following subclinical symptoms,[47,48] likely due to the biological, psychological and social development youths experience, which culminate at approximately 16 to 30 years.[49] The identification of young people who are at an increased risk of developing BD is challenging. One obstacle is to define transdiagnostic risk markers related to the experience of CT as well as BD-specific markers.[50–52] Therefore, new research should investigate how CT may interact with other known risk factors or how it may mediate the risk of developing BD.

A plethora of studies provided evidence that CT plays a crucial role in the development of major mental health conditions, in addition to other environmental factors such as cannabis misuse and genetic risk markers.[53–58] The mechanistic processes leading from CT to the development of mental health problems remain unclear, although some genetic and psychological risk factors have been identified.[48,59,60] Most studies examined the relationship between the occurrence of CT and clinical characteristics of BD, including illness onset and chronicity in adulthood, with the majority using cross-sectional designs.[11] To better understand the role of CT as a risk factor for the development of BD, both cross-sectional and longitudinal studies have included young people who have experienced CT and show BD symptoms or who are at an increased risk of developing BD. Therefore, a developmental perspective is needed to better understand the onset of BD and to optimize early identification in young people. Here, we briefly summarize the most prominent vulnerability and neurodevelopmental hypotheses.

Theories from a Developmental and Vulnerability Perspective
Diathesis-Stress Model
The diathesis-stress model is the most widely accepted theory to explain why some young people with certain psychological (such as behavioral or cognitive problems) and biological risk factors (such as genetic variants) are more likely to be negatively affected by later environmental stressors, such as CT.[61] According to this theory, existing vulnerabilities interact with the later experience of CT, which increases the likelihood of developing a mental health condition.[61] The more risk factors a young person carries, the more likely this individual may develop a mental health condition. For example, individuals who carry genetic risk variants are considered to be more vulnerable - or at high genetic risk - of developing BD after the experience of CT than without such experience. Increased familial risk or early emotional difficulties[48,62,63] in young people are also considered to be a predisposition toward developing BD.

In the last few years, this vulnerability stress model has been refined for the onset of schizophrenia (SZ) to encompass neural processes[64–66], and is also accepted and used in the wider psychosis field, including for individuals with BD.[67] In comparison to the original model, this revised vulnerability stress model proposes that CT triggers the activation of the hypothalamic-pituitary-adrenal (HPA) axis, influencing stress-sensitive neural processes linked to behavioral or cognitive deficits in BD and psychosis.[67]

Differential Susceptibility Model
The differential susceptibility model builds on the diathesis-stress model. Susceptibility is seen as the inhibition of the typically present potential for plastic adaptation after the experience of CT as part of the diathesis-stress model.[68] The differential susceptibility model proposes that more susceptible individuals perform poorly in highly stressful or triggering environments. However, these individuals perform better in positive and supportive environments when compared to less susceptible individuals.[69,70] According to this model, "differential susceptibility" describes the ability of an individual to positively adapt one's behavior to supportive environmental conditions following aversive experiences.[68–70] Therefore, this model provides theoretical foundations for preventative

interventions to support and enhance young people's resilience.

Stress Sensitization Hypothesis

The stress sensitization hypothesis posits that the interaction between genetic risk factors and environmental stressful events may lead to atypical brain development and ultimately mental health conditions. The occurrence of CT may intensify already existing neurodevelopmental consequences of pre- and perinatal insults that may adversely affect the development of neural networks, in particular during sensitive time windows of neurodevelopment. In a revised model, Holtzman et al. proposed a detailed stress sensitization hypothesis, which integrates the notions of stress sensitization during childhood, as posited by the original model, with sensitive neurodevelopmental stages.[67] It has been suggested that psychosis, or BD, may develop when CT disrupts typical developmental steps on genetic, molecular, neural, endocrine or epigenetic levels. It could be that the development of BD may follow similar pathways given the overlap of genetic and environmental risk factors, including the experience of CT.

Risk Factors for the Development of Bipolar Disorder

Risk factors for developing BD have been refined over the years and cover a range of biological, psychological and environmental markers.[62,71] Here, we emphasize biological and psychological risk factors that are linked to CT, namely: emotional difficulties, cognitive deficits, altered neural function, altered circadian neuroendocrine, and immune response markers. It is worth noting that these factors can also be observed in other mental health conditions and may therefore reflect transdiagnostic markers of CT exposure. Risk mechanisms that may determine who develops BD or another mental health condition are not yet fully understood. However, evidence for CT as a risk factor has emerged.

Offspring of parents with a diagnosis of a psychiatric disorder, such as BD, SZ or major depressive disorder (MDD), have been identified to be at enhanced risk of developing BD due to increased genetic or familial risk.[62] Similarly, the experience of abuse and neglect is positively related to the occurrence and severity of prodromal symptoms in individuals with chronic BD[72] or emotional problems of subclinical depressive or anxiety-related symptoms.[62] The likelihood of developing BD may be further increased when familial or genetic vulnerability is combined with the exposure to CT. For example, Post et al. reported that such combined risk was significantly associated with an earlier illness onset of BD.[73.]

Further evidence of detrimental effects on clinical characterics has been revealed in the form of higher cognitive and social cognitive deficits,[74] altered brain structural measures, perturbed brain activity and network connectivity (see the *Childhood Trauma in Adults with Bipolar Disorder* section below) as well as greater prevalence of co-existing mental health conditions. In addition, emerging evidence suggests that endocrine, immune or genetic dysfunctions are related to the severity of BD and a history of CT, which may also be linked to the greater prevalence of physical health conditions. While these studies provide valuable insight into risk factors related to increased vulnerability to developing BD, they also examined these risk factors in adult individuals with BD; sometimes up to 25–30 years after the onset of the disorder. Thus, it is crucial to better understand the development of BD at different developmental stages (in children, youths and young adults) in order to optimize current identification and prediction efforts.

Findings from Children, Youths and Young Adults
Cross-Sectional Studies

A growing number of studies are emerging that focus on elucidating susceptibility markers for BD in young people. In particular, three populations have been targeted: children and youths with early-onset BD, youths and young adults at high risk of developing BD, and youths and young adults with BD.

Children and Youths with Early-Onset BD: Four studies in children and youths with early-onset BD focused on associations between CT, in particular physical and sexual abuse, and clinical characteristics[75–78] (Table 1). Consistently among these studies, children and youths with early-onset BD were exposed to greater frequency and severity of CT than children and youths without any mental health condition. This finding was interpreted as supporting evidence of CT being one of the risk factors for the early onset of BD. Furthermore, three of these studies reported significant positive associations between increased CT levels and greater severity of depressive and anxiety symptoms, emotional difficulties as well as suicidal thoughts and behaviors. In contrast, one study did not find

Table 1 Study Characteristics – Cross-Sectional Studies in Young People

Study	High Risk Individuals – (Young) Individuals with BD				Risk Markers		CT Assessment	Clinical Characteristic	Main Findings
	n	Age Mean (SD)	% Females	Illness Phase	Marker	n (%)			
Children and youths with early-onset BD									
78	446 BD	12.7 (3.2)	BD (abuse): 50 BD (no abuse): 48.9	EO	• CT • First-degree relatives with mood disorder	• CT: 92 (20) • Relatives: 308 (69)	KSADS (physical abuse and sexual abuse)	• Duration of BD • Severity of symptoms • Co-existing mental health conditions	• Increased likelihood of lifetime history of PTSD, psychosis, conduct disorder after the exposure to any abuse • Increased likelihood of longer duration of BD, PTSD and psychosis corrected for confounders after history of physical abuse • Increased likelihood of PTSD after experience of sexual abuse
77	152 BD	10.9 (3.4[a])	~40[a]	EO	CT	(11)	KSADS-PL -PLUS (Physical and sexual abuse)	• Severity of symptoms • Frequency and severity of subclinical symptoms • More frequent episodes • More hospitalizations • Co-existing mental health conditions	• Significant associations between physical abuse and greater severity of clinical and subclinical symptoms. • Greater likelihood of co-existing mental health conditions after the experience of physical abuse. • Significant associations between sexual abuse and greater severity of clinical and subclinical symptoms, more frequent episodes, more hospitalizations and more co-existing mental health conditions.
76	81 BD	15.70 (1.89)	57	EO	• CT	47 (58)	ACE scale	• Duration of episode • Duration of hospitalization • Severity of symptoms • Global functioning • Treatment outcome	• No significant differences of more severe symptomatology or greater severity than those without CT experience
75	59 BD	13.76 (3.12)	51	EO	CT	Mean not reported (64.4)	CTQ	• Symptoms of irritability, aggressive and suicidal behaviors	• Significant effect of physical abuse on suicidal thoughts and behaviours in females. • Significant effect of CT on irritability in males. • Significant relationship between emotional and sexual abuse and aggressive behaviors in males.

(Continued)

Table 1 (Continued).

Study	High Risk Individuals – (Young) Individuals with BD				Risk Markers		CT Assessment	Clinical Characteristic	Main Findings
	n	Age Mean (SD)	% Females	Illness Phase	Marker	n (%)			
Youths with prodromal symptoms									
79	108 BD[b]	16.8 (3.3)	56.5	Prodromal symptoms	• Clinical risk • Family history of mental illness	• 84 (78) • 34 (31)	Childhood Trauma and Abuse scale (adapted)	Attenuated symptoms	• Significantly greater frequency and severity of physical abuse in BD.
Young adults with BD									
80	52 BD	21.7 (2.2)	74	Not reported[a]	• CT • Family history of mood disorder	• CT: 28 (53.9) • Relatives: Not reported	CTQ	• Severity of symptoms	• Significant positive association between CT and increased family history of mood disorders and more distant relatives. • Mediation effect of CT on relationship between family history of BD and diagnosis of BD
81	90 BD	25.78 (2.11)	73.3	Not reported[a]	Family history of mood disorder	63 (69.7)	CTQ	• Severity of symptoms	• Significant positive association between all subtypes of CT with severity of BD.[c] • Physical and emotional abuse differentiated individuals with BD from MDD

Notes: [a]Only reported for all included individuals. [b] Past or current history of manic episode. [c] Findings reported based on one-way ANOVAs with healthy controls, non-help seeking individuals and individuals with mild anxiety and depression symptoms.

Abbreviations: ACE, Adverse Childhood Experiences Scale; BD, individuals with bipolar disorder; CT, childhood trauma; CTQ, Childhood Trauma Questionnaire; EO, early-onset BD; FE, first episode; HR, individuals at high risk; KSADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SD, standard deviation.

any significant differences in greater symptomatology, longer duration of episodes or hospitalizations between young people with a history of CT and without such history.[76] Two out of the four studies also reported a negative impact of physical and sexual abuse on longer duration of BD episodes and co-existing mental health conditions,[78] number of hospitalizations and severity of subclinical symptoms before the first manic or depressive episode.[77] In summary, three of the four studies suggest that children and youths with early-onset BD suffer from more severe symptomatology after the experience of CT than without such a history. Overall, the findings in young people converge to suggest a detrimental effect of CT on clinical characteristics as shown in adult studies.[77,78]

Youths and Young Adults at High Risk of Developing BD: Stowkowy et al. presented findings based on youths at increased risk of developing BD defined as having a family history of mental illness[79] (Table 1). In this study, young individuals at high familial risk showed significantly greater frequency and severity of physical abuse when compared to healthy controls, non-help seeking individuals and individuals with mild subclinical depression and anxiety symptoms. These youths also displayed a greater severity of prodromal symptoms of BD in comparison to the other three groups. These findings support the notion of increased risk for CT and BD in people with a family history of mental illness. Due to the cross-sectional nature of this study, causal inferences or temporal dependencies between familial and clinical risks could not be tested.

Youths and Young Adults with BD: Two studies included young people with a clinical diagnosis of BD and studied the link between family history of mood disorders and experience of CT[80,81] (Table 1). The findings of both studies are consistent with cross-sectional studies showing greater severity of symptoms being associated with higher levels of CT exposure in adults. Beyond these relationships, CT mediates the relationship between family history and diagnosis of BD,[80] providing novel insights into a combined risk of family history with a history of CT. Vieira et al. differentiated young adults with BD from young adults with MDD based on the experience of greater levels of physical and emotional abuse in young adults with BD compared to MDD.[81]

These emerging cross-sectional studies are in keeping with findings from cross-sectional and retrospective adult studies supporting the role of CT as a risk factor with short-term effects, such as earlier age at illness onset as well as greater severity of prodromal and clinical symptoms. In addition, a negative impact on typically assessed clinical characteristics in adult studies has been replicated. Due to the cross-sectional nature of these studies, no interpretations of potentially longer-term effects on clinical markers in young people with BD can be made. Nonetheless, in a preliminary summary based on two studies that investigated two risk markers at the same time,[79,80] findings are in favor of the stress-diathesis model suggesting that the experience of CT, family history of mood disorders and prodromal symptoms serve as markers of increased vulnerability to developing BD across a range of clinical characteristics. Future studies utilizing moderation and mediation analyses among at least two potential risk factors may result in support for the diathesis-stress model or the differential susceptibility model. Given the lack of neurodevelopmental or hormonal markers in the only study examining clinical high risk,[79] we cannot comment on whether these findings suggest that neurodevelopmental markers may reflect early markers for BD.

Longitudinal Studies

It is thought that exposure to CT enhances the risk of developing BD as proposed by two longitudinal studies based on population and registry-based studies.[79] These studies reported an increased risk of earlier onset of BD after parental loss during early childhood,[82] and an enhanced risk of experiencing the first onset of mania following the occurrence of physical neglect or sexual abuse.[83] Further support for the effect of CT during development on functional outcome in adults with first-episode psychosis and BD has been presented by several studies.[84,85] Specifically, physical and sexual abuse has a devastating long-term effect, in addition to short-term consequences of greater severity of subclinical symptoms.[85] In contrast, another study in adults with BD did not find a significant relationship between sexual trauma and either of the used chronicity measures of duration of illness or severity of symptoms.[86] However, the authors showed an increased probability of poor long-term outcome based on childhood family problems, which encompassed family history of mood disorder. These studies in adults with BD and psychosis suggest that CT may have detrimental effects on long-term functional outcome. Greater insight into potentially similar long-lasting effects in young

people is needed for early identification and intervention before consequences may occur and manifest.

Children and Youths with Early-Onset BD:
Two early-onset studies[87,88] (Table 2) reported significant associations of CT with poor functioning, greater symptom severity[87] and a greater likelihood of co-existing mental health conditions,[88] which resemble findings in adult studies. In a preliminary summary based on this small number of studies, it is still warranted that these children and youths will need to be followed up for a longer period of time to gain greater insight. In particular, these youths are still under the age of 18 years and will likely benefit from follow-up assessment and treatment. It will be crucial to support these particularly vulnerable children and youths over the course of years based on the known chronicity of early-onset outcomes.[48,62]

Youths and Young Adults at High Risk of Developing BD:
Two recent studies included youths and young adults at high risk of developing BD or followed up a student sample[89,90] (Table 2). Emotional maltreatment was associated with an earlier age at illness onset in young people at high familial risk.[89] Furthermore, emotional abuse was associated with more severe depressive symptoms in young adult females with BD symptoms.[90] These findings are difficult to interpret in the context of longitudinal outcome given that the outcome measures are the same as used for the cross-sectional studies (ie, age at onset and severity of symptoms), and may reflect rather short-term or medium-term outcome measures given the short follow-up duration.

In a preliminary summary based on four studies, only little support for a role of CT on a longitudinal course of BD has been presented. This discrepancy with the adult longitudinal studies may be two-fold. Firstly, despite the long durations of follow-up assessments in some of the longitudinal studies, the long-term effect may not have yet manifested since the last follow-up assessment occurred still during young adulthood. Secondly, we speculate whether the regular follow-up assessments may have had a positive effect on these young people. For future studies, we suggest to use the long-term outcome measure of general functioning or functional outcome, as a proxy for social functioning[91,92] as an established outcome measure in adult major mental health conditions, including BD. Additionally, the use of general functioning as an outcome measure allows the differentiation between short-term and long-term outcome measures. Longer durations of follow-up study visits beyond the known time windows of being at risk of developing BD are necessary for greater insight.

Childhood Trauma in Adults with Bipolar Disorder

Given the scarcity of available longitudinal studies in young people, we provide a summary of how the experience of CT may impact on clinical, cognitive, neural and biological characteristics in adults with first-episode or chronic BD. Such knowledge is pivotal to emphasize the importance of early identification and intervention in high-risk individuals *before* the transition to BD and the potentially negative effects on reduced quality of life. Here, we review the most widely studied associations between CT and outcome measures of i) mood and psychotic symptoms, ii) cognitive functions, iii) brain alterations and iv) peripheral biological markers.

Childhood Trauma and Mood and Psychotic Symptoms

The occurrence of CT has been linked to more severe clinical expression of mood symptoms in individuals with BD. A recent meta-analysis found that individuals with BD who have a history of CT reported significantly greater severity of both depressive and manic symptoms compared to BD participants who did not experience trauma in childhood.[12]

Regarding psychotic symptoms, the relationship between CT and psychotic symptom severity (eg, positive symptoms) is more complex. Here, we provide an overview of recent studies that have examined these relationships and compare the strength of the relationship between CT history and psychotic symptom severity. To gain a better understanding, we differentiated the correlational findings by relationships (bivariate and partial) between the experience of CT (total score and subtypes of CT) and psychotic symptom severity (positive symptoms and negative symptoms) in contrast to previously reviewed studies of relationships between the occurrence of CT and general psychotic symptom severity (Table 3).

Five studies[93–97] reported findings on the association between the frequency of CT and positive symptom severity (Table 4). An additional study focused on severity of delusions[98] in a large BD sample. Different CT scores were used across studies, ranging from a total CT score[93,95–97] to scores for subtypes of CT (for example, physical neglect).[93–97]

Table 2 Study Characteristics - Longitudinal Studies in Young People

Study	High Risk Individuals – (Young) Individuals with BD				High Risk Markers		CT Assessment	Clinical Characteristic	Main Findings
	n	Age Mean (SD)	% Females	Illness Phase	Marker	n (%)			
Children and youths with early-onset BD									
87	367 BD	12.6[a]	47	EO	• CT • Family history of mood disorder	• 71 (19) • 207 (56)	KSADS (physical abuse and sexual abuse)	• Severity of symptoms • Global functioning • Treatment outcome	• 4 years follow-up time; on average interviewed 10 times over period of 93 months • CT was significantly related to poorer longitudinal course, family history, earlier onset of first episode and more severe depressive symptoms, including subclinical symptoms at baseline.
88	375 BD	CT/ Traumatic events 16.7 (3.8) No CT/ Traumatic events 18.3 (3.5)	CT 45.3 No CT 54.2	EO	• CT/ Traumatic events • Family history of BD	• 316 (84) • 59 (16)	• Traumatic Events Screen • KSADS (physical abuse and sexual abuse)	• Severity of symptoms (subclinical and clinical) • Age of onset • Global functioning • Treatment outcome	• 9 years follow-up time; on average assessed every 7 months • BD with CT/Traumatic events history showed significantly earlier age of onset, more reduced functioning and reduced mood symptoms. • Significant relationships between physical abuse/sexual abuse and earlier age of onset and enhanced likelihood of co-existing mental illnesses. • Longitudinally, BD with history of abuse displayed poorer mood symptoms (in particular hypomanic and manic symptoms) compared to BD without such a history.
Youths and young adults at high risk of developing BD									
89	102	16.0 (2.7)	46.3	48 HR 54 Mood disorder	Family history of BD	102 (100)	CTQ (short form)	• Age of onset	• 12 years follow-up time; assessed at 1, 5 and 12 years • Significant association between emotional maltreatment with earlier age of onset.

(*Continued*)

Table 2 (Continued).

Study	High Risk Individuals – (Young) Individuals with BD				High Risk Markers			CT Assessment	Clinical Characteristic	Main Findings
	n	Age Mean (SD)	% Females	Illness Phase	Marker	n (%)				
[90]	134	24.64 (4.08)	64	HC[b]	CT	• Emotional abuse: 15 (11) • Physical abuse: 12 (9) • Sexual abuse: 13 (10)		3 general questions covering emotional abuse, physical abuse and sexual abuse	• Severity of symptoms (subclinical and clinical)	• 5 years follow-up time; assessed at 5 times • Significant relationship between abuse, in particular emotional abuse, and more severe depressive symptoms in females • No significant associations between abuse and hypomanic or manic symptoms

Note: [a] SD not reported for overall group; [b] Based on population sample.
Abbreviations: BD, individuals with bipolar disorder; CHR, chronic stage; CT, childhood trauma; CTQ, Childhood Trauma Questionnaire; EO, early-onset BD; HC, healthy controls; HR, individuals at high risk; KSADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version; PTSD, post-traumatic stress disorder; SD, standard deviation.

None of the five studies reported a significant correlation with total CT scores in individuals with first-episode or chronic BD. However, increased severity of delusions was associated with increased total CT scores.[98] In contrast, when specific CT subtypes were considered, significant positive correlations were observed with i) physical abuse[94,97] ii) emotional abuse[94,96] iii) physical neglect[94] and iv) emotional neglect[96,97] in individuals with first-episode and chronic BD. Importantly, both significant findings by Garcia et al. were for females only.[96]

Four studies reported correlational findings on the relationship between total CT score, or on at least one subtype of CT, and severity of negative symptoms[93,95–97] (Table 5). These studies found weak correlations with only one reaching statistical significance in individuals with first-episode BD.[96] In this study, higher levels of both physical neglect and emotional neglect were associated with greater severity of negative symptoms in females with psychosis.[96] This association with neglect subtypes of CT provides support for a proposed "neglect-negative symptom" link, albeit this is based on female participants in this one study.[99] Total CT scores were not associated with negative symptom severity in any of these studies.

Overall, meta-analytic evidence demonstrates an increased risk of psychosis severity among people with BD that have experienced CT compared to those who did not.[12] While evidence for this relationship has been presented, this association is likely more complex when specific trauma and/or psychotic symptoms are taken into account[100] as can be observed from i) inconsistent findings, ii) heterogeneous diagnostic samples and iii) the use of different measures of CT. In summary, findings support the hypothesis of a relationship with positive symptomatology, particularly when examining specific positive symptoms (eg, delusions).

Childhood Trauma and Cognition

In addition to being associated with a more severe clinical presentation of the disorder, CT also impacts cognitive performance in BD and psychosis.[74,101] In particular, childhood physical neglect improves moral decision-making in adult life,[102] while emotional and sexual abuse is associated with deficits in verbal and visual recall memory, verbal fluency and cognitive flexibility.[103,104] Overall trauma exposure, independent of the type of trauma, was also associated with poorer inhibitory control.[105] Similarly, data-driven cognitive clustering studies found that CT exposure was a significant predictor of poor cognitive

Table 3 Overview of Study Characteristics – Associations Between Childhood Trauma and General Psychotic Symptom Severity in Adults

Study	Diagnosis (n)	Bipolar Disorder Group			Healthy Control Group			Psychosis Assessment	Phase of Illness
		n	Age Mean (SD)	% Females	n	Age Mean (SD)	% Females		
[93]	SZ (30), BD (17), HC (41)	17	Not reported	Not reported	41	38.3 (14.4)	44%	PANSS	Chronic
[166]	BD I (192), BD II (78)	270	43 (12.5)	61%	NA	NA	NA	PDI	Not Reported
[95]	FEP (75); SZ (26), SZ-P (20), SZ-A (3). PD NOS (13), BD I (5), MDD w/P (3), Brief PD (3), DD (1), Substance-induced PD (1)	5	Not reported	Not reported	51	26.9 (5.6)	33%	BPRS, SANS	FEP
[94]	BD I (59), BD II (34), BD NOS (5); SZ (90), SZ-P (19), SZ-A (23), Other PD (31)	98	31.4 (11.5)	63%	NA	NA	NA	PANSS	Not Reported
[97]	SZ (30), SZ-P (3), SZ-A (7), Other PD (17), BD I (33), BD II (2), BD NOS (2), MDD w/P (2)	34	Not reported	Not reported	264	30.1 (7.9)	44%	PANSS	FEP
[96]	SZ-P, SZ, BD, MDD w/P, Other PD[a]	Not reported	Not reported	Not reported	58	23.95 (4.5)	48%	PANSS	FEP

Note: [a] Participant sample size not reported.
Abbreviations: BPRS; Brief Psychiatric Rating Scale; BD, bipolar affective disorder; BD I, bipolar affective disorder type 1; BD II, bipolar affective disorder type 2; DD, delusional disorder; FEP, first episode psychosis; HC, healthy control; MDD, major depressive disorder; NA, not applicable; NOS, not otherwise specified; PANSS, Positive and Negative Symptoms Scale; PD, psychotic disorder; PDI, Peters Delusions Inventory; SANS, Scale for the Assessment of Negative Symptom; SD, standard deviation; SI-P, substance-induced psychosis; SZ, schizophrenia; SZ-A, schizoaffective disorder; SZ-P, schizophreniform disorder; w/P, with psychotic features.

performance.[106,107] These results are in contrast with other studies reporting no significant impact of trauma on cognitive performance.[93,108–110] One reason may include the confounding effects of IQ levels,[111] which are sensitive to CT exposure.[103,112]

Social cognitive skills are also affected by the experience of CT.[113] Females with BD exposed to emotional abuse performed better than trauma-exposed males to an emotional decision-making task and scored higher than abused males to an affective go/no-go task.[114] Independent of sex, individuals with BD exposed to physical abuse, emotional neglect and/or physical neglect performed worse when identifying anger compared to non-exposed individuals. Furthermore, individuals exposed to emotional neglect also showed worse recognition of angry faces compared to those who were not exposed.[115] This was in contrast to two other studies that did not find an effect of CT exposure on emotion processing or memory performance in individuals with BD,[115,116] but rather reported trauma-related deficits in the performance of a complex

Theory of Mind task.[108] Finally, sensory processing is often impaired during emotion processing in affective disorders, but not in individuals with BD exposed to CT.[117]

Childhood Trauma and Brain Alterations

Magnetic resonance imaging (MRI) studies aimed to identify the neural correlates of CT exposure in individuals with BD. However, results have been inconsistent, in part due to methodological differences. Increasing overall severity of CT exposure has been associated with decreased volume of the corpus callosum,[118] the amygdala,[119] the right dorsolateral prefrontal cortex (DLPFC) and the right thalamus[120] in individuals with BD. Some of these effects have been reported to be driven by subtypes of CT, especially levels of neglect (emotional or physical).[119,120]

When comparing groups of individuals exposed versus non-exposed to CT, decreased hippocampal and amygdalar volumes were associated with a diagnosis of bipolar-I and bipolar-II disorders rather than an effect of CT exposure.[121] Interestingly, the same authors suggested that trauma exposure

Table 4 Associations Between Childhood Trauma and Positive Psychotic Symptom Severity in Adults

Study	Diagnosis (n)	Clinical symptom	Severity of Positive Symptoms Associated with Childhood Trauma Severity						Analysis
			SA	PA	EA	PN	EN	Total CT score	
93	47	Positive	NA	NA	NA	NA	NA	0.011	Pearson
166	BD I (192), BD II (78), HC (NA)	Delusions	0.15[a]	0.24[c]	0.28[c]	0.08	0.1	0.21[b]	Spearman
95	BD-I (5), HC (51)	Positive	NA	NA	NA	NA	NA	0.021 (SSD; $n = 49$); 0.06 (Other Psychosis; $n = 26$)	Spearman
94	BD I (59), BD II (34), NOS (5), BD w/P (42), BD (98)	Positive	0.09	0.14[a]	0.23[c]	0.20[c]	0.12	NA	Spearman
97	BD I (33), BD II (2), BD NOS (2), HC (264)	Positive	0.02	0.27[b]	0.13	0.11	0.25[b]	0.16	Spearman
96	PD (79), HC (58)	Positive	0.25 (Male) 0.20 (Female)	0.13 (Male) 0.15 (Female)	0.13 (Male) 0.47[b] (Female)	−0.08 (Male) 0.27 (Female)	0.06 (Male) 0.50[b] (Female)	0.05 (Male) 0.43 (Female)	Spearman

Note: [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$.
Abbreviations: BD, bipolar affective disorder; BD I, bipolar affective disorder type 1; BD II, bipolar affective disorder type 2; CT, childhood trauma; EA, emotional abuse; EN, emotional neglect; HC, healthy control; NA, not applicable; NOS, not otherwise specified; PA, physical abuse; PD, psychotic disorder; PN, physical neglect; SA, sexual abuse; SSD, schizophrenia spectrum disorder.

may impact the morphology of subfields of the hippocampus rather than the overall structure: compared to individuals not exposed to CT, the bilateral cornus ammonis 1 (CA1), pre-subiculum and subiculum volumes were larger in individuals with BD exposed to CT. This was in the context of smaller volumes of these subfields in healthy individuals exposed to trauma when compared to their non-exposed counterparts.[122] Another study proposed that CT exposure could act as a potential moderator of the effects of BD on the brain.[123] In particular, in individuals exposed to CT, reduced volumes of

Table 5 Associations Between Childhood Trauma and Negative Psychotic Symptom Severity in Adults

Study	Diagnosis (n)	Clinical Symptom	Severity of Negative Symptoms Associated with Childhood Trauma Severity						Analysis
			SA	PA	EA	PN	EN	Total CT Score	
93	SZ (30) BD NOS (17)	Negative	NA	NA	NA	NA	NA	0.05	Pearson
95	BD I (5), HC (51)	Negative	NA	NA	NA	NA	NA	0.05	Spearman
97	BD I (33), BD II (2), BD NOS (2), HC (264)	Negative	−0.05	0.13	0.05	0.06	0.08	0.05	Spearman
96	PD (79), HC (58)	NA	0.17 (Male) −0.15 (Female)	0.22 (Male) 0.06 (Female)	−0.17 (Male) 0.21 (Female)	0.15 (Male) 0.38[a] (Female)	0.12 (Male) 0.38[a] (Female)	0.16 (Male) 0.23 (Female)	Spearman

Note: [a] $p < 0.05$.
Abbreviations: BD, bipolar affective disorder; BD I, bipolar affective disorder type 1; BD II, bipolar affective disorder type 2; CT, childhood trauma; EA, emotional abuse; EN, emotional neglect; HC, healthy control; NA, not applicable; NOS, not otherwise specified; PA, physical abuse; PD, psychotic disorder; PN, physical neglect; SA, sexual abuse; SZ, schizophrenia.

the orbitofrontal cortex (OFC) and thalamus were evident in a group of individuals with BD when compared to a group of healthy individuals, and reduced volume of the thalamus when compared to a group with SZ.[123]

Diffusion tensor imaging (DTI) studies reported reduced fractional anisotropy (FA; a marker of the microstructural organization of white matter fiber tracts) in widespread regions throughout the brain, including the uncinate fasciculus,[119] that connects the amygdala to the OFC,[124] when comparing individuals exposed to CT to those who were not exposed. This effect was found in contrast to the lack of difference in FA when comparing exposed and non-exposed healthy individuals.[119,125] Furthermore, average FA in brain areas showing initial group differences mediated the association between childhood abuse and BD.[125]

Functional MRI studies have reported that the severity of childhood neglect was associated with reduced amygdala - ventromedial prefrontal cortex functional connectivity at rest in BD.[119] In mixed cohorts of individuals with BD and SZ, CT exposure was associated with increased activation in the left temporo-parietal junction when processing emotional faces (negative versus positive emotions).[126] In the context of no trauma-related behavioral differences, CT exposure was associated with increased activation in the left inferior parietal lobule (IPL) and the cuneus while performing a working memory task,[109] and with increased activation in the left inferior frontal gyrus (IFG) during a response inhibition task.[110] The latter study also showed that general psychotic symptom severity mediated the relationship between CT exposure and levels of IFG activation.[110]

Finally, a Proton Magnetic Resonance Spectroscopy study showed that exposure to CT was associated with decreased glutamate concentrations in the left DLPFC in healthy individuals, but not in a mixed group of individuals with BD or SZ.[93]

Childhood Trauma and Peripheral Markers in Bipolar Disorder

Inflammatory Markers
Reviews and meta-analyses have reported increased levels of peripheral inflammatory markers in BD, including elevated levels of interleukin (IL)-1β, IL-4, IL-6, IL-10, tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), IL-6 receptor antagonist (IL-1RA), but also soluble receptors that can inhibit (soluble IL-2 receptor, sIL-2R) or enhance (sIL-6R; soluble TNF receptor-1, sTNFR1) the action of cytokines.[127–129] Importantly, a meta-analysis of 25 studies found that CT

exposure was also associated with increased levels of IL-6, TNF-α and CRP in both clinical and non-clinical samples.[130] Studies investigating the impact of CT exposure on levels of peripheral inflammation in BD reported inconsistent findings. In a study of mixed individuals with BD or SZ, increased levels of CRP were associated with an increased number of CT types.[131] Importantly, increased levels of CRP were reported to be more likely related to CT, especially sexual abuse, age and body mass index than to a diagnosis of BD per se.[132] Another group also found no association between the severity of CT exposure and peripheral levels of CRP, IL-6 or TNF-α in BD. Instead, elevated levels of CRP were associated with the severity of childhood sexual abuse in individuals with SZ only.[133] The same group also reported that in the context of a direct association between increased inflammation and increased striatal volume, the relationship between systemic peripheral inflammation and variations of grey matter volume was not moderated by CT in individuals with BD, but in patients with SZ and healthy individuals.[134] Overall, these findings indicate that the observed elevated levels of peripheral inflammatory markers in BD (especially, IL-6, TNF-α or CRP) may be related to the previous experience of CT, rather than the development of the disorder itself.

Neuroendocrine Markers
Accumulating evidence supports both short- and long-term HPA axis disruption following CT exposure in individuals with BD.[135,136] In particular, findings from both preclinical and clinical studies converge toward a mediating role of the HPA axis function on endocrine, immune, behavioral, cognitive and neural responses to stress.[137] Individuals with BD show elevated basal cortisol levels and blunted cortisol awakening response compared to groups of healthy individuals,[138,139] especially during manic and euthymic phases.[136] Changes in levels of cortisol in response to an experimental stressor in individuals with BD were however not different to changes observed in a group of healthy individuals.[140] Although a blunted cortisol response to laboratory-induced stressors has been reported in healthy individuals exposed to physical abuse,[141,142] only a handful of studies have investigated the neuroendocrine impact of CT in BD. In addition to blunted cortisol awakening response,[139] lower response to the dexamethasone test (Δ-cortisol)[143] has been reported in association with CT exposure in individuals with BD. Offspring of individuals with BD exposed to CT also show decreased salivary cortisol levels during daytime when compared to healthy individuals.[144] More recently, a study reported higher hair

cortisol concentrations, a marker of chronic stress, in individuals with either chronic BD or SZ with a history of CT, relative to both healthy controls and patients without a history of CT.[145] This was in contrast to another study reporting no effects of CT on hair cortisol concentrations in newly diagnosed individuals with BD.[146]

Other studies have investigated the relationship between cortisol changes in response to an MRI session, considered an experimental stressor, and brain function during the performance of emotional tasks. Compared to healthy controls, individuals with mood disorders, including BD and MDD, showed increased amygdalar, subgenual anterior cingulate cortex and thalamic activation, as well as decreased precuneal, postcentral, insular, putamen and medial frontal activation when processing emotional faces.[147] Another study reported that CT was a moderator of the relationship between changes in cortisol levels and activation in a region including the right lingual, fusiform and parahippocampal gyri, in individuals with BD performing an emotional processing fMRI task. In particular, individuals with BD exposed to high (but not low) levels of CT showed decreased activation in this region. This study also reported that changes in cortisol levels in response to the task were associated with decreased task-related functional connectivity between the left amygdala and the left DLPFC, in individuals with BD who reported high (but not low) levels of CT.[148]

Gene Expression and DNA Methylation

Changes in gene expression associated with HPA axis function are potentially key factors implicated in the development of BD following exposure to CT. To the best of our knowledge, only one study reported changes in gene expression associated with exposure to childhood emotional abuse in individuals with BD. This study reported modified co-expression of Diacylglycerol kinase eta - Homo Sapiens (*DGKH*) and Nuclear Receptor Subfamily 3 Group C Member 1 (*NR3C1*) when compared to the other genes of the HPA axis.[63] These changes in gene expression may be the consequence of epigenetic changes, mostly due to changes in DNA methylation of the genes implicated in the stress response.[149] For example, emotional abuse/neglect was associated with lower levels of methylation in the intron 7 of the FK506 binding protein 5 (*FKBP5*) gene, a co-chaperone protein that regulates glucocorticoid receptor sensitivity,[150] in individuals with BD carrying the T allele of the single nucleotide polymorphism rs1360780 of the

FKBP5 gene.[151] Other studies showed that decreased methylation in some CpG sites within the 5-hydroxytryptamine 3a receptor (*5HT3AR*) gene mediated the association between childhood physical abuse and the number of mood episodes reported in a cohort of individuals with BD, borderline personality and attention-deficit hyperactivity disorders.[152] Others found no changes in DNA methylation in the glucocorticoid receptor 1F gene (*GR-1F*)[153] or in the KIT Ligand (*KITLG*) gene[154] in association with CT exposure in BD. The latter result was in the context of a significant association between methylation of this gene and CT exposure in a group of healthy volunteers.[154] These data support the possibility that gene expression may be a mechanistically important avenue to integrate into larger scale longitudinal studies examining the contribution of CT to mental health outcomes.

Ensuring Continuous Improvement in Understanding the Role of Childhood Trauma in Developing Bipolar Disorder

Emerging evidence from studies in young people who are at increased risk of developing BD due to family history and/or exposure to CT adds new insights to existing adult studies.[48,62,155] Integration of this knowledge into ongoing identification, intervention and treatment programs to support young people who display early-onset, prodromal or clinical symptoms is required. At the same time, postnatal treatment to improve mothers' depressive episodes, psychoeducational programs for parents with mood disorders and early interventions for improving cognitive problems in children are highly recommended.[48,62,156,157]

Novel evidence from studies in young people at high risk of developing BD proposes to focus on the developmental perspective when ensuring and optimizing ongoing efforts. It is known that the prenatal and first seven postnatal years of life are highly critical for brain development, which lay the foundations for affective and cognitive development[49,158] as well as HPA axis function.[137,159] Exposure to CT during these critical developmental phases has potentially negative short-term and longer-term consequences on the development of affective and cognitive functions due to aberrant changes to brain structural and functional processes.[160] Devastating effects of CT on suboptimal attachment in relationships have also been linked to the onset of BD.[60,62] Therefore, existing screening and

identification programs aim to identify young people at increased familial and clinical risk showing aberrant developmental signs. The integration of CT history as one additional risk factor towards the development of BD could result in more effective identification. In particular, detailed information on the timing of CT during development, severity and specific subtype may improve such targeted identification and could be run in parallel with clinical screenings.

Both psychotherapeutic and pharmacological treatments are offered to individuals with BD with few randomized clinical trials (RCT) published in young people with BD or individuals at high risk of BD. Advantages of including subjective information of CT history in both pharmacological and psychotherapeutic interventions in individuals with BD, including young people with BD, have been highlighted recently.[161] For cognitive behavioral psychotherapies and psychoeducational interventions, better outcomes than treatment as usual[156] were observed with a similar finding found in youths with BD.[162] A possible explanation for these findings is that such approaches offer individuals help to cope with their experiences of adverse events as well as with the resulting heightened stress reactivity[163,164] and greater exposure to recent stressful events.[156,165] Further support for integrating CT experience with other treatment approaches, such as pharmacological treatment, in individuals with BD has also been provided.[161] Reduced efficacy of treatment with mood-stabilizing agents in individuals with BD was linked to the occurrence and severity of CT. Refractoriness to treatment with lithium was associated with a lifetime diagnosis of CT-related PTSD in adults with BD.[166] A comparable result was found in young people with BD, where greater severity of physical abuse was linked to poor response to lithium.[167]

Already 15 years ago, recommendations have been made regarding screening programs for young people with early-onset BD and young people at high risk of BD due to family history of mood disorders and/or experience of CT with the aim of supporting young people in the long-run.[156] However, despite progress in developing interventions encompassing existing psychoeducational, psychotherapeutic and pharmacological avenues,[157] further work is required to overcome the challenge of ensuring these screening and early intervention programs are commonly available to young people in need. Moreover, the identification of biomarkers may improve the efficacy of pharmacological RCTs.[48] Early promising findings of increased low-grade inflammation in

adults with BD may be of use for future clinical trials using anti-inflammatory drugs (for example, Minocycline, Acetylsalicylic acid and Celecoxib) as adjunct strategies to treat young people with a first-onset episode; although current recommendations are weak due to a lack of studies in young people.[157,168] However, a recent RCT reported that, while inefficient as an adjunct treatment for BD, infliximab, a TNF-α antagonist, reduced the severity of depressive symptoms in individuals with BD exposed to physical or sexual abuse, relative to CT-exposed individuals with BD who used the placebo.[169] Such progress of blood-based markers in addition to known high-risk markers warrants future research studies in young people.

We also identified two reasons for the lack of interaction between CT, family history of mood disorder and prodromal symptoms as risk factors, and clinical outcome measures of BD. Firstly, most studies examined the role of CT as the only risk factor for the development of BD without considering other risk factors (eg, adverse socio-economic environment, cannabis/drug use and abuse). Secondly, other known related factors (such as genetic, epigenetic, cognitive, neural, endocrine and cytokine markers) have rarely been included. We propose that future research into more complex interactive effects between (some of) these factors may lead to greater mechanistic understanding. Using more advanced statistical approaches for such interaction analyses is another option.[69] Further possibilities include the study of the differential susceptibility model with the aim of proving (or disproving) whether intervention programs with supporting conditions may result in greater probability of positive adaptation[70] than treatment as usual. Importantly, more longitudinal studies with a consistently defined long-term outcome measure (for example, general functioning) are needed to optimize treatment strategies based on relevant measures.

Overall, this review proposes that CT exposure is a critical factor impacting on the future development of BD in those already at risk. Especially, individuals with BD exposed to CT develop more severe clinical expressions of the disorder, are diagnosed earlier and are more likely to develop other mental and physical illnesses as well as suicidal behaviors. This is usually accompanied by different biological (stress and inflammation), cognitive and brain morphology/function changes compared to those who did not experience CT. In addition, the present review highlighted the lack of neurobiological studies in youths at risk for the disorder that could determine biological targets for early interventions and/or treatments in

CT-exposed youths before the onset of the first-episode of BD. It will be, therefore, critical to advance these studies and integrate neurobiological measures with neuroimaging data within large consortia to identify the effects of CT in the development of BD. Importantly, this review recommends that exposure to CT should be systematically assessed in clinical practice as proposed by the US Centres for Disease Control and Prevention.[170] Identifying youths displaying subclinical symptoms or young people with first-episode BD who were exposed to CT as early as possible will improve individually tailored therapeutic strategies to the individual's developmental stage, onset and progression of the disorder. In particular, established trauma-related treatments, such as prolonged exposure therapy and eye-movement desensitization and reprocessing, have been shown to be beneficial in decreasing the severity of trauma-related symptoms as well as psychotic symptoms in individuals with a psychotic disorder.[171,172]

Conclusions

In conclusion, exposure to CT during neurodevelopmental stages earlier in life, including young adulthood, contributes to an increased risk of developing BD. This process involves disruption of the psychological and biological systems mediating responses to stressful events and may remain difficult to describe in precise mechanistic terms until the culmination of large-scale longitudinal studies, such as the UK Biobank, the Avon Longitudinal Study of Parents and Children (ALSPAC), the Adolescent Brain Cognitive Development (ABCD) study and the IMAGEN project.[173–176] These are well placed to address the interactions of CT with biological markers (eg, genetic, brain-derived, hormonal or inflammatory-based) to determine the contributions to the development of BD, its course and severity. Understanding the nature of and key players in this protracted course of causal events and the ensuing altered trajectories of individuals' mental wellbeing and resilience will be vital to the potential progress of effective monitoring, management and intervention standards.

Disclosure

The authors report no conflicts of interest for this work.

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