Neuropsychiatric Disease and Treatment

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REVIEW

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

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

Yann Quidé[1,2]
Leonardo Tozzi[3]
Mark Corcoran[4]
Dara M Cannon[5]
Maria R Dauvermann[6,7]

[1]School of Psychiatry, University of New South Wales (UNSW), Sydney, NSW, Australia; [2]Neuroscience Research Australia, Randwick, NSW, Australia; [3]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA; [4]School of Psychology, National University of Ireland Galway, Galway, Ireland; [5]Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, School of Medicine, National University of Ireland Galway, Galway, Ireland; [6]Department of Psychiatry, University of Cambridge, Cambridge, UK; [7]McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA

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]

Correspondence: Maria R Dauvermann
Department of Psychiatry, University of Cambridge, Clifford Allbutt Building, Cambridge Biomedical Campus Box 58, Cambridge CB2 0XY, UK
Tel +441223 465246
Email md874@medschl.cam.ac.uk

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/NDT.S285540

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 radioligands), and biological markers (eg, genetics and other "omics" approaches).[44] Most studies have investigated these modalities separately, but the emergence of big datasets and new methodological advances allow multimodal investigation of finer phenotypic features with better power to detect smaller effects and capture complex interactions. 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 characteristics 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), presubiculum 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 socioeconomic 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.

References

1. American Psychiatric Publishing. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5™*. 5th ed. American Psychiatric Publishing, Inc.;2013. doi:10.1176/appi.books.9780890425596
2. Dunayevich E, Keck PE. Prevalence and description of psychotic features in bipolar mania. *Curr Psychiatry Rep*. 2000;2:286–290. doi:10.1007/s11920-000-0069-4
3. Pope HG, Lipinski JF. Diagnosis in schizophrenia and manic-depressive illness: a reassessment of the specificity of "schizophrenic" symptoms in the light of current research. *Arch Gen Psychiatry*. 1978;35:811–828. doi:10.1001/archpsyc.1978.01770310017001
4. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. *Nat Rev Dis Primers*. 2018;4:18008.
5. Misiak B, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. *Mol Neurobiol*. 2018;55:5075–5100.
6. May-Chahal C, Cawson P. Measuring child maltreatment in the United Kingdom: a study of the prevalence of child abuse and neglect. *Child Abuse Negl*. 2005;29(9):969–984. doi:10.1016/j.chiabu.2004.05.009
7. Koenen KC, Roberts AL, Stone DM, Dunn EC. Theepidemiology of early childhood trauma. In: Pain C, Vermetten E, Lanius RA, editors. *The Impact of Early Life Trauma on Health and Disease: The Hidden Epidemic*. Cambridge University Press; 2010:13–24.
8. Álvarez M-J, Masramon H, Peña C, et al. Cumulative effects of childhood traumas: polytraumatization, dissociation, and schizophrenia. *Community Ment Health J*. 2015;51:54–62. doi:10.1007/s10597-014-9755-2
9. Duhig M, et al. The prevalence and correlates of childhood trauma in patients with early psychosis. *Aust N Zeal J Psychiatry*. 2020. doi:10.1177/0004867415575379
10. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull*. 2012;38:661–671.
11. Palmier-Claus JE, Berry K, Bucci S, Mansell W, Varese F. Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *Br J Psychiatry*. 2016;209(6):454–459. doi:10.1192/bjp.bp.115.179655
12. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry*. 2016;3(4):342–349. doi:10.1016/S2215-0366(15)00544-1
13. Etain B, et al. Preferential association between childhood emotional abuse and bipolar disorder. *J Trauma Stress*. 2010;23:376–383.
14. Morgan C, Gayer-Anderson C, Beards S, et al. Threat, hostility and violence in childhood and later psychotic disorder: population-based case–control study. *Br J Psychiatry*. 2020;217:575–582.
15. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation bipolar treatment outcome network: II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord*. 2001;67(1–3):45–59. doi:10.1016/S0165-0327(01)00432-3
16. Kupka RW, Luckenbaugh DA, Post RM, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *American Journal of Psychiatry*. 2005;162:1273–1280. doi:10.1176/appi.ajp.162.7.1273
17. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry*. 2005;186(2):121–125. doi:10.1192/bjp.186.2.121
18. Post RM, Altshuler LL, Kupka R, et al. Verbal abuse, like physical and sexual abuse, in childhood is associated with an earlier onset and more difficult course of bipolar disorder. *Bipolar Disord*. 2015;17(3):323–330. doi:10.1111/bdi.12268
19. Janssen I, et al. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatr Scand*. 2004;109:38–45.
20. Kessler RC, McLaughlin KA, Green JG, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry*. 2010;197(5):378–385. doi:10.1192/bjp.bp.110.080499

21. Read J, Fosse R, Moskowitz A, Perry B. The traumagenic neurodevelopmental model of psychosis revisited. *Neuropsychiatry*. 2014;4(1):65–79. doi:10.2217/npy.13.89
22. Matheson SL, Shepherd AM, Pinchbeck RM, Laurens KR, Carr VJ. Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychol Med*. 2013;43(2):225–238. doi:10.1017/S0033291712000785
23. Schäfer I, Fisher HL. Childhood trauma and psychosis - what is the evidence? *Dialogues Clin Neurosci*. 2011;13:360–365.
24. Hailes HP, Yu R, Danese A, Fazel S. Long-term outcomes of childhood sexual abuse: an umbrella review. *Lancet Psychiatry*. 2019;6(10):830–839. doi:10.1016/S2215-0366(19)30286-X
25. Copeland WE, Shanahan L, Hinesley J, et al. Association of childhood trauma exposure with adult psychiatric disorders and functional outcomes. *JAMA Netw Open*. 2018;1(7):e184493–e184493. doi:10.1001/jamanetworkopen.2018.4493
26. Scott KM, McLaughlin KA, Smith DAR, Ellis PM. Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. *Br J Psychiatry*. 2012;200:469–475. doi:10.1192/bjp.bp.111.103267
27. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2(8):e356–e366. doi:10.1016/S2468-2667(17)30118-4
28. Bonoldi I, Simeone E, Rocchetti M, et al. Prevalence of self-reported childhood abuse in psychosis: a meta-analysis of retrospective studies. *Psychiatry Res*. 2013;210(1):8–15. doi:10.1016/j.psychres.2013.05.003
29. Sommer IE, Daalman K, Rietkerk T, et al. Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. *Schizophr Bull*. 2010;36:633–641.
30. Wigman JTW, van Winkel R, Jacobs N, et al. A twin study of genetic and environmental determinants of abnormal persistence of psychotic experiences in young adulthood. *Am J Med Genetics Part B*. 2011;156(5):546–552. doi:10.1002/ajmg.b.31193
31. Wigman JTW, van Winkel R, Raaijmakers QAW, et al. Evidence for a persistent, environment-dependent and deteriorating subtype of subclinical psychotic experiences: a 6-year longitudinal general population study. *Psychol Med*. 2011;41(11):2317–2329. doi:10.1017/S0033291711000304
32. Thompson AD, et al. Sexual trauma increases the risk of developing psychosis in an ultra high-risk "prodromal" population. *Schizophr Bull*. 2014;40:697–706.
33. Yung AR, Cotter J, Wood SJ, et al. Childhood maltreatment and transition to psychotic disorder independently predict long-term functioning in young people at ultra-high risk for psychosis. *Psychol Med*. 2015;45(16):3453–3465. doi:10.1017/S003329171500135X
34. Tennant C, Bebbington P, Hurry J. Parental death in childhood and risk of adult depressive disorders: a review. *Psychol Med*. 1980;10(2):289–299. doi:10.1017/S0033291700044044
35. Carr CP, Martins CMS, Stingel AM, Lemgruber VB, Juruena MF. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. *J Nerv Ment Dis*. 2013;201(12):1007–1020. doi:10.1097/NMD.0000000000000049
36. Green JG, McLaughlin KA, Berglund PA, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Arch Gen Psychiatry*. 2010;67(2):113–123. doi:10.1001/archgenpsychiatry.2009.186
37. Duarte D, et al. Childhood-maltreatment subtypes in bipolar patients with suicidal behavior: systematic review and meta-analysis. *Braz J Psychiatry*. 2020;42:558–567.
38. Kalmakis KA, Chandler GE. Health consequences of adverse childhood experiences: a systematic review. *J Am Assoc Nurse Pract*. 2015;27:457–465.
39. Almuneef M, Qayad M, Aleissa M, Albuhairan F. Adverse childhood experiences, chronic diseases, and risky health behaviors in Saudi Arabian adults: a pilot study. *Child Abuse Negl*. 2014;38(11):1787–1793. doi:10.1016/j.chiabu.2014.06.003
40. Ramiro LS, Madrid BJ, Brown DW. Adverse childhood experiences (ACE) and health-risk behaviors among adults in a developing country setting. *Child Abuse Negl*. 2010;34(11):842–855. doi:10.1016/j.chiabu.2010.02.012
41. Bellis MA, Hughes K, Leckenby N, et al. Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey. *J Public Health (Oxf)*. 2015;37:445–454.
42. Bellis MA, Hughes K, Leckenby N, Perkins C, Lowey H. National household survey of adverse childhood experiences and their relationship with resilience to health-harming behaviors in England. *BMC Med*. 2014;12:72.
43. Norman RE, et al. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Med*. 2012;9:e1001349.
44. Suvisaari J, Mantere O, Keinänen J, et al. Is it possible to predict the future in first-episode psychosis? *Front Psychiatry*. 2018;9.
45. Ching CRK, et al. What we learn about bipolar disorder from large-scale neuroimaging: findings and future directions from the ENIGMA Bipolar Disorder Working Group. *Hum Brain Mapp*. n/a.
46. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet*. 2019;51:793–803.
47. Insel TR. Next-generation treatments for mental disorders. *Sci Transl Med*. 2012;4(155):155ps19–155ps19. doi:10.1126/scitranslmed.3004873
48. Duffy A, Carlson G, Dubicka B, Hillegers MHJ. Pre-pubertal bipolar disorder: origins and current status of the controversy. *Int J Bipolar Disord*. 2020;8:18.
49. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci*. 2008;9:947–957. doi:10.1038/nrn2513
50. Kroll JL. New directions in the conceptualization of psychotic disorders. *Curr Opin Psychiatry*. 2007;20:573–577. doi:10.1097/YCO.0b013e3282f08759
51. Jaffee SR. Child maltreatment and risk for psychopathology in childhood and adulthood. *Annu Rev Clin Psychol*. 2017;13:525–551. doi:10.1146/annurev-clinpsy-032816-045005
52. Troisi A. Childhood trauma, attachment patterns, and psychopathology: an evolutionary analysis. *Childhood Trauma Mental Disord*. 2020;125–142.
53. Day R, Nielsen JA, Korten A, et al. Stressful life events preceding the acute onset of schizophrenia: a cross-national study from the World Health Organization. *Cult Med Psych*. 1987;11:123–205.
54. van Os J, Kenis G, Rutten BPF. The environment and schizophrenia. *Nature*. 2010;468:203–212. doi:10.1038/nature09563
55. Murray RM, Englund A, Abi-Dargham A, et al. Cannabis-associated psychosis: neural substrate and clinical impact. *Neuropharmacology*. 2017;124:89–104.
56. Aas M, Haukvik UK, Djurovic S, et al. BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;46:181–188. doi:10.1016/j.pnpbp.2013.07.008
57. Green MJ, Raudino A, Cairns MJ, et al. Do common genotypes of FK506 binding protein 5 (FKBP5) moderate the effects of childhood maltreatment on cognition in schizophrenia and healthy controls? *J Psychiatr Res*. 2015;70:9–17. doi:10.1016/j.jpsychires.2015.07.019
58. Theleritis C, Fisher HL, Shäfer I, et al. Brain derived neurotropic factor (BDNF) is associated with childhood abuse but not cognitive domains in first episode psychosis. *Schizophr Res*. 2014;159(1):56–61. doi:10.1016/j.schres.2014.07.013

59. Etain B, Henry C, Bellivier F, Mathieu F, Leboyer M. Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord*. 2008;10:867–876.
60. Heim C, Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Exp Neurol*. 2012;233 (1):102–111. doi:10.1016/j.expneurol.2011.10.032
61. Heim C, Nemeroff CB. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry*. 1999;46:1509–1522.
62. Duffy A, Jones S, Goodday S, Bentall R. Candidate risks indicators for bipolar disorder: early intervention opportunities in high-risk youth. *Int J Neuropsychopharmacol*. 2016;19(1):pyv071. doi:10.1093/ijnp/pyv071
63. Grillault Laroche D, Curis E, Bellivier F, et al. Childhood maltreatment and HPA axis gene expression in bipolar disorders: a gene network analysis. *Psychoneuroendocrinology*. 2020;120:104753. doi:10.1016/j.psyneuen.2020.104753
64. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev*. 1997;104:667–685. doi:10.1037/0033-295X.104.4.667
65. Walker E, Mittal V, Tessner K. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. *Annu Rev Clin Psychol*. 2008;4:189–216.
66. Pruessner M, Cullen AE, Aas M, Walker EF. The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. *Neurosci Biobehav Rev*. 2017;73:191–218. doi:10.1016/j.neubiorev.2016.12.013
67. Holtzman CW, et al. Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience*. 2013;249:172–191.
68. Belsky J. Attachment, mating, and parenting. *Hum Nat*. 1997;8:361–381. doi:10.1007/BF02913039
69. Roisman GI, Newman DA, Fraley RC, et al. Distinguishing differential susceptibility from diathesis–stress: recommendations for evaluating interaction effects. *Dev Psychopathol*. 2012;24:389–409.
70. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull*. 2009;135:885–908. doi:10.1037/a0017376
71. Jr LS, Manchia M, Carpiniello B, et al. Clinical, genetic, and brain imaging predictors of risk for bipolar disorder in high-risk individuals. *Expert Rev Mol Diagn*. 2020;20(3):327–333. doi:10.1080/14737159.2020.1727743
72. Noto MN, Noto C, Caribé AC, et al. Clinical characteristics and influence of childhood trauma on the prodrome of bipolar disorder. *Br J Psychiatry*. 2015;37:280–288.
73. Post RM, Altshuler LL, Kupka R, et al. Age of onset of bipolar disorder: combined effect of childhood adversity and familial loading of psychiatric disorders. *J Psychiatr Res*. 2016;81:63–70. doi:10.1016/j.jpsychires.2016.06.008
74. Dauvermann MR, Donohoe G. The role of childhood trauma in cognitive performance in schizophrenia and bipolar disorder – A systematic review. *Schizophrenia Res*. 2019;16:1–11. doi:10.1016/j.scog.2018.11.001
75. Cazala F, Bauer IE, Meyer TD, et al. Correlates of childhood trauma in children and adolescents with bipolar disorder spectrum: a preliminary study. *J Affect Disord*. 2019;247:114–119.
76. Benarous X, M Raffin, N Bodeau, et al. Adverse childhood experiences among inpatient youths with severe and early-onset psychiatric disorders: prevalence and clinical correlates. *Child Psychiatry Hum Dev*. 2017;48:248–259.
77. Du Rocher Schudlich T, Youngstrom EA, Martinez M, et al. Physical and sexual abuse and early-onset bipolar disorder in youths receiving outpatient services: frequent, but not specific. *J Abnorm Child Psychol*. 2015;43:453–463. doi:10.1007/s10802-014-9924-3
78. Romero S, Birmaher B, Axelson D, et al. Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. *J Affect Disord*. 2009;112(1–3):144–150. doi:10.1016/j.jad.2008.04.005
79. Stowkowy J, Goldstein BI, MacQueen G, et al. Trauma in youth at-risk for serious mental illness. *J Nerv Ment Dis*. 2020;208 (1):70–76. doi:10.1097/NMD.0000000000001069
80. Jansen K, Cardoso TA, Fries GR, et al. Childhood trauma, family history, and their association with mood disorders in early adulthood. *Acta Psychiatr Scand*. 2016;134(4):281–286. doi:10.1111/acps.12551
81. Vieira IS, Pedrotti Moreira F, Mondin TC, et al. Resilience as a mediator factor in the relationship between childhood trauma and mood disorder: a community sample of young adults. *J Affect Disord*. 2020;274:48–53. doi:10.1016/j.jad.2020.04.011
82. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H. Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiatry*. 2003;60(12):1209–1215. doi:10.1001/archpsyc.60.12.1209
83. Gilman SE, Ni MY, Dunn EC, et al. Contributions of the social environment to first-onset and recurrent mania. *Mol Psychiatry*. 2015;20(3):329–336. doi:10.1038/mp.2014.36
84. Alameda L, Ferrari C, Baumann PS, et al. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. *Psychol Med*. 2015;45 (13):2727–2736. doi:10.1017/S0033291715000690
85. Shalev A, et al. Longitudinal course and risk factors associated with psychosis in bipolar youths. *Bipolar Disord*. 2020;22:139–154.
86. Angst J, Gamma A, Rössler W, Ajdacic V, Klein DN. Childhood adversity and chronicity of mood disorders. *Eur Arch Psychiatry Clin Neurosci*. 2011;261(1):21–27. doi:10.1007/s00406-010-0120-3
87. Birmaher B, Gill MK, Axelson DA, et al. Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. *AJP*. 2014;171:990–999. doi:10.1176/appi.ajp.2014.13121577
88. Andreu Pascual M, Levenson JC, Merranko J, et al. The effect of traumatic events on the longitudinal course and outcomes of youth with bipolar disorder. *J Affect Disord*. 2020;274:126–135. doi:10.1016/j.jad.2020.05.131
89. Koenders MA, Mesman E, Giltay EJ, Elzinga BM, Hillegers MHJ. Traumatic experiences, family functioning, and mood disorder development in bipolar offspring. *Br J Clin Psychol*. 2020;59:277–289.
90. Haussleiter IS, Neumann E, Lorek S, Ueberberg B, Juckel G. Role of child maltreatment and gender for bipolar symptoms in young adults. *Int J Bipolar Disord*. 2020;8(1):10. doi:10.1186/s40345-019-0173-9
91. Vlad M, Raucher-Chéné D, Henry A, Kaladjian A. Functional outcome and social cognition in bipolar disorder: is there a connection? *Eur Psychiatry*. 2018;52:116–125. doi:10.1016/j.eurpsy.2018.05.002
92. I M, et al. Functional Impairment and clinical correlates in adolescents with bipolar disorder compared to healthy controls. a case-control study. *J Can Acad Child Adolescent Psychiatry / Journal De l'Academie Canadienne De Psychiatrie De L'enfant Et De L'adolescent*. 2020.
93. Corcoran M, Hawkins EL, O'Hora D, et al. Are working memory and glutamate concentrations involved in early-life stress and severity of psychosis? *Brain Behav*. 2020;10(6):e01616. doi:10.1002/brb3.1616
94. Østefjells T, Lystad JU, Berg AO, et al. Metacognitive beliefs mediate the effect of emotional abuse on depressive and psychotic symptoms in severe mental disorders. *Psychol Med*. 2017;47 (13):2323–2333. doi:10.1017/S0033291717000848
95. Lindgren M, Mäntylä T, Rikandi E, et al. Childhood adversities and clinical symptomatology in first-episode psychosis. *Psychiatry Res*. 2017;258.

96. Lindgren M, Mäntylä T, Rikandi E, et al. Sex differences in the effect of childhood trauma on the clinical expression of early psychosis. *Compr Psychiatry*. 2016;68.
97. Aas M, Andreassen OA, Aminoff SR, et al. A history of childhood trauma is associated with slower improvement rates: findings from a one-year follow-up study of patients with a first-episode psychosis. *BMC Psychiatry*. 2016;16(1):126. doi:10.1186/s12888-016-0827-4
98. B E, Lajnef M, Bellivier F, et al. Revisiting the association between childhood trauma and psychosis in bipolar disorder: a quasi-dimensional path-analysis. *J Psychiatr Res*. 2017;84.
99. Gallagher BJ, Jones BJ. Childhood stressors and symptoms of schizophrenia. *Clin Schizophr Relat Psychoses*. 2013;7:124–130. doi:10.3371/CSRP.GAJO.020113
100. Bailey T, Alvarez-Jimenez M, Garcia-Sanchez AM, et al. Childhood trauma is associated with severity of hallucinations and delusions in psychotic disorders: a systematic review and meta-analysis. *Schizophr Bull*. 2018;44(5):1111–1122. doi:10.1093/schbul/sbx161
101. Vargas T, Lam PH, Azis M, et al. Childhood trauma and neurocognition in adults with psychotic disorders: a systematic review and meta-analysis. *Schizophr Bull*. 2019;45(6):1195–1208. doi:10.1093/schbul/sby150
102. Larsen EM, Ospina LH, Cuesta-Diaz A, et al. Effects of childhood trauma on adult moral decision-making: clinical correlates and insights from bipolar disorder. *J Affect Disord*. 2019;244:180–186. doi:10.1016/j.jad.2018.10.002
103. Bücker J, Kozicky J, Torres IJ, et al. The impact of childhood trauma on cognitive functioning in patients recently recovered from a first manic episode: data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM).. *J Affect Disord*. 2013;148(2–3):424–430. doi:10.1016/j.jad.2012.11.022
104. Savitz JB, Merwe LVD, Stein DJ, Solms M, Ramesar RS. Neuropsychological task performance in bipolar spectrum illness: genetics, alcohol abuse, medication and childhood trauma. *Bipolar Disord*. 2008;10(4):479–494. doi:10.1111/j.1399-5618.2008.00591.x
105. Marshall DF, Passarotti AM, Ryan KA, et al. Deficient inhibitory control as an outcome of childhood trauma. *Psychiatry Res*. 2016;235:7–12. doi:10.1016/j.psychres.2015.12.013
106. Jiménez E, et al. Impact of childhood trauma on cognitive profile in bipolar disorder. *Bipolar Disord*. 2017;19:363–374.
107. Szmulewicz A, Millett CE, Shanahan M, Gunning FM, Burdick KE. Emotional processing subtypes in bipolar disorder: a cluster analysis. *J Affect Disord*. 2020;266:194–200. doi:10.1016/j.jad.2020.01.082
108. Quidé Y, Cohen-Woods S, O'Reilly N, et al. Schizotypal personality traits and social cognition are associated with childhood trauma exposure. *Br J Clin Psychol*. 2018;57(4):397–419. doi:10.1111/bjc.12187
109. Quidé Y, O'Reilly N, Rowland JE, et al. Effects of childhood trauma on working memory in affective and non-affective psychotic disorders. *Brain Imaging Behav*. 2017;11(3):722–735. doi:10.1007/s11682-016-9548-z
110. Quidé Y, O'Reilly N, Watkeys OJ, Carr VJ, Green MJ. Effects of childhood trauma on left inferior frontal gyrus function during response inhibition across psychotic disorders. *Psychol Med*. 2018;48(9):1454–1463. doi:10.1017/S0033291717002884
111. Aas M, Steen NE, Agartz I, et al. Is cognitive impairment following early life stress in severe mental disorders based on specific or general cognitive functioning? *Psychiatry Res*. 2012;198(3):495–500. doi:10.1016/j.psychres.2011.12.045
112. Martins DS, Hasse-Sousa M, Petry-Perin C, et al. Perceived childhood adversities: impact of childhood trauma to estimated intellectual functioning of individuals with bipolar disorder. *Psychiatry Res*. 2019;274:345–351. doi:10.1016/j.psychres.2019.02.046
113. Rokita KI, Dauvermann MR, Donohoe G. Early life experiences and social cognition in major psychiatric disorders: a systematic review. *Eur Psychiatry*. 2018;53:123–133. doi:10.1016/j.eurpsy.2018.06.006
114. Russo M, Proujansky R, Gilbert A, Braga RJ, Burdick KE. Initial evidence for sex-specific effects of early emotional abuse on affective processing in bipolar disorder. *Eur Psychiatry*. 2014;29:52–57.
115. Russo M, Mahon K, Shanahan M, et al. The association between childhood trauma and facial emotion recognition in adults with bipolar disorder. *Psychiatry Res*. 2015;229(3):771–776. doi:10.1016/j.psychres.2015.08.004
116. Fijtman A, Bücker J, Strange BA, et al. Emotional memory in bipolar disorder: impact of multiple episodes and childhood trauma. *J Affect Disord*. 2020;260:206–213. doi:10.1016/j.jad.2019.09.003
117. Serafini G, Gonda X, Pompili M, et al. The relationship between sensory processing patterns, alexithymia, traumatic childhood experiences, and quality of life among patients with unipolar and bipolar disorders. *Child Abuse Negl*. 2016;62:39–50. doi:10.1016/j.chiabu.2016.09.013
118. Bücker J, Muralidharan K, Torres IJ, et al. Childhood maltreatment and corpus callosum volume in recently diagnosed patients with bipolar I disorder: data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). *J Psychiatr Res*. 2014;48(1):65–72. doi:10.1016/j.jpsychires.2013.10.012
119. Souza-Queiroz J, Boisgontier J, Etain B, et al. Childhood trauma and the limbic network: a multimodal MRI study in patients with bipolar disorder and controls. *J Affect Disord*. 2016;200:159–164. doi:10.1016/j.jad.2016.04.038
120. Duarte DGG, Neves MDCL, Albuquerque MR, et al. Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: A voxel-based morphometric study. *J Affect Disord*. 2016;197:74–80. doi:10.1016/j.jad.2016.02.068
121. Janiri D, Sani G, Rossi PD, et al. Amygdala and hippocampus volumes are differently affected by childhood trauma in patients with bipolar disorders and healthy controls. *Bipolar Disord*. 2017;19(5):353–362. doi:10.1111/bdi.12516
122. Janiri D, Sani G, De Rossi P, et al. Hippocampal subfield volumes and childhood trauma in bipolar disorders. *J Affect Disord*. 2019;253:35–43. doi:10.1016/j.jad.2019.04.071
123. Poletti S, Vai B, Smeraldi E, et al. Adverse childhood experiences influence the detrimental effect of bipolar disorder and schizophrenia on cortico-limbic grey matter volumes. *J Affect Disord*. 2016;189:290–297. doi:10.1016/j.jad.2015.09.049
124. Catani M, Dell'acqua F, Thiebaut de Schotten M. A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev*. 2013;37(8):1724–1737. doi:10.1016/j.neubiorev.2013.07.001
125. Stevelink R, Abramovic L, Verkooijen S, et al. Childhood abuse and white matter integrity in bipolar disorder patients and healthy controls. *Eur Neuropsychopharmacol*. 2018;28:807–817.
126. Aas M, Kauppi K, Brandt CL, et al. Childhood trauma is associated with increased brain responses to emotionally negative as compared with positive faces in patients with psychotic disorders. *Psychol Med*. 2017;47(4):669–679. doi:10.1017/S0033291716002762
127. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol Psychiatry*. 2013;74(1):15–25. doi:10.1016/j.biopsych.2013.01.007
128. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry*. 2016;21:1696–1709.
129. Fernandes BS, Steiner J, Molendijk ML, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry*. 2016;3(12):1147–1156. doi:10.1016/S2215-0366(16)30370-4
130. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Molecular Psychiatry*. 2016;21(5):642–649. doi:10.1038/mp.2015.67

131. Aas M, et al. Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. *Brain Behav Immun*. 2017;65:342–349. doi:10.1016/j.bbi.2017.06.005
132. Moraes JB, Maes M, Barbosa DS, et al. Elevated C-reactive protein levels in women with bipolar disorder may be explained by a history of childhood trauma, especially sexual abuse, body mass index and age. *CNS Neurol Disord Drug Targets*. 2017;16(4):514–521. doi:10.2174/1871527316666170407151514
133. Quidé Y, Bortolasci CC, Spolding B, et al. Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and bipolar-I disorder. *Psychol Med*. 2019;49(16):2736–2744. doi:10.1017/S0033291718003690
134. Quidé Y, Bortolasci CC, Spolding B, et al. Systemic inflammation and grey matter volume in schizophrenia and bipolar disorder: moderation by childhood trauma severity. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;110013.
135. Dauvermann MR, Donohoe G. Cortisol stress response in psychosis from the high-risk to the chronic stage: a systematic review. *Ir J Psychol Med*. 2019;36:305–315. doi:10.1017/ipm.2019.27
136. Belvederi Murri M, Prestia D, Mondelli V, et al. The HPA axis in bipolar disorder: systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016;63:327–342. doi:10.1016/j.psyneuen.2015.10.014
137. Syed SA, Nemeroff CB. Early life stress, mood, and anxiety disorders. *Chronic Stress*. 2020. doi:10.1177/2470547017694461
138. Girshkin L, Matheson SL, Shepherd AM, Green MJ. Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. *Psychoneuroendocrinology*. 2014;49:187–206. doi:10.1016/j.psyneuen.2014.07.013
139. Monteleone AM, Cascino G, Marciello F, et al. Clinical and neuroendocrine correlates of childhood maltreatment history in adults with bipolar disorder. *Bipolar Disord*. n/a.
140. Girshkin L, O'Reilly N, Quidé Y, et al. Diurnal cortisol variation and cortisol response to an MRI stressor in schizophrenia and bipolar disorder. *Psychoneuroendocrinology*. 2016;67:61–69. doi:10.1016/j.psyneuen.2016.01.021
141. Carpenter LL, Carvalho JP, Tyrka AR, et al. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biol Psychiatry*. 2007;62(10):1080–1087. doi:10.1016/j.biopsych.2007.05.002
142. Carpenter LL, Shattuck TT, Tyrka AR, Geracioti TD, Price LH. Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology*. 2011;214(1):367–375. doi:10.1007/s00213-010-2007-4
143. Watson S, et al. Family history, early adversity and the hypothalamic-pituitary-adrenal (HPA) axis: mediation of the vulnerability to mood disorders. *Neuropsychiatr Dis Treat*. 2007;3:647–653.
144. Schreuder MM, Vinkers CH, Mesman E, et al. Childhood trauma and HPA axis functionality in offspring of bipolar parents. *Psychoneuroendocrinology*. 2016;74:316–323. doi:10.1016/j.psyneuen.2016.09.017
145. Aas M, Ueland T, Inova A, et al. Childhood trauma is nominally associated with elevated cortisol metabolism in severe mental disorder. *Front Psychiatry*. 2020;11. doi:10.3389/fpsyt.2020.00391
146. Coello K, Munkholm K, Nielsen F, Vinberg M, Kessing LV. Hair cortisol in newly diagnosed bipolar disorder and unaffected first-degree relatives. *Psychoneuroendocrinology*. 2019;99:183–190. doi:10.1016/j.psyneuen.2018.09.020
147. Peters AT, Van Meter A, Pruitt PJ, et al. Acute cortisol reactivity attenuates engagement of fronto-parietal and striatal regions during emotion processing in negative mood disorders. *Psychoneuroendocrinology*. 2016;73:67–78. doi:10.1016/j.psyneuen.2016.07.215
148. Quidé Y, Girshkin L, Watkeys OJ, Carr VJ, Green MJ. The relationship between cortisol reactivity and emotional brain function is differently moderated by childhood trauma, in bipolar disorder, schizophrenia and healthy individuals. *Eur Arch Psychiatry Clin Neurosci*. 2020. doi:10.1007/s00406-020-01190-3
149. Watkeys OJ, Kremerskothen K, Quidé Y, Fullerton JM, Green MJ. Glucocorticoid receptor gene (NR3C1) DNA methylation in association with trauma, psychopathology, transcript expression, or genotypic variation: a systematic review. *Neurosci Biobehav Rev*. 2018;95:85–122. doi:10.1016/j.neubiorev.2018.08.017
150. Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology*. 2009;34(Supplement 1):S186–S195. doi:10.1016/j.psyneuen.2009.05.021
151. Saito T, Shinozaki G, Koga M, et al. Effect of interaction between a specific subtype of child abuse and the FKBP5 rs1360780 SNP on DNA methylation among patients with bipolar disorder. *J Affect Disord*. 2020;272:417–422. doi:10.1016/j.jad.2020.03.120
152. Perroud N, Zewdie S, Stenz L, et al. Methylation of serotonin receptor 3A in ADHD, borderline personality, and bipolar disorders: link with severity of the disorders and childhood maltreatment. *Depress Anxiety*. 2016;33(1):45–55. doi:10.1002/da.22406
153. Schür RR, van Leeuwen JMC, Houtepen LC, et al. Glucocorticoid receptor exon 1F methylation and the cortisol stress response in health and disease. *Psychoneuroendocrinology*. 2018;97:182–189. doi:10.1016/j.psyneuen.2018.07.018
154. He Y, Vinkers CH, Houtepen LC, de Witte LD, Boks MP. Childhood adversity is associated with increased KITLG methylation in healthy individuals but not in bipolar disorder patients. *Front Psychiatry*. 2019;9. doi:10.3389/fpsyt.2018.00743
155. Etain B, Aas M. Childhood maltreatment in bipolar disorders. *Curr Top Behav Neurosci*. 2020. doi:10.1007/7854_2020_149
156. Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol*. 2006;18:1181–1211. doi:10.1017/S0954579406060573
157. Post RM, et al. Toward prevention of bipolar disorder in at-risk children: potential strategies ahead of the data. *J Affect Disord*. 2020;272:508–520.
158. Paus T, Zijdenbos A, Worsley K, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science*. 1999;283(5409):1908–1911. doi:10.1126/science.283.5409.1908
159. Doom JR, Gunnar MR. Stress physiology and developmental psychopathology: past, present and future. *Dev Psychopathol*. 2013;25:1359–1373. doi:10.1017/S0954579413000667
160. Teicher MH, Samson JA, Maltreatment C. Psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry*. 2013;170:1114–1133. doi:10.1176/appi.ajp.2013.12070957
161. Jaworska-Andryszewska P, Rybakowski JK. Childhood trauma in mood disorders: neurobiological mechanisms and implications for treatment. *Pharmacol Rep*. 2019;71(1):112–120. doi:10.1016/j.pharep.2018.10.004
162. Goldstein TR, Fersch-Podrat RK, Rivera M, et al. Dialectical behavior therapy for adolescents with bipolar disorder: results from a pilot randomized trial. *J Child Adolesc Psychopharmacol*. 2014;25:140–149. doi:10.1089/cap.2013.0145
163. Cohen AN, Hammen C, Henry RM, Daley SE. Effects of stress and social support on recurrence in bipolar disorder. *J Affect Disord*. 2004;82(1):143–147. doi:10.1016/j.jad.2003.10.008
164. Johnson SL, Roberts JE. Life events and bipolar disorder: implications from biological theories. *Psychol Bull*. 1995;117:434–449. doi:10.1037/0033-2909.117.3.434

165. Ostiguy CS, Ellenbogen MA, Linnen A-M, et al. Chronic stress and stressful life events in the offspring of parents with bipolar disorder. *J Affect Disord*. 2009;114(1–3):74–84. doi:10.1016/j.jad.2008.08.006
166. Cakir S, Durak RT, Ozyildirim I, Ince E, Sar V. Childhood trauma and treatment outcome in bipolar disorder. *J Trauma Dissociation*. 2016;17(4):397–409. doi:10.1080/15299732.2015.1132489
167. Etain B, Lajnef M, Brichant-Petitjean C, et al. Childhood trauma and mixed episodes are associated with poor response to lithium in bipolar disorders. *Acta Psychiatr Scand*. 2017;135(4):319–327. doi:10.1111/acps.12684
168. Ng QX, Ramamoorthy K, Loke W, et al. Clinical role of aspirin in mood disorders: a systematic review. *Brain Sci*. 2019;9(11):296. doi:10.3390/brainsci9110296
169. McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(8):783. doi:10.1001/jamapsychiatry.2019.0779
170. Merrick MT, Ford DC, Ports KA. Vital signs: estimated proportion of adult health problems attributable to adverse childhood experiences and implications for prevention — 25 States, 2015–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(44):999–1005. doi:10.15585/mmwr.mm6844e1
171. van den Berg D, de Bont PAJM, van der Vleugel BM, et al. Long-term outcomes of trauma-focused treatment in psychosis. *Br J Psychiatry*. 2018;212(3):180–182. doi:10.1192/bjp.2017.30
172. Brand RM, McEnery C, Rossell S, Bendall S, Thomas N. Do trauma-focussed psychological interventions have an effect on psychotic symptoms? A systematic review and meta-analysis. *Schizophr Res*. 2018;195:13–22. doi:10.1016/j.schres.2017.08.037
173. Mascarell Maričić L, et al. The IMAGEN study: a decade of imaging genetics in adolescents. *Mol Psychiatry*. 2020;1–24.
174. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun*. 2020;11:2624. doi:10.1038/s41467-020-15948-9
175. Golding J, Pembrey M, Jones R. ALSPAC Study Team, ALSPAC–the avon longitudinal study of parents and children. I. Study methodology. *Paediatr Perinat Epidemiol*. 2001;15:74–87. doi:10.1046/j.1365-3016.2001.00325.x
176. Karcher NR, Barch DM. The ABCD study: understanding the development of risk for mental and physical health outcomes. *Neuropsychopharmacology*. 2020;1–12.