

**The role of childhood trauma in cognitive performance in schizophrenia and bipolar disorder – A systematic review**

**Running title:** Childhood trauma and cognition in psychosis

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## **Abstract**

Childhood trauma (CT) has repeatedly been associated with cognitive deficits in patients with psychosis but many inconsistencies have been reported so that the nature of the relationship remains unclear. The purpose of this review was to better characterize the contribution of CT to cognitive deficits by considering the type, severity and frequency of childhood traumatic events and their relationships with psychosis at all stages.

Relevant studies were identified via electronic and manual literature searches and included original studies that investigated the relationship between CT and higher cognitive performance or social cognitive performance in patients with schizophrenia, bipolar disorder and psychosis at all stages of the illness stages (i.e. ultra-high risk, first episode or chronic phase).

Overall, a majority of studies reported that patients who experienced CT displayed deficits in general cognitive ability compared to patients with psychosis without such a history. Associations between CT and other cognitive function were more mixed. When comparing patient groups, the association between CT and cognitive function was more inconsistent in patients with chronic schizophrenia than in healthy participants, ultra-high risk individuals, first-episode patients and patients with chronic bipolar disorder.

In understanding the variability in the reported relationships between CT and cognition across study populations, we highlight the variety of questionnaires used and discuss the likelihood of there being differences in cognitive function based on specific stressors, severity and frequency. Finally, we consider future research steps that may shed light on psychobiological mechanisms underlying CT and cognitive performance in patients with psychosis.

**Keywords:** Childhood trauma; schizophrenia; psychosis; cognitive function; social cognitive function

**Abbreviations**

CAQ	Childhood Adversity Questionnaire
CATS	Child Abuse and Trauma Scale
CECA-Q	Childhood Experience of Care Abuse Questionnaire
CT	Childhood trauma
CTQ	Childhood Trauma Questionnaire
ETI	Early Trauma Inventory
IQ	Intelligence Quotient
MACE Scale	Maltreatment and Abuse Chronology of Exposure Scale
RFQ	Risky Families Questionnaire

## 1 Introduction

### 1.1 Stress and cognition in schizophrenia and bipolar disorder

Cognitive deficits are highly predictive of social and occupational function in schizophrenia (Green, 2016, Green et al., 2012) (Horan et al., 2012) and related psychotic disorders, such as bipolar disorder with psychotic features (Vlad et al., 2018) and psychosis (Lysaker et al., 2018). These deficits often precede the emergence of clinical symptoms, and are relatively stable during the course of schizophrenia and bipolar disorder (Hill et al., 2008, Kuswanto et al., 2015a, Kuswanto et al., 2015b). Epidemiological and clinical studies have also consistently highlighted the impact of stress-related environmental risk factors, including childhood trauma (CT) or childhood adversity (including physical abuse, physical neglect, emotional abuse, emotional neglect and sexual abuse) (Day et al., 1987, Lataster et al., 2012, Mayo et al., 2017, Holtzman et al., 2013, Bechdolf et al., 2010, Gershon et al., 2013, Thompson et al., 2009, van Os et al., 2010, Walder et al., 2014), urbanicity (McGrath et al., 2004, Newbury et al., 2017), and cannabis use (Murray et al., 2017) in the development of psychosis (Aiello et al., 2012, Fusar-Poli et al., 2017, Misiak et al., 2017).

The potential predisposition of genetic risk factors to both CT and cognitive deficits in psychosis has received growing attention in recent years, in particular with the onset of candidate gene studies. Functional polymorphisms of the Catechol-O-Methyltransferase (COMT) genotype (Green et al., 2014), the FK506 binding protein 5 gene (Green et al., 2015) and brain-derived neurotrophic factor (BDNF) Val66Met polymorphism (Theleritis et al., 2014, Aas et al., 2013) have been associated to cognitive deficits after the experience of CT.

A relationship between CT exposure and cognitive deficits in psychosis has previously been hypothesized (Gilbertson et al., 2002, Cancel et al., 2015, Belanoff et al., 2001, Millan et al., 2012). Recent reviews have discussed the role of CT and cognitive function in psychosis in terms of (1) cognitive function and first-episode of psychosis (Aas et al., 2014) and (2) biological stress pathways in schizophrenia (Ruby et al., 2014). Despite these compelling relationships between CT and cognitive function in patients with psychosis due to inconsistent findings it is not known whether these relationships differ according to the type of psychotic disorder (i.e. schizophrenia, bipolar disorder and psychosis) and the phase of the disorder. The investigation of associations between CT and cognitive function in psychosis across these psychotic disorders is warranted given the similarities in genetic impact (Cardno and Owen, 2014) on the one hand, and evidence of differentiation between the disorders based on cognitive performance (Aas et al., 2012b) and brain structure abnormalities (Liberg et al., 2016) on the other hand. Furthermore, evidence of differences in cognitive function, brain structure and brain function over the course of the psychotic disorders (Lewandowski et al., 2011) - from the stages of ultra-high risk, first episode, to chronic illness - which is supported by evidence showing that CT changes brain development (Teicher et al., 2016).

In addition, it has been suggested that stress experience and stress response are probable factors to explain the relationship between CT and cognitive deficits in patients with psychosis and healthy participants (Sapolsky et al., 1986, Wolf, 2003). However, studies vary widely on the investigation of CT ranging from *general* CT (as measured with total CT scores) and *specific* CT events (for example, physical abuse or physical neglect) in patients with schizophrenia, bipolar disorder or psychosis. The differentiation between *general* versus *specific* CT across psychotic disorders is warranted after evidence of *specific* CT events, such as emotional abuse, relating to bipolar disorder has been reported (Etain et al., 2010, Etain et al., 2008), whereas physical abuse appears to be more prevalent in schizophrenia (Etain et al., 2010, Etain et al., 2008).

The objective of this systematic review was to summarize the evidence for an association between CT and cognitive function in patients with psychosis by considering three major

points: (1) Types of psychosis, (2) Phases of the psychotic disorders, and (3) Comparison between the *general* versus *specific* events of CT. To this end, we reviewed original studies that investigated the role of CT on cognitive or social cognitive performance in patients with schizophrenia, bipolar disorder and psychosis across all phases of the illness in two steps: Firstly, we reviewed the *general* role of CT on general cognitive ability, memory function and executive function as well as social cognitive function (such as emotion recognition and Theory of Mind). Secondly, we considered detailed information of *specific* stressors, and frequency and severity of CT. We discussed whether patients with different types of psychotic disorders at different stages can be differentiated based on these relationships which could improve clinical diagnosis. Finally, we considered future research steps that can advance our insights into psychobiological mechanisms by embracing the diversity of CT experience as one of the crucial components to understand the complex relationships between CT and cognitive function in psychosis.

## 2 Materials and methods

### 2.1 Literature search strategy

We conducted a systematic literature search using PubMed and PsycINFO for original papers studying the relationship between adverse childhood events and general cognitive and social cognitive performance in patients with schizophrenia, bipolar disorder, and psychosis, published between 1993 and December 2017. We used combinations of the following key terms: ((childhood trauma OR childhood adverse OR childhood adversity OR childhood maltreatment OR developmental trauma OR early life stress OR social stress OR chronic stress OR physical abuse OR sexual abuse OR emotional abuse OR neglect) AND (cognition OR cognitive OR higher cognition OR social cognition) AND (schizophrenia OR bipolar disorder OR psychosis)). Adverse childhood events, such as loss of a family member, divorce of parents, or migration were not included in the literature search. We included only studies that assessed the direct relationship between CT and higher cognition (e.g. general cognitive ability, working memory) and/or between childhood trauma and social cognition (e.g. theory of mind, emotion recognition) in adult patients with schizophrenia, bipolar disorder and psychosis. Neuroimaging studies were excluded. Studies were also searched through references of selected articles. Authors have been contacted for detailed information if not reported in the manuscript.

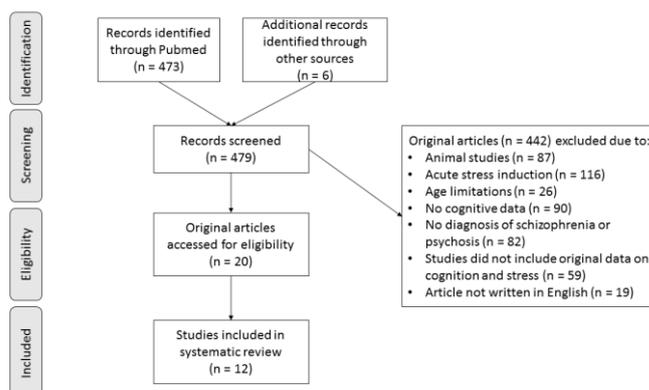
### 2.2 Inclusion criteria

Identified studies were screened and selected for inclusion using the following criteria: (1) Original and peer-reviewed articles published in an English language journal, (2) Adult patients with schizophrenia, bipolar disorder or psychosis, and healthy participants were included in the study; (3) Data on chronic stress were reported; (4) Data on higher cognitive or social cognitive performance were reported.

### 2.3 Study characteristics

The literature search identified 473 studies in total, of which eight studies were original studies that matched the study criteria. Six additional studies were identified through review of references of these papers. The PRISMA flow diagram is presented in Figure 1 which displays the number of included and excluded studies as well as the reasons for exclusion. After the initial 12 studies were included, we re-ran the literature search as described above and identified nine additional studies in which a healthy participant group was missing but all other inclusion criteria were reported as outlined above. These nine additional studies were included in the systematic research. Therefore, in total 21 studies were included.

Figure 1. Flow diagram selection of study process



These 21 studies were grouped into studies that addressed higher cognitive function or social cognitive function. For higher cognitive function, three studies were conducted in individuals at ultra-high risk of psychosis (Ucok et al., 2015) or in patients with first-episode psychosis

(Aas et al., 2011, Aas et al., 2012a), three studies included patients with chronic bipolar disorder (Poletti et al., 2017, Bucker et al., 2013, Marshall et al., 2016), nine studies were conducted in patients with chronic schizophrenia (Green et al., 2015, Green et al., 2014, McCabe et al., 2012, Kelly et al., 2016, Shannon et al., 2011, Schenkel et al., 2005, Lysaker et al., 2002, Ruby et al., 2017, Li et al., 2017) and three studies in patients with mixed psychosis group – consisting primarily of patients with chronic schizophrenia (van Os et al., 2017, Aas et al., 2012b, Mansueto et al., 2017).

For social cognitive function, three studies examined whether the experience of CT was associated with social cognitive performance in: (1) patients with first-episode psychosis and healthy participants (Garcia et al., 2016), (2) patients with psychosis and healthy participants (Schalinski et al., 2017), (3) and patients at either ultra-high risk of psychosis, patients with first-episode psychosis, patients with chronic bipolar disorder or schizophrenia, and healthy participants (Palmier-Claus et al., 2016).

### **3 Results**

#### **3.1 Childhood trauma and cognitive function in individuals at ultra-high risk of psychosis and patients with first-episode psychosis**

A range of neuropsychological tests was administered to measure general cognitive ability, memory function, and executive function in the three included studies of individuals at ultra-high risk of psychosis and patients with first-episode psychosis (Table 1). Of these, two studies administered the Childhood Experience of Care Abuse Questionnaire (CECA-Q) (Aas et al., 2011, Aas et al., 2012a), and one study used the Childhood Trauma Questionnaire (CTQ) (Ucok et al., 2015). The CTQ and the CECA-Q are self-report questionnaires designed to assess childhood trauma occurring before the age of 17 years (for the CECA-Q) and 18 years (for the CTQ). For the CTQ, five subscales of childhood trauma are assessed (i.e. physical abuse, physical neglect, emotional abuse, emotional neglect, sexual abuse). Typically, pre-defined cut-offs are used to determine frequency and severity of childhood trauma for each of the five subscales according to the manual (Bernstein et al., 1994). Similarly for the CECA-Q, pre-determined criteria and cut-offs are applied to assess severity on each of the subscales for traumatic childhood events (i.e. lack of parental care, physical abuse and sexual abuse) (Bifulco et al., 2005).

One out of three studies reported a total severity score which was based on the CTQ (Ucok et al., 2015). While no study reported frequency findings directly, two out of three studies dichotomized frequency/severity of CT experience on the basis of absent/low versus high levels (Aas et al., 2012a, Aas et al., 2011), and one study did so on the basis of low versus high levels (Ucok et al., 2015) (Online Resource 1).

##### **3.1.1 General role and stressor-specific roles of childhood trauma on cognitive function**

In the only study that tested individuals at ultra-high risk for psychosis, the authors reported two significant associations between CT and cognitive function. Firstly, individuals with experience of physical trauma performed worse on executive function than individuals without such exposure. Secondly, a significant negative association between increased physical neglect exposure and poorer performance on working memory was also reported (Ucok et al., 2015). No associations with either emotional or sexual abuse, physical or emotional neglect and any cognitive measure were reported. Finally, when experience of CT as a general measure was combined into a total score, no significant associations were observed.

In patients with first-episode psychosis, both studies reported significant negative correlations between greater CT experience and reduced performance on measures of either general cognitive ability (Aas et al., 2011, Aas et al., 2012a) or executive function (Aas et al., 2012a). Of note, comparable CT levels between patients with first-episode psychosis and healthy participants were reported, in contrast to the higher rate of CT levels in individuals at the ultra-high risk phase (Ucok et al., 2015). Each of these studies reported associations with the general CT score only and not individual types of CT.

Table 1. Childhood trauma and cognitive function in patients at ultra-high risk of psychosis, patients with first-episode psychosis and healthy participants

Study	Participants (Patients / Healthy participants) <i>N</i>	Gender (Patients / Healthy participants) Male : Female	Age (Patients / Healthy participants) Mean / SD	Stress questionnaire	Cognitive domains and tests	Main findings
<b>Patients at ultra-high risk of psychosis</b>						
Ucok et al. 2015	UHR = 53	UHR = 39 : 14	UHR = 21.10 ± 4.80	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Rey auditory verbal learning test for verbal learning and memory</li> <li>• Stroop task for executive function, cognitive flexibility and processing speed</li> <li>• WCST for executive function and working memory</li> <li>• Continuous performance test for sustained attention</li> <li>• WAIS-R, trail making test and N-Back task for working memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• UHR with physical trauma performed worse in contrast to UHR w/o physical trauma on executive function</li> <li>• Significant negative correlation between physical neglect and working memory in UHR with CT</li> <li>• No significant differences between UHR with or w/o emotional trauma, sexual trauma, emotional neglect and general cognitive ability, memory and executive function</li> </ul>
<b>Patients with first-episode psychosis and healthy participants</b>						
Aas et al. 2012a	FEP = 83 HP = 63	FEP = 52 : 32 HP = 26 : 37	FEP = 27.40 ± 7.90 HP = 28.00 ± 7.70	CECA-Q	<ul style="list-style-type: none"> <li>• NART for premorbid IQ</li> <li>• WAIS-R for full-scale IQ, attention, concentration, processing speed, verbal fluency, visuo-spatial perception and verbal intelligence</li> <li>• Rey auditory verbal learning test and WMS-R for verbal learning and memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• CT was significantly negatively correlated with performance on general cognitive ability and executive function in FEP when contrasted to HP</li> </ul>

					<ul style="list-style-type: none"> <li>• Compendium of Neuropsychological Tests and WAIS-R for working memory and executive function</li> </ul>	
<b>Aas et al. 2011</b>	FEP = 138 HP = 138	FEP= 73 : 65 HP = 64 : 74	FEP = 30.6 ± 10.9 HP = 32.2 ± 9.3	CECA-Q	<ul style="list-style-type: none"> <li>• NART for premorbid IQ</li> <li>• WAIS-R for full-scale IQ</li> <li>• WMS-R for verbal and visual learning and memory, executive functions and working memory, attention, mental speed, language, visuo-construction/</li> <li>• perceptual abilities, verbal intelligence</li> <li>• WAIS-R for attention,/concentration and processing speed, language, verbal intelligence</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• In FEP with CT, significant associations between CT events and poorer performance on general cognitive ability when compared to FEP w/o CT</li> </ul>

Abbreviations: CECA-Q, Childhood Experience of Care Abuse Questionnaire; CT, Childhood trauma; CTQ, Childhood Trauma Questionnaire; FEP, patients with first-episode psychosis; HP, healthy participants; IQ, intelligence quotient; NART, National Adult Reading Test; UHR, Ultra – high risk subjects of schizophrenia; WAIS-III, Wechsler Adult Intelligence Scale - III; WAIS-R, Wechsler Adult Intelligence Scale - Revised; WCST, Wisconsin Card Sorting Test; WMS-III, Wechsler Memory Scale; WMS-R, Wechsler Memory Scale – Revised; WTAR, Wechsler Test of Adult Reading.

Study	Participants (Patients / Healthy participants) <i>N</i>	Stress questionnaire	Stressful events (Patients / Healthy participants)	Stress severity (Patients / Healthy participants) Mean / SD	Stress frequency (Patients / Healthy participants) Percentage or <i>N</i>	Combination of CT frequency and severity (Patients / Healthy participants) Percentage or <i>N</i>
<b>Patients at ultra-high risk of psychosis</b>						
Ucok et al., 2015	UHR = 53	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Total CTQ = 40.4 ± 12.6</li> <li>• Physical abuse = 6.4 ± 2.8</li> <li>• Emotional abuse = 9.5 ± 4.5</li> <li>• Sexual abuse = 5.8 ± 3.0</li> <li>• Emotional neglect = 14.7 ± 5.0</li> <li>• Physical neglect = 4.1 ± 1.5</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into low and high CT levels</li> <li>• High CT levels:</li> <li>• Physical abuse = 41.5%</li> <li>• Emotional abuse = 57.7%</li> <li>• Sexual abuse = 24.4%</li> <li>• Emotional neglect = 59.6%</li> <li>• Physical neglect = 0%</li> </ul>
<b>Patients with first-episode psychosis and healthy participants</b>						
Aas et al., 2012a	FEP = 83 HP = 63	CECA-Q	<ul style="list-style-type: none"> <li>• Either parent died</li> <li>• Separation from either parent</li> <li>• Physical abuse</li> <li>• Sexual abuse</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent/non-severe and severe CT levels</li> </ul>
Aas et al., 2011	FEP = 138 HP = 138	CECA-Q	<ul style="list-style-type: none"> <li>• Either parent died</li> <li>• Separation from either parent</li> <li>• Physical abuse</li> <li>• Sexual abuse</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent/non-severe and severe CT levels</li> <li>• Either parent died = 9% (FEP) versus 8% (HP)</li> <li>• Separation from either parent = 50% (FEP) versus 31% (HP)</li> <li>• Physical abuse = 24% (FEP) versus 13% (HP)</li> </ul>

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- Sexual abuse = 16% (FEP)  
versus 8% (HP)
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Supplementary Table 1. Childhood trauma assessment and analysis - Patients at ultra-high of psychosis, patients with first-episode psychosis and healthy participants

Abbreviations: CECA-Q, Childhood Experience of Care Abuse Questionnaire; CTQ, Childhood Trauma Questionnaire; CT, Early-life stress; FEP, patients with first-episode psychosis; HP, healthy participants; UHR, Ultra – high risk subjects of schizophrenia.

### **3.2 Childhood trauma and cognitive function in patients with chronic schizophrenia, bipolar disorder or psychosis**

In the 15 studies reviewed, a variety of neuropsychological tasks were used to measure general cognitive ability, memory function and executive function (Table 2). Across these studies, three different questionnaires and one standardized interview were used for the retrospective subjective assessment of CT: (1) the Risky Families Questionnaire (RFQ; (Taylor et al., 2006)), (2) the CTQ, (3) the Childhood Adversity Questionnaire (CAQ; (Rosenman and Rodgers, 2004), and (4) the Early Trauma Inventory (ETI; (Bremner et al., 2000)). Instead of questionnaires, one additional study based their assessment of childhood adversity on information retrieved from medical charts and unstructured patient interviews (Online Resource 2). The RFQ assesses severity of adverse childhood events, including harsh parenting and overt family conflict (Taylor et al., 2006). The CAQ measures the frequency of childhood maltreatment across 21 items (Rosenman and Rodgers, 2004). The ETI is a 56-item clinical interview for the assessment of physical abuse, emotional abuse, and sexual abuse before and after the age of 18 years. In addition, general traumatic events are measured ranging from parental loss to natural disasters. Frequency is assessed based on the developmental stage, onset and termination of the events, perpetrator, and effect on the individual (Bremner et al., 2000).

Five studies reported total severity scores, which were based on the RFQ (Poletti et al., 2017), the CAQ (Green et al., 2014), the CTQ (Marshall et al., 2016, Mansueto et al., 2017), and information retrieved from medical charts and non-standardized interviews (Schenkel et al., 2005). Thirteen studies used a composite score of severity and frequency and used dichotomous variables of CT exposure of (1) low versus high levels (Poletti et al., 2017, Aas et al., 2012b, Shannon et al., 2011, Mansueto et al., 2017), (2) absent versus high levels (Bucker et al., 2013, Kelly et al., 2016), (3) absent versus existent levels (van Os et al., 2017, Green et al., 2014, Green et al., 2015, McCabe et al., 2012, Schenkel et al., 2005) or (iv) below versus above the median split (Aas et al., 2012b) for the subscales or total scores. However not all studies reported mean group-level data for these measures. One study also utilized CT severity and frequency as a continuous variable (van Os et al., 2017).

#### **3.2.1 General versus stressor-specific roles of childhood trauma on cognitive function in patients with chronic bipolar disorder**

For patients with bipolar disorder, four studies found evidence of an association between greater CT experience and poorer cognitive performance (Bucker et al., 2013, Poletti et al., 2017, Aas et al., 2012b, Marshall et al., 2016) (Table 2). This association was observed for measures of general cognitive ability (Poletti et al., 2017, Aas et al., 2012b), memory function (Bucker et al., 2013) and executive function (Marshall et al., 2016). A similar negative association was also observed in a healthy participant group in the study by Bucker et al. (2013) and in a combined patient/healthy participant group in the study by Poletti et al. (2017) (Bucker et al., 2013, Poletti et al., 2017). Of these studies, only Aas et al. (2012b) reported stressor-specific roles, which provided the basis for a significant association between increased levels of physical abuse, sexual abuse and physical neglect which was linked with reduced general cognitive ability in patients with bipolar disorder but not in patients with schizophrenia (Aas et al., 2012b). No significant associations between other specific stressors, such as emotional neglect were observed for general cognitive ability, memory or executive function.

Table 2. Childhood trauma and cognitive function in patients with established bipolar disorder, schizophrenia, psychosis and healthy participants

Study	Participants (Patients / Healthy participants) <i>N</i>	Gender (Patients / Healthy participants) Male : Female	Age (Patients / Healthy participants) Mean / SD	Stress questionnaire	Cognitive domains and tests	Main findings
<b>Patients with established bipolar disorder and healthy participants</b>						
<b>Poletti et al. 2017</b>	BD = 76 HP = 90	BD = 51 : 51 HP = 24 : 33	BD = 47.75 ± 11.58 HP = 29.60 ± 10.55	RFQ	<ul style="list-style-type: none"> <li>• BACS for verbal memory, working memory, psychomotor speed and coordination, selective attention, semantic fluency, letter fluency</li> <li>• WCST for executive functions</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Significant effect of high levels of CT on poorer global cognitive ability across BD and HP groups</li> <li>• Significant effect of high levels of CT on poorer speed of processing in BD with opposite pattern in HP</li> </ul>
<b>Bucker et al. 2013</b>	BP = 64 HP = 28	BP = 28 : 36 HP = 11 : 17	BP = 22.89 ± 4.36 HP = 22.78 ± 4.90	CTQ (28 – item version)	<ul style="list-style-type: none"> <li>• NART and Kaufman Brief Intelligence Test for intellectual ability</li> <li>• TMT, Stroop Test and Color Naming Trials for processing speed and executive function</li> <li>• CVLT for attention and verbal memory</li> <li>• WMS-III for working memory</li> <li>• CANTAB for attention, working memory, executive function and nonverbal memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Poorer performance in memory for BP with CT in contrast to BP w/o CT</li> <li>• Poorer performance in memory for BP with CT in contrast to HP w/o CT</li> <li>• Significant negative correlation between greater number of CT events and poorer performance on memory in BP group</li> <li>• Significant negative associations between greater number of CT events and poorer performance on (i) executive functioning and (ii) memory in HP group</li> </ul>

<b>Marshall et al. 2016</b>	BP = 233 HP = 90	BP w CT = 32 : 85 BP w/o CT = 42 : 74 HP w CT = 8 : 9 HP w/o CT = 28 : 45	BP w CT = $40.90 \pm 11.40$ BP w/o CT = $38.70 \pm 13.10$ HP w CT = $36.50 \pm 14.20$ HP w/o CT = $37.40 \pm 14.10$	CTQ (28 – item version)	<ul style="list-style-type: none"> <li>• WASI for general cognitive ability</li> <li>• Go/No-Go Task for attention and inhibitory control</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Significant main effect of CT on executive function</li> <li>• Significantly negative correlation between present CT and reduced executive function in BP group</li> </ul>
<b>Patients with established schizophrenia and bipolar disorder</b>						
<b>Aas et al. 2012b</b>	SZ = 239 BP = 167	SZ + BP = 214 : 192	SZ + BP = $30.07 \pm 3.00$	CTQ (28 – item version)	<ul style="list-style-type: none"> <li>• WASI for general cognitive function, perception, visuospatial abilities and verbal abilities</li> <li>• CVLT for verbal memory, verbal fluency and executive function</li> <li>• WMS-III for working memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Significant relationships between PA, sexual abuse, physical neglect and poorer performance on general cognitive ability and executive function in BP group</li> <li>• No significant relationships between emotional neglect and general cognitive ability, memory and executive function</li> </ul>
<b>Patients with psychosis and healthy participants</b>						
<b>van Os et al. 2017</b>	PSY = 1119 (SZ = 940) Siblings of PSY <sup>a</sup> = 1059 HP = 586	PSY = 850 : 269 Siblings of PSY <sup>1</sup> = 487 : 572 HP = 270 : 316	PSY = $27.57 \pm 7.95$ Siblings of PSY <sup>1</sup> = $27.83 \pm 8.27$ HP = $30.42 \pm 10.58$	CTQ (25-item version)	<ul style="list-style-type: none"> <li>• Baseline: WAIS-III for general cognitive functioning</li> <li>• 3 year follow-up: WAIS-III for general cognitive functioning</li> <li>• 6 year follow-up: WAIS-III short-form for general cognitive functioning</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Negative association between higher scores of CT in HP and reduced general cognitive ability at 3 time points</li> <li>• No difference between groups for moderating effect of CT on time or general cognitive ability over 6 years</li> </ul>

<b>Patients with psychosis</b>						
<b>Mansueto et al. 2017<sup>b</sup></b>	PSY = 532	PSY = 402 : 130	PSY = 27.61 (7.61)	CTQ (25-item version)	<ul style="list-style-type: none"> <li>• WAIS-III for general cognitive ability</li> <li>• World Learning Task for verbal memory</li> <li>• CTQ for attention and vigilance</li> <li>• RST for reasoning and working memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• PSY with CT performed worse on memory function than patients without CT.</li> </ul>
<b>Patients with established schizophrenia and healthy participants</b>						
<b>Green et al. 2015</b>	SZ = 617 HP = 659	SZ = 415 : 202 HP = 291 : 368	SZ = 39.65 ± 10.82 HP = 42.48 ± 13.58	CAQ (20-item version)	<ul style="list-style-type: none"> <li>• WTAR for premorbid IQ</li> <li>• RBANS for immediate memory, delayed memory, attention, language, construction</li> <li>• WAIS for working memory</li> <li>• COWAT for executive functioning</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Significant main effect of childhood maltreatment and general cognitive ability for both SZ and HP groups separately.</li> </ul>
<b>Green et al. 2014</b>	SZ = 617 HP = 659	SZ = 415 : 202 HP = 291 : 368	SZ = 39.65 ± 10.82 HP = 42.48 ± 13.58	CAQ (20-item version)	<ul style="list-style-type: none"> <li>• WTAR for premorbid IQ</li> <li>• RBANS for attention and memory function</li> <li>• WAIS for executive function</li> <li>• COWAT for executive function</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Association between CT and cognitive performance not reported</li> </ul>
<b>McCabe et al. 2012</b>	SZ = 408 HP = 267	SZ = 65.7 % male HP = 43.4 % male	SZ = 40.72 ± 11.07 HP = 39.27 ± 13.70	CAQ (20 item version)	<ul style="list-style-type: none"> <li>• WTAR and WASI for general cognitive function</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Negative associations between number of CT events and general cognitive ability across SZ and HP groups</li> <li>• In HP group only: Negative associations between number of CT events and general cognitive ability</li> </ul>

<b>Patients with established schizophrenia</b>						
<b>Ruby et al. 2017</b>	SZ = 28	SZ = 20 : 8	SZ = 31.50 (9.70)	ETI	<ul style="list-style-type: none"> <li>• WAIS-III for general cognitive ability</li> <li>• WMS-R for verbal and visual memory, attention and delayed recall</li> <li>• WCST for executive function</li> <li>• TMT for processing speed and visual attention</li> <li>• COWAT for verbal fluency</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• No association between CT and cognitive function found</li> </ul>
<b>Li et al. 2017</b>	SZ = 162	SZ = 58 : 104	SZ = 37.82 ± 10.16	CTQ (28 – item version)	<ul style="list-style-type: none"> <li>• RBANS for immediate memory, visuospatial construction, language, attention and delayed memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Significant negative correlations between physical abuse, sexual abuse and CT with executive function.</li> <li>• Significant negative correlations between physical neglect with memory and executive function.</li> </ul>
<b>Kelly et al. 2016</b>	SZ = 80	SZ = 56 : 24 Females with PA = 10 Females w/o PA = 14 Males with PA = 11 Males w/o PA = 45	Females with PA = 37.80 ± 10.80 Females w/o PA = 32.60 ± 11.90 Males with PA = 30.90 ± 7.70 Males w/o PA = 31.6 ± 9.80	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• RBANS for immediate memory, delayed memory, visuo-spatial construction, language and attention</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• No significant differences for general cognitive ability and memory between the groups</li> </ul>
<b>Shannon et al. 2011</b>	SZ = 85	SZ = 67 : 18	SZ = 41.10 ± 11.70	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• NART for premorbid IQ</li> <li>• WMS-III for verbal memory, working memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• SZ with CT performed better on general cognitive ability than SZ w/o CT</li> <li>• SZ with CT performed worse on memory than SZ w/o CT</li> <li>• SZ with CT performed better on working memory than SZ w/o CT</li> </ul>

<b>Schenkel et al. 2005</b>	SZ = 40	SZ = 25 : 15 SZ with ACE = 10 : 8 SZ w/o ACE = 15 : 7	SZ = 41.90 ± 10.70	Medical charts and interview	<ul style="list-style-type: none"> <li>• Shipley Institute of Living Scale Vocabulary Subtest for verbal intelligence</li> <li>• Hayling Sentence Completion Task for verbal processing speed and verbal inhibition</li> <li>• Brixton Spatial Anticipation Task for non-verbal problem-solving and sequencing skills</li> <li>• COWAT for verbal fluency</li> <li>• Contour Integration Test for visual context processing</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• SZ with a history of abuse performed worse than SZ w/o a history of abuse on general cognitive ability</li> <li>• No significant correlations between history of abuse and executive function</li> <li>• In a factor analysis of hospitalizations, cognitive domains, childhood problems and clinical symptoms- childhood problems and greater clinical symptomatology with cognitive impairment were significant</li> <li>• Significant effect across groups for the association between reduced general cognitive ability with greater exposure to abuse</li> </ul>
<b>Lysaker et al. 2002</b>	SZ = 36	SZ = 36 : 0	SZ = 46.00 ± 10.00	CAQ	<ul style="list-style-type: none"> <li>• WAIS-III for premorbid intelligence and working memory</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• No findings reported for relationships between trauma, general cognitive ability and executive function</li> </ul>

<sup>a</sup> No psychiatric diagnosis

<sup>b</sup> Only baseline data reported

Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia; BD, patients with bipolar disorder; CANTAB, Cambridge Neuropsychological Automated Test Battery; CATS, The Child Abuse and Trauma Scale; CAQ, Childhood Adversity Questionnaire; COWAT, Controlled Oral Word Association Test; CT, Childhood trauma; CTQ, Childhood Trauma Questionnaire; CVLT, California Verbal Learning Test; ETI, Early Trauma Inventory; HP, healthy participants; IQ, intelligence quotient; NART, National Adult Reading Test; PSY, patients with psychosis; RBANS, Repeated Battery for Assessment of Neuropsychological Status; RFQ, Risky Families Questionnaire; RST, Response Shifting Task; SD, Standard Deviation; SZ, Patients with schizophrenia; TMT, Trail Making Task; WASI, Wechsler Abbreviated Scale of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale - III; WCST, Wisconsin Card Sorting Test; WSM-III, Wechsler Memory Scale; WTAR, Wechsler Test of Adult Reading.

<b>Study</b>	<b>Participants (Patients / Healthy participants) N</b>	<b>Stress questionnaire</b>	<b>Stressful events (Patients / Healthy participants)</b>	<b>Stress severity (Patients / Healthy participants) Mean / SD</b>	<b>Stress frequency (Patients / Healthy participants) Percentage</b>	<b>Combination of CT frequency and severity (Patients / Healthy participants) Percentage or N</b>
<b>Poletti et al., 2017</b>	BD = 76 HP = 90	RFQ	<ul style="list-style-type: none"> <li>• Harsh parenting</li> <li>• Overt family conflict</li> </ul>	<ul style="list-style-type: none"> <li>• Total Score:</li> <li>• BD = 27.15 ± 8.87</li> <li>• HP = 24.20 ± 6.33</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization of low and high scores</li> </ul>
<b>Bucker et al., 2013</b>	BP = 64 HP = 28	CTQ (28 – item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent and high CT levels</li> <li>• High levels:</li> <li>• BP with trauma = 40.6%</li> <li>• HP with trauma = 32.1%</li> </ul>
<b>Aas et al., 2012b</b>	SZ = 174 BP = 167	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into low and high CT levels</li> <li>• High CT levels:</li> <li>• Physical abuse = 15.6%</li> <li>• Emotional abuse = 34.2%</li> <li>• Sexual abuse = 21.6%</li> <li>• Emotional neglect = 9.3%</li> <li>• Physical neglect = 46.4%</li> <li>• Total score - low levels (below median) = 54.19%</li> <li>• Total score - high levels (above median) = 45.07%</li> </ul>

<b>Marshall et al., 2016</b>	BP = 233 HP = 90	CTQ (28 – item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Total CTQ = <math>60.30 \pm 12.50</math> (BP) versus <math>52.00 \pm 8.20</math> (HP)</li> <li>• Physical abuse = <math>15.60 \pm 4.80</math> (BP) versus <math>12.80 \pm 4.10</math> (HP)</li> <li>• Emotional abuse = <math>8.90 \pm 4.00</math> (BP) versus <math>8.80 \pm 3.30</math> (HP)</li> <li>• Sexual abuse = <math>10.90 \pm 6.70</math> (BP) versus <math>7.60 \pm 4.10</math> (HP)</li> <li>• Emotional neglect = <math>15.60 \pm 4.60</math> (BP) versus <math>13.50 \pm 4.00</math> (HP)</li> <li>• Physical neglect = <math>7.70 \pm 1.60</math> (BP) versus <math>9.10 \pm 1.90</math> (HP)</li> </ul>	• Not reported	• Not reported
<b>van Os et al., 2017</b>	PSY = 1119 Siblings of PSY <sup>a</sup> = 1059 HP = 586	CTQ (25-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	• Not reported	• Not reported	<ul style="list-style-type: none"> <li>• Continuous variable</li> <li>• Dichotomous variable of absent and existent CT exposure at baseline.</li> <li>• Total scores for existent levels: <ul style="list-style-type: none"> <li>• PSY = 27.3%</li> <li>• Siblings = 18.6%</li> <li>• HP = 15.4%</li> </ul> </li> </ul>
<b>Mansueto et al., 2017<sup>b</sup></b>	PSY = 532	CTQ (25-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	• Total CTQ = $1.62 (\pm 0.51)$	• Not reported	<ul style="list-style-type: none"> <li>• Dichotomization into non-severe or severe CT levels</li> <li>• Non-severe CT levels 429</li> <li>• Severe CT levels = 103</li> </ul>

<b>Green et al., 2015</b>	SZ = 617 HP = 659	CAQ (20-item version)	<ul style="list-style-type: none"> <li>• Total score</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> <li>• Any CAQ exposure</li> <li>• Abuse or neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported for all participants</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent or existent CT levels</li> <li>• Existent CT levels:</li> <li>• Physical abuse = 27.5% (SZ) – 13.6% (HP)</li> <li>• Emotional abuse = 44.7% (SZ) – 20.4% (HP)</li> <li>• Sexual abuse = 7.3% (SZ) – 1.2% (HP)</li> <li>• Emotional neglect = 55.3% (SZ) – 26% (HP)</li> <li>• Physical neglect = 25.3% (SZ) – 17.2% (HP)</li> <li>• Any CAQ exposure = 93.1% (SZ) – 74.5% (HP)</li> <li>• Abuse or neglect = 69.4% (SZ) – 44.2% (HP)</li> </ul>
<b>Green et al., 2014</b>	SZ = 617 HP = 659	CAQ (20-item version)	<ul style="list-style-type: none"> <li>• Total score</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Loss</li> <li>• Family dysfunction</li> <li>• Financial difficulties</li> </ul>	<ul style="list-style-type: none"> <li>• Total CAQ score:</li> <li>• SZ = 6.25 ± 4.87</li> <li>• HP = 2.85 ± 3.19</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent or existent CT levels</li> <li>• Physical abuse = 20.26% (SZ) – 10.32% HP</li> <li>• Emotional abuse = 32.90% (SZ) – 15.48% (HP)</li> <li>• Sexual abuse = 5.35% (SZ) – 0.91% (HP)</li> <li>• Emotional neglect = 40.68% (SZ) – 20.91% (HP)</li> <li>• Loss = 40.68% (SZ) – 31.11% (HP)</li> <li>• Family dysfunction =</li> </ul>

						66.29% (SZ) – 54.02% (HP)
						• Financial difficulties = 18.6% (SZ) – 13.05% (HP)
<b>McCabe et al., 2012</b>	SZ = 408 HP = 267	CAQ (20 item version)	<ul style="list-style-type: none"> <li>• Five factors of stress types</li> <li>• Abusive Parenting</li> <li>• Loss, Poverty and Sexual Abuse</li> <li>• Neglectful Parenting</li> <li>• Dysfunctional Parenting</li> <li>• Sibling Loss</li> </ul>	• Not reported	• Not reported	<ul style="list-style-type: none"> <li>• Dichotomization into absent or existent CT levels</li> <li>• Abusive Parenting = 63.3% (SZ) – 40.9% (HP)</li> <li>• Loss, Poverty and Sexual Abuse = 45.6% (SZ) – 35.5% (HP)</li> <li>• Neglectful Parenting = 51.0% (SZ) – 23.3% (HP)</li> <li>• Dysfunctional Parenting = 68.9% (SZ) – 34.6% (HP)</li> <li>• Sibling Loss = 5.3% (SZ) – 4.4% (HP)</li> </ul>
<b>Ruby et al., 2017</b>	SZ = 28	ETI	<ul style="list-style-type: none"> <li>• General events</li> <li>• Physical abuse events</li> <li>• Emotional abuse events</li> <li>• Sexual abuse events</li> <li>• Sum of all events</li> <li>• Negative rating of all events</li> </ul>	<ul style="list-style-type: none"> <li>• General events = 4.7 (<math>\pm 2.8</math>)</li> <li>• Physical abuse events = 2.2 (<math>\pm 1.8</math>)</li> <li>• Emotional abuse events = 2.7 (<math>\pm 2.7</math>)</li> <li>• Sexual abuse events = .88 (<math>\pm 1.8</math>)</li> <li>• Sum of all events = 10.4 (<math>\pm 6.8</math>)</li> </ul>	• Not reported	• Not reported
<b>Li et al., 2017</b>	SZ = 162	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	• Not reported	• Not reported	<ul style="list-style-type: none"> <li>• Physical abuse = 26.5%</li> <li>• Emotional abuse = 21.2%</li> <li>• Sexual abuse = 35.8%</li> <li>• Emotional neglect = 55.8%</li> </ul>

						<ul style="list-style-type: none"> <li>• Physical neglect = 66.5%</li> </ul>
<b>Kelly et al., 2016</b>	SZ = 80	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Focus on physical abuse</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent and high CT levels</li> <li>• High CT levels:</li> <li>• Females with PA = 12.5%</li> <li>• Females w/o PA = 17.5%</li> <li>• Males with PA = 13.75%</li> <li>• Males w/o PA = 56.25%</li> </ul>
<b>Shannon et al., 2011</b>	SZ = 85	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent/low versus moderate/high CT levels of total CTQ score:</li> <li>• High CT levels = 45%</li> <li>• High CT levels for different CT events:</li> <li>• Physical abuse = 10.6%</li> <li>• Emotional abuse = 14.1% (PSY)</li> <li>• Sexual abuse = 17.6%</li> <li>• Emotional neglect = 18.8%</li> <li>• Physical neglect = 16.4%</li> <li>• High CT levels:</li> <li>• 29.4% high CT levels for one CT event</li> <li>• 15.3% high levels for two or more categories</li> </ul>
<b>Schenkel et al., 2005</b>	SZ = 40	Medical charts and interview	<ul style="list-style-type: none"> <li>• History of childhood abuse or neglect</li> <li>• Physical abuse</li> <li>• Sexual abuse</li> <li>• Neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Low severity of CT events = 12.5%</li> <li>• Moderate severity of CT events = 50%</li> <li>• High severity of CT</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Dichotomization into absent or existent CT levels</li> <li>• Any experience of physical abuse, sexual</li> </ul>

				events = 37.5%		<ul style="list-style-type: none"> <li>abuse and/or neglect = 45%</li> <li>• Physical abuse = 15%</li> <li>• Sexual abuse = 10%</li> <li>• Neglect and physical abuse = 2.5%</li> <li>• Neglect and sexual abuse = 2.5%</li> <li>• Physical and sexual abuse = 10%</li> <li>• Physical abuse, sexual abuse and neglect = 5%</li> <li>• Moderate frequency of at least 2 events = 62.5%</li> <li>• Severe frequency of at last 2 events = 37.5%</li> <li>• Low severity of CT events = 12.5%</li> <li>• Moderate severity of CT events = 50%</li> <li>• High severity of CT events = 37.5%</li> </ul>
<b>Lysaker et al., 2002</b>	SZ = 36	CAQ	• Physical abuse	• 20.0 (± 5.3)	• Not reported	• Not reported

Supplementary Table 2. Childhood trauma assessment and analysis - Patients with established bipolar disorder, schizophrenia, psychosis and healthy participants.

<sup>a</sup> No psychiatric diagnosis

<sup>b</sup> Only baseline data reported

Abbreviations: BD, patients with bipolar disorder; CATS, The Child Abuse and Trauma Scale; CAQ, Childhood Adversity Questionnaire; CTQ, Childhood Trauma Questionnaire; CT, Early-life stress; ETL, Early Trauma Inventory; HP, healthy participants; PSY, patients with psychosis; RFQ, Risky Families Questionnaire; SZ, Patients with schizophrenia.

### 3.2.2 General versus stressor-specific roles of childhood trauma on cognitive function in patients with chronic schizophrenia

In studies of patients with schizophrenia, patients generally showed significantly higher rates of CT and reduced cognitive performance compared to healthy participants. Five studies reported significant *negative* associations between increased CT exposure and poorer cognitive performance, one study reported significant *positive* associations between increased CT exposure and improved cognitive performance, and five studies reported no significant associations between CT exposure and cognitive performance (see Table 2).

Among the studies that reported an association between increased CT levels and poorer cognitive performance, two studies reported that increased CT levels were associated with poorer general cognitive ability in both patients and healthy participants (McCabe et al., 2012, Green et al., 2015). Four further studies showed significant negative associations between increased CT history and reduced cognition in patients only, either in terms of memory function (Shannon et al., 2011, Mansueto et al., 2017, Li et al., 2017), executive function (Li et al., 2017) or general cognitive ability (Schenkel et al., 2005). In the study by Shannon et al. (2011), however, results were equivocal as increased CT experience was also associated with *improved* general cognitive ability and working memory function.

In four additional studies, no associations between CT and cognitive function were observed (Green et al., 2014, Lysaker et al., 2002, Kelly et al., 2016, Ruby et al., 2017). In one study by van Os et al. (2017), separate within-group analyses in patients and healthy participants identified a relationship between higher rates of CT and reduced general cognitive ability in healthy participants only but not in patients with schizophrenia (van Os et al., 2017). Differences between the studies cannot be easily accounted for in terms of differences in gender frequency or samples sizes.

Three studies focused their investigation on the role of *specific* CT types and either general cognitive ability (Kelly et al., 2016, Schenkel et al., 2005), memory function (Kelly et al., 2016, Li et al., 2017) or executive function (Li et al., 2017) in patients with schizophrenia rather than exploring general adversity relationships. Evidence for a relationship between increased levels of physical abuse, sexual abuse and physical neglect on either reduced memory or executive function was observed in two studies (Schenkel et al., 2005, Li et al., 2017), while one study failed to find evidence of a relationship between these stressors and cognitive function (Kelly et al., 2016).

### 3.3 Childhood trauma and social cognitive function

In three studies that included a measure of social cognition, the measures used included Theory of Mind and emotion recognition (Palmier-Claus et al., 2016), and the MATRICS emotional self-regulation subtest (Garcia et al., 2016, Schalinski et al., 2017) (see Table 3).

Two of the three studies used the original version of the CTQ to assess frequency and severity of CT experience (Garcia et al., 2016, Palmier-Claus et al., 2016), while Schalinski et al. (2017) assessed CT with the Maltreatment and Abuse Chronology of Exposure (MACE) Scale (Teicher and Parigger, 2015, Schalinski et al., 2017) (Online Resource 3). The 75-item MACE Scale assesses ten subscales of CT until the age of 18 years, such as physical abuse, verbal abuse, non-verbal emotional abuse, witnessing inter-parental abuse and abuse of siblings, peer-related verbal abuse, physical bullying, intra-familial, extra-familial and peer-related sexual abuse, emotional neglect and physical neglect. Severity scores were calculated based on dichotomized CT exposure of absent versus present experience for each year. In

addition, multiplicity scores were defined as a number of different stressful event types (Teicher and Parigger, 2015). Group data for severity of CT was reported in two studies (Palmier-Claus et al., 2016, Schalinski et al., 2017). No further data for frequency or the composite score for severity and frequency for comparison between studies were available.

### **3.3.1 General versus stressor-specific roles of childhood trauma on social cognitive function**

Two studies reported significant associations between greater CT exposure and poorer social cognitive performance, one in female patients with first-episode psychosis only (Garcia et al., 2016) and one in patients with psychosis more broadly (Schalinski et al., 2017). In contrast, Palmier-Claus et al. (2016) found no evidence of an association between CT levels and social cognitive performance for either Theory of Mind or emotion recognition in either patients or healthy participants (Palmier-Claus et al., 2016).

Schalinski et al. (2017) is the only study that investigated the association between *specific* stressful events and social cognition, reporting a significant negative association between increased levels of physical neglect at age eleven with poorer performance on social cognition in patients with psychosis only (Schalinski et al., 2017).

Table 3. Childhood trauma and social cognitive function in patients at ultra-high risk of psychosis, patients with first episode of psychosis, patients with established schizophrenia and healthy participants

Study	Participants (Patients / Healthy participants) N	Gender (Patients / Healthy participants) Male : Female	Age (Patients / Healthy participants) Mean / SD	Stress questionnaire	Cognitive domains and tests	Main findings
<b>Schalinski et al. 2017</b>	PSY = 168 (SZ = 134) HP = 50	PSY = 112 : 56 HP = 28 : 22	PSY = 27.90 ± 8.40 HP = 26.80 ±7.90	MACE Scale	<ul style="list-style-type: none"> <li>• MCCB for speed of processing, attention, working memory, verbal learning, visual learning, reasoning and social cognition</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• Negative association between early abuse at age 3 years with general cognitive ability, memory function and executive function in PSY when compared to HC</li> <li>• Negative association between physical neglect at age 11 years with social cognition in PSY</li> </ul>
<b>Palmier-Claus et al. 2016</b>	SZ = 20 FEP = 20 UHR = 14 HP = 120	SZ = 13 : 7 FEP = 16 : 4 UHR = 6 : 8 HP = 35 : 85	SZ = 39.6 ± 8.9 FEP = 24.6 ± 5.2 UHR = 22.6 ± 5.2 HP = 20.1 ± 2.5	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• ToM</li> <li>• Emotion recognition</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• No significant effects of CT on ToM or emotion recognition</li> </ul>
<b>Garcia et al. 2016</b>	FEP = 79 HP = 58	FEP = 48 : 31 HP = 30 : 28	FEP (M) = 24.4 ± 4.5 FEP (F) = 26.8 ± 5.9 HP (M) = 24.0 ± 4.8 HP (F) = 23.9 ± 4.2	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• MCCB for speed processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, social cognition</li> </ul>	<u>CT and cognitive performance</u> <ul style="list-style-type: none"> <li>• CT was significantly related to poorer social cognitive performance in female patient with FEP only</li> </ul>

Abbreviations: CANTAB, Cambridge Neuropsychological Automated Test Battery; CTQ, Childhood Trauma Questionnaire; CT, Childhood trauma; HP, healthy participants; MACE Scale, Maltreatment and Abuse Chronology of Exposure; NART, National Adult Reading Test.

Study	Participants (Patients / Healthy participants) N	Stress questionnaire	Stressful events (Patients / Healthy participants)	Stress severity (Patients / Healthy participants) Mean / SD	Stress frequency (Patients / Healthy participants) Percentage	Combination of CT frequency and severity (Patients / Healthy participants) Percentage, N, or Mean / SD
<b>Patients at ultra-high risk of psychosis, patients with first episode of psychosis, patients with established schizophrenia and healthy participants</b>						
<b>Schalinski et al., 2017</b>	PSY = 168 (SZ = 134) HP = 50	MACE	<ul style="list-style-type: none"> <li>• Physical abuse</li> <li>• Verbal abuse</li> <li>• Non-verbal emotional abuse</li> <li>• Witnessing interparental abuse</li> <li>• Abuse of siblings</li> <li>• Peer-related verbal abuse</li> <li>• Physical bullying</li> <li>• Intra-, extra-familial and peer-related sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• PSY = 29.1 (15.4)</li> <li>• HP = 13.7 (8.6)</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Duration in years:</li> <li>• PSY = 6.8 (6.3)</li> <li>• HP = 1.7 (2.8)</li> <li>• Participants with multiplicity:</li> <li>• PSY = 140 (83.3%)</li> <li>• HP = 22 (44%)</li> </ul>
<b>Palmier-Claus et al., 2016</b>	UHR = 14 FEP = 20 SZ = 20 HP = 120	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Total CTQ:</li> <li>• 45.8 ± 16.2 (UHR)</li> <li>• 39.9 ± 12.3 (FEP)</li> <li>• 45.1 ± 15.5 (SZ)</li> <li>• 31.2 ± 7.5 (HP)</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>
<b>Garcia et al., 2016</b>	FEP = 79 HP = 58	CTQ (28-item version)	<ul style="list-style-type: none"> <li>• Total CTQ</li> <li>• Physical abuse</li> <li>• Emotional abuse</li> <li>• Sexual abuse</li> <li>• Emotional neglect</li> <li>• Physical neglect</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>

Supplementary Table 3. Childhood trauma and social cognitive function in patients at ultra-high risk of psychosis, patients with first episode of psychosis, patients with established schizophrenia and healthy participants

Abbreviations: CTQ, Childhood Trauma Questionnaire; CT, Early-life stress; HP, healthy participants; MACE Scale, Maltreatment and Abuse Chronology of Exposure.

## **4 Discussion**

### **4.1 Childhood trauma and cognitive function in schizophrenia, bipolar disorder and other psychotic disorders**

The purpose of this systematic review was to summarize and discuss findings on relationships between CT and cognitive function in patients with schizophrenia, bipolar disorder with psychotic features and psychosis across all phases. In addition, we contrasted *general* versus *specific* events of CT on cognitive function. Significantly reduced cognitive function following the experience of CT was observed in patients with bipolar disorder and schizophrenia as well as healthy participants. Across study groups, associations between CT experience and cognitive performance were more variable in patients with chronic schizophrenia than in for either healthy participants, ultra high-risk individuals, first-episode patients, or patients with chronic bipolar disorder, possibly owing to the high levels of cognitive heterogeneity in this group. In addition, associations between increased CT levels and reduced cognitive function varied considerably according to the self-reported CT severity in the studies – for example, whether the group comparisons were based on patients and healthy participants with present (i.e. low and high CT severity), only low CT severity or only high CT severity. The severity level is important for the interpretation of the findings which encompass resilience, susceptibility and compensation. For social cognition, CT studies were too few and equivocal to allow conclusions to be drawn.

An important focus of our review was to examine the *general* versus *specific* roles of CT on cognitive function. Across all patient and healthy participant groups, general cognitive ability was the domain most frequently associated with increased CT experience. Based on this data, CT may be understood as representing a moderator of general cognitive ability, both in patients with psychosis and healthy participants when CT frequency/severity is high. An equally important focus of our review was to assess whether *specific* types of CT differed in their cognitive effects. Here we found that the most consistently reported association between CT and cognition was for physical trauma, physical neglect or physical abuse which was significantly negatively correlated with both general and domain specific aspects of cognition.

This systematic review complements and substantially expands evidence covered by previous reviews (Aas et al., 2014, Millan et al., 2012, Ruby et al., 2014) by synthesizing the ever growing number of studies focused on the effects of CT on cognitive function in patients with psychosis at different stages of the illnesses. It highlights the variability in cognitive performance that is observed following *general* versus *specific* stressor types and severity/frequency. Furthermore, the evidence we present for deficits in general cognitive ability in healthy participants taking part in psychosis studies is consistent with evidence in non-psychiatric cognitive studies of children, adolescents (Pechtel and Pizzagalli, 2011) and healthy adults following the experience of CT (Majer et al., 2010, Pechtel and Pizzagalli, 2011, Nakao et al., 2013, Fuge et al., 2014, Philip et al., 2016, Lovallo et al., 2016, Lovallo et al., 2013).

### **4.2 Variability in cognitive effects following childhood trauma**

While making these inferences, the evidence of inconsistencies between studies is also noteworthy. Potential reasons for the inconsistent findings of both decreased and increased cognitive performance in patients with schizophrenia, bipolar disorder and psychosis include the high variability of CT measurement and analysis approaches used. Three major points have been identified: Firstly, different stress questionnaires were administered that varied based on the assessment of a general CT score and specific stressful event type, CT severity

and CT frequency. Secondly, use of dichotomous variables of CT scores differed between studies (i.e. total CT score; absent versus present CT scores); and thirdly, group data on severity and frequency were partly lacking. The inconsistent utilization of both CT assessment and data reporting across studies did not allow a comparison despite the application of standardized questionnaires and scoring of frequency/severity levels. However, the fact that the same measurement inconsistencies were found across all groups makes it difficult to explain the schizophrenia group-related inconsistencies purely on this basis.

We further discuss differences in individual stress sensitivities that could explain both increased and decreased cognitive function: While healthy individuals with low exposure to CT may be able to overcome these challenges so that they only become evident following more severe CT exposure, the same may not be true for patients. However, the lack of reported data on CT frequency/severity on an individual level or a subgroup of study participants does not allow us to prove or disprove this hypothesis. Recent findings strongly suggest though that the role of recent stress in an individual's life (Allott et al., 2015, Reininghaus et al., 2016a, Reininghaus et al., 2016b) and the potentially stressful testing situation (Muehlhan et al., 2011, Philip et al., 2016) impact on the performance and stress coping mechanism for patients with psychosis and healthy participants. However, those cumulative stress factors have only begun to be researched in the context of CT and cognitive function in patients with psychosis (Trotta et al., 2015, Ajnakina et al., 2016, Peters et al., 2016).

The inconsistent findings regarding the association between CT and cognition in this review may be also explained by the well documented variability in cognitive performance in schizophrenia. Variability in cognitive performance is partly explained by genetic risk in schizophrenia (Blokland et al., 2016), although at least some of these genetic risk factors are likely to influence also cognitive function in other psychotic disorders (Van Assche et al., 2017, Parellada et al., 2017, Ranlund et al., 2018). Secondary environmental factors, such as low occupational level and social isolation, have also been associated with cognitive performance in chronic schizophrenia and, to a lesser extent, in bipolar disorder (Karpov et al., 2017). Above and beyond the relationships between these genetic and environmental factors on cognition, these factors may also be important for the degree to which individuals can compensate for the deleterious outcomes of CT. Emerging research suggests that gender could be implicated in the relationship between CT and cognitive function in patients with psychosis (Pruessner et al., 2017a, Kocsis-Bogar et al., 2018).

### **4.3 Limitations and suggestions for further investigations**

One limitation of this systematic review is the small number of studies available for each diagnostic group across the different illness stages. This limited our ability to make inferences about whether there are reliable distinctions about the roles of different illness stages regarding the relationships between CT and cognitive functions. In addition, other factors in the association between CT and cognition that we were unable to consider in this systematic review include biological factors such as endocrine processes, inflammatory processes and genetics. These factors were not included in this systematic review due to the very small number of available studies in psychosis for a systematic review.

Significant decreases in IL-6 levels and increases in HPA-axis hormone concentrations after acute stress have been repeatedly reported in healthy participants (Marsland et al., 2017, Steptoe et al., 2007, Slavish et al., 2015) and patients with first episode of psychosis (Pruessner et al., 2017b, Capuzzi et al., 2017). Similarly, increased levels of IL-6 after acute

stress in healthy participants with experience of CT and increased hypothalamus-pituitary-adrenal (HPA)-axis reactivity in female healthy participants with prenatal exposures were found (Carpenter et al., 2010, Carpenter et al., 2017). Importantly, endocrine alterations have been shown to affect brain structure and function in the general population (Sapolsky et al., 1986, McEwen et al., 2015) and in psychosis (Ruby et al., 2014, Phillips et al., 2006, Quide et al., 2017, Cancel et al., 2017, Cancel et al., 2015) which is further supported by animal work (Bergink et al., 2014).

Data from CT studies are likely to be somewhat skewed by the lower prevalence of CT exposure in healthy participants than in patients with psychosis. In addition, many healthy participants have not experienced any CT events, whereas those with CT exposure have often experienced several types of stressful events with varying degrees of frequency and severity (Aas et al., 2012b, Shannon et al., 2011, Schenkel et al., 2005) which is rarely considered in the analysis and interpretation of data. Support for the relevance of severity levels on brain function comes from a recent review suggesting that these factors impact differently on brain function and functional networks (Teicher et al., 2016).

## 5 Conclusion

To our knowledge, this is the first systematic review to highlight the relevance of differentiating between a *general* role of CT or *specific* CT types and the varying factors for severity and frequency on cognitive function in individuals with schizophrenia, bipolar disorder and psychosis across all phases. Evidence of a deleterious role of CT on cognition is shown and gaps in our knowledge are highlighted which is based on the inconsistent use of CT assessment, data reporting and lack of a healthy control group in some studies.

Addressing these limitations in our current understanding about the relationship between CT and cognition has the potential to significantly improve our insights into the psychobiological pathways underlying cognitive deficits after the CT experience in patients with schizophrenia, bipolar disorder and psychosis. Optimized measurement of *specific* CT events and consistent reporting of CT severity is essential to elucidate these psychological mechanisms, as previously suggested for major depressive disorder (Steine et al., 2017). Furthermore, we suggest to study different CT severity levels in schizophrenia, bipolar disorder and psychosis because different CT severity levels allow a more detailed interpretation of reduced cognitive function in the context of resilient, susceptible and compensatory mechanisms which may necessitate different individualized treatment approaches. Additionally, we propose that longitudinal study designs for investigating cognitive function after CT experience should be integrated with the measurement at least one of the following stress markers: Daily stress levels, endocrine concentrations, immunological concentrations, and genetic markers to gain a better biological understanding of the long-term consequences changes of CT on adults. We promote a better understanding of relationships between CT experience and cognitive function in schizophrenia, bipolar disorder and psychosis across all phases of the disorders for optimized prevention and treatment approaches for coping after CT experience, cognitive function and psychosis.

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**Figure legend**

**Figure 1.** Flow diagram selection of study process

**Table legend**

**Table 1.** Childhood trauma and cognitive function in patients at ultra-high of psychosis, patients with first-episode psychosis and healthy participants

**Table 2.** Childhood trauma and cognitive function in patients with established bipolar disorder, schizophrenia, psychosis and healthy participants

**Table 3.** Childhood trauma and social cognitive function in patients at ultra-high risk of psychosis, patients with first episode of psychosis, patients with established schizophrenia and healthy participants

**Supplementary Table 1.** Childhood trauma assessment and analysis - Patients at ultra-high of psychosis, patients with first-episode psychosis and healthy participants

**Supplementary Table 2.** Childhood trauma assessment and analysis - Patients with established bipolar disorder, schizophrenia, psychosis and healthy participants

**Supplementary Table 3.** Childhood trauma and social cognitive function in patients at ultra-high risk of psychosis, patients with first episode of psychosis, patients with established schizophrenia and healthy participants