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Impact of childhood trauma on positive and negative symptom remission in first episode psychosis

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ABSTRACT

Objective: Early life adversity is suspected to play an important role for onset and course of psychosis, but its relationship with longer-term clinical outcome is not entirely clear. In this longitudinal study, we investigated the impact of childhood trauma (CT) on positive and negative symptom remission in first episode psychosis (FEP) patients over two years.
Methods: A total of 210 FEP patients were assessed with the Childhood Trauma Questionnaire. Patients reporting moderate to severe trauma (CT; $N = 114$; 54.3%) were compared to those without trauma (N-CT; $N = 96$; 45.7%). Positive (PSR) and negative symptom remission (NSR) were determined monthly over 24 months following established criteria using the Scale for Assessment of Positive Symptoms and the Scale for Assessment of Negative Symptoms. Global Functioning was evaluated at baseline and 24 months of follow-up.
Results: Compared to N-CT patients, CT patients had achieved significantly lower rates of PSR at 12 months and significantly lower rates of NSR at 24 months. A dose-response relationship was observed between the number of trauma categories fulfilled and the number of patients not achieving PSR and NSR at these time points. Higher trauma scores were significantly associated with poor functioning and higher positive and negative symptom severity at 24 months, but not at baseline and 12 months of follow-up.
Conclusion: Differential effects of CT on clinical outcome may not be apparent at psychosis onset, but only become evident through poor symptomatic remission and general functioning over time. Targeted diagnostic and therapeutic efforts after illness onset might limit these detrimental consequences.

1. Introduction

Numerous studies have provided persuasive evidence for an association between early life adversity and an increased risk for psychosis onset (Varese et al., 2012). Support for a causal link comes from a recent comprehensive review on the subject confirming a dose-response relationship between childhood trauma (CT) and elevated risk for developing psychosis (Misiak et al., 2017).

Several studies have furthermore investigated the impact of childhood adversity on the trajectory of symptoms after psychosis onset. Here, two recent systematic reviews suggest that exposure to adverse events in childhood is associated with the persistence of psychotic experiences and poor treatment outcome (Thomas et al., 2019; Trotta et al., 2015). Early psychosis patients with CT experiences, compared to non-childhood trauma (N-CT) patients, showed higher levels of positive, negative, depressive and manic symptoms, as well as poorer functioning, at repeated time points over three years of treatment (Alameda et al., 2016; Alameda et al., 2017). In a longitudinal observational study over three years including patients with psychotic disorders, siblings and controls, CT was related with heightened psychotic symptoms at both baseline and three years of follow-up, but symptoms in the CT group improved to a similar extent over time as in the N-CT group (van Dam et al., 2015). A recent study was suggestive of CT effects on illness course as it reported reduced improvement of global functioning over a one-year follow-up period in FEP patients with CT (Aas et al., 2016). A review on relapse rates in psychosis requiring hospital admission following CT shows inconsistent findings (Petros et al., 2016).

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Interestingly, only few studies have investigated effects of childhood adversity on remission status following the onset of psychosis. In a study with psychiatric inpatients, those with a history of CT, compared to N-CT patients, had a 1.83 higher odds ratio for non-remission over a four months follow-up period, but the difference was not significant (Schalinski et al., 2015). In first episode-psychosis (FEP) patients, sexual or physical abuse was not related to symptomatic or functional remission at 18 months of treatment (Conus et al., 2010). Similarly, a previous study in a large group of patients with a first presentation of psychosis found no association between childhood adversity and symptomatic remission or relapse rate over one year of follow-up (Trotta et al., 2016).

These conflicting findings could be related to variations in the populations studied and in the definition of remission, including different instruments, follow-up periods and assessment intervals. The importance of a reliable assessment of remission status in psychosis is supported by a growing body of research demonstrating that symptom remission has significant implications for functional outcome (Alvarez-Jimenez et al., 2012; Cassidy et al., 2010a; Jordan et al., 2014) and quality of life (Brissos et al., 2011; Emsley et al., 2007; Haro et al., 2014; Haynes et al., 2012; Heering et al., 2015; Kokacya et al., 2016; Madhivanan et al., 2017). Consensus criteria for symptomatic remission have been recently documented and tested (Andreasen et al., 2005; Cassidy et al., 2010a). It has furthermore been proposed that a consistent definition of *both* positive (PSR) and negative symptomatic remission (NSR) is critical to allow reliable inferences about future functional outcome (Cassidy et al., 2010a).

Primary aim of our study was to assess the impact of childhood trauma on positive and negative symptom remission, defined according to previously established criteria, in FEP patients during their initial 24 months of treatment in a specialized early intervention program. We furthermore tested the association of childhood trauma with symptom severity and functioning at different times of follow-up.

2. Material and methods

2.1. Participants

A total of 210 FEP patients (144 men and 66 women; mean age 23.73 ± 4.43 years) had provided data on childhood trauma in the context of previous studies. All patients were enrolled in the Prevention and Early Intervention Program for Psychosis (PEPP) in Montreal, Canada (Iyer et al., 2015). PEPP is an early intervention service for patients experiencing a first episode of a psychotic disorder (non-affective or affective) based on DSM-IV criteria. Patients must be between 14 and 35 years of age, have an IQ > 70, and be able to communicate in either English or French. Patients were not accepted into the program if they had been treated with antipsychotic medication for more than one month prior to admission or their psychotic symptoms were drug-induced. PEPP offers low dose pharmacotherapy, assertive case management, regular symptom monitoring, and various psychosocial interventions over a period of two years. All patients provided informed consent to have their data used for research purposes and signed a consent form approved by the Research Ethics Board of the Douglas Mental Health University Institute. For minors, additional written informed consent was obtained from a parent or guardian.

2.2. Assessment of childhood trauma

Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998; Bernstein et al., 2003). The CTQ is a 25-item self-report retrospective measure of experiences of abuse and neglect during childhood. Individual items are rated on a five-point Likert scale, and scores of each item are summed up (some items require recoding) to constitute five subscales (physical neglect, emotional neglect, physical abuse, emotional abuse, and sexual abuse). Total scores for abuse and neglect were calculated by adding up scores in the respective subscales. The sum of all five subscales was used as the total trauma rating. Scores for each of the five subscales were categorized into none, mild, moderate, and severe levels of maltreatment, using cut-off scores based on validation studies in healthy and clinical populations (Bernstein and Fink, 1998). For the purpose of the present study, CTQ total and subscales category scores were further categorized into binary variables labeling patients with mild or no trauma as the non-childhood trauma (N-CT) and those in the moderate to severe category as the childhood trauma (CT) group. A cumulative measure of CT was furthermore created by adding up the number of trauma types (emotional abuse, emotional neglect, physical abuse, physical neglect, sexual abuse) on which patients scored in the moderate to severe range. Good reliability and validity of retrospective reports of childhood adversity in patients with a recent onset of psychosis has been demonstrated (Fisher et al., 2011).

2.3. Assessment of remission

Symptom remission was defined according to severity criteria established by the Schizophrenia Working Group (Andreasen et al., 2005). Patients were considered to be in PSR if their score was 2 or less on all global subscales of the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984a) (i.e. hallucinations, delusions, bizarre behavior, formal though disorder) and to be in NSR if they scored 2 or less on all global subscales except 'attention' of the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984b) (i.e. affective flattening, alogia, avolition-apathy, anhedonia-asociality). In the present study, remission status was verified every month over a period of 24 months based on regular symptom evaluations by trained raters with high levels of inter-rater reliability (Jordan et al., 2018). When symptom ratings were not available, they were reconstructed based on clinical notes. In case of missing information, we employed the last observation carried forward method (LOCF). Data that did not include baseline and 12-month, respectively baseline and 24-month evaluations and showed a gap in evaluations of more than 6 consecutive months were excluded from analysis. The present study employed a duration of three continuous months as a meaningful time in remission (Cassidy et al., 2010a) and furthermore considered remission times of as short as one month in order to capture subtle improvements and to calculate total months in remission.

The following measures of PSR and NSR were determined at 12 and 24 months of follow-up: (1) binary variables indicating if remission was achieved for at least one month, (2) binary variables indicating if remission was achieved for at least three consecutive months, and (3) continuous variables indicating the number of total months in remission.

2.4. Assessment of demographic and clinical characteristics

Demographic information included gender, age, ethnicity, education and relationship status. Socioeconomic status of patients and their parents was determined using the Four-factor Index of Social Status (Hollingshead, 1975). Information on substance use and dependence and psychotic disorder diagnoses, classified into affective and non-affective psychosis, was based on the Structured Interview for DSM IV Axis I disorders (First et al., 1997). Duration of untreated illness (DUI) and duration of untreated psychosis (DUP) in weeks were determined through the Circumstances of Onset and Relapse Schedule (CORS) (Norman et al., 2004), a semi-structured interview based on the Interview for the Retrospective Assessment of Schizophrenia (IRAOS) (Hafner et al., 1992). For an assessment of medication effects, the individual dose of antipsychotic medication at 12 and 24 months of follow-up was transferred into Chlorpromazine equivalents (CPZE) based on minimum effective doses (Woods, 2003; Woods, 2005). For depot medication, the daily dose was divided by the number of days until the next injection.

2.5. Assessment of symptom severity and functioning

Positive and negative symptom severity at baseline and follow-up was assessed with the SAPS (Andreasen, 1984a) and the SANS (Andreasen, 1984b). Depression at all time points was assessed with the Calgary Depression Scale (Addington et al., 1990). Overall functioning was assessed with the Global Assessment of Functioning (GAF) scale (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington, DC 1994 (pp. 25–35)). Baseline ratings represent the severity of symptoms and functioning leading up to the initial episode, follow-up ratings at 12 and 24 months refer to the month prior to the assessment. All clinical ratings were conducted by trained research staff.

2.6. Statistical analyses

CTQ, DUP and DUI scores and CPZE were log-transformed to correct for skewed distributions. Chi-squared tests, *t*-tests, and univariate ANOVAs were employed to calculate differences between N-CT and CT patients in demographic, clinical and remission variables and in medication dose at 12 and 24 months. Demographic, clinical and medication variables that were significantly different between groups were entered as covariates in the ANOVAs assessing CT effects on remission. Spearman correlations were calculated to determine associations between trauma severity, months in remission, global functioning and symptom severity. Chi-square tests were used to determine if a dose response relationship between the number of trauma types (no trauma, one trauma, two or more traumas) and positive and negative remission status at 12 and 24 months was present.

3. Results

3.1. Demographic variables and clinical characteristics at baseline

Out of all 210 FEP patients included in the study, a total of 114 patients (54.3%) reported moderate to severe childhood trauma (CT) whereas 96 patients (45.7%) reported no or only mild childhood trauma (N-CT). Forty-seven patients (22.4%) reported one kind of trauma, 30 (14.3%) reported two, 19 (9.0%) reported three, 10 (4.8%) reported four and 8 (3.8%) reported all five kinds of trauma. Table 1 shows differences between CT and N-CT patients in demographic variables and clinical characteristics at baseline. Patients with a history of CT had experienced a significantly longer duration of untreated illness (DUI) compared to N-CT patients. The proportion of patients not taking antipsychotic medication at 12 and 24 months was similar in the CT and N-CT groups (15.5% vs. 15.7%, $p = .971$ and 10.5% vs. 13%, $p = .723$; respectively). However, in patients which did take neuroleptic medication, those with CT experiences received significantly higher doses at 12 and 24 months of follow-up compared to patients without CT ($t(117) = -2.05$; $p = .043$ and $t(71) = -3.31$; $p = .001$; respectively). Thus, DUI and medication dose were included as covariates in subsequent analyses where appropriate.

3.2. Symptom remission over 12 and 24 months

Of the 210 patients with CTQ data, complete data on PSR were available for 144 patients (68.6%) over 12 months, and for 101 patients (48.1%) over 24 months. Data on NSR were available for 134 patients (63.8%) over 12 months, and for 89 patients (42.4%) over 24 months. Table 2 shows total rates and group differences in PSR and NSR at the 12- and 24- month assessment times. While most FEP patients had achieved at least one month of PSR within the first year of follow-up, this rate was significantly lower in CT compared to N-CT patients (79.5 vs. 94.4%; $\chi^2 = 6.99$, $P = .008$). CT patients were also less likely than N-CT patients to show sustained PSR of at least three months (68.5% vs. 88.7%; $\chi^2 = 8.73$, $P = .003$) and had fewer total months in PSR within the first year ($F(1) = 5.89$, $P = .016$). The latter remained significant when DUI was included as a covariate ($F = 4.21$; $p = .042$).

Over 24 months of follow-up, almost all patients had achieved PSR for at least one month, with no difference between CT and N-CT patients (93.6% vs. 96.3%, $P = .54$). Here, fewer CT than N-CT patients had achieved NSR for at least one month (65.9% vs. 85.4%; $\chi^2 = 3.67$, $P = .030$). The prevalence of continuous NSR over three months and the total months in NSR over 24 months were not significantly different between CT and N-CT patients (all $P > .096$).

For cases with data on PSR at 12 and 24 months and on NSR at 12 and 24 months, the LOCF method had been used in 8 (5.6%), 9 (8.9%), 49 (36.6%) and 33 (37.1%) cases, respectively. Sensitivity analyses in subgroups without these cases revealed similar CT effects on poor PSR at 12 months. Patients who had experienced CT were less likely to experience at least three months of continued PSR ($\chi^2 = 7.82$; $p = .005$) and fewer total months in PSR ($F = 5.59$; $p = .019$). However, the finding of poor NSR at 24 months in patients with trauma history could not be confirmed in the smaller group (all $p > .42$).

Table 1
Demographic information and clinical characteristics at baseline in FEP patients with and without childhood trauma.

	Available N, total (N-CT/CT)	Total group	N-CT	CT	Statistic	*p*-value
Demographic information						
Gender, male N(%)	210 (96/114)	144(69)	60(41.7)	84(58.3)	$\chi^2 = 3.025$	0.082
Age of entry to FEP program, mean (SD)	210 (96/114)	23.7 (4.43)	23.58 (4.63)	23.85 (4.46)	$t = -0.431$	0.667
Ethnicity, Caucasian, N (%)	203 (92/111)	124 (61.1)	57 (62.0)	67 (60.4)	$\chi^2 = 0.054$	0.816
Education, ≥ high school, N (%)	205 (95/110)	141 (68.8)	66 (69.5)	75 (68.2)	$\chi^2 = 0.040$	0.842
Relationship status, single, N (%)	210 (96/114)	190 (91.5)	83 (86.5)	107 (93.9)	$\chi^2 = 3.313$	0.069
Substance abuse and dependence, N (%)	203 (94/109)	110 (54.2)	47 (50.0)	63 (57.8)	$\chi^2 = 1.236$	0.266
SES Patient, ≤ lower middle class, N (%)	163 (78/85)	104 (63.8)	47 (60.3)	57 (67.1)	$\chi^2 = 0.815$	0.367
SES Mother, ≤ lower middle class, N (%)	97 (46/51)	32 (33.0)	16 (34.8)	16 (31.4)	$\chi^2 = 0.127$	0.721
SES Father, ≤ lower middle class, N (%)	95 (48/47)	29 (30.5)	14 (29.2)	15 (31.9)	$\chi^2 = 0.085$	0.771
Clinical characteristics at baseline						
DUP in weeks, median (SD)[a]	181 (91/90)	18.57 (114)	15.43 (88.1)	20.71 (136)	$t = -1.56$	0.119
DUI in weeks, median (SD)[a]	184 (90/94)	255.3 (269)	199.4 (236)	290.4 (289)	$t = -2.90$	0.004
Non-affective psychosis, N (%) (vs. affective psychosis)	206 (95/111)	147(71)	62(42.2)	85(57.8)	$\chi^2 = 3.206$	0.073
GAF, mean (SD)	209 (96/113)	30.06 (8.88)	29.35 (7.69)	30.66 (9.78)	$t = -1.062$	0.289
SAPS, mean (SD)	207 (96/111)	33.96 (15.9)	34.10 (16.8)	33.83 (15.2)	$t = 0.124$	0.901
SANS, mean (SD)[b]	207 (94/113)	25.76 (14.5)	24.14 (14.3)	27.12 (14.5)	$t = -1.482$	0.140
CDS, mean (SD)	206 (96/110)	4.62 (4.71)	3.989 (4.00)	5.172 (5.20)	$t = -1.842$	0.067
BPRS -total, mean (SD)	194 (90/104)	65.31 (13.88)	64.62 (14.4)	65.91 (13.4)	$t = 0.645$	0.520

N-CT – no childhood trauma; CT– childhood trauma; SES – Socioeconomic status; DUP – Duration of untreated psychosis; DUI – Duration of untreated illness; GAF – Global Assessment of Functioning; SAPS – Scale for the Assessment of Positive symptoms; SANS – Scale for the Assessment of Negative symptoms; CDS – Calgary Depression Scale; [a] statistics based on log-transformed data; [b] excluding items assessing attention.

Table 2
Positive and negative symptom remission over one and two years of treatment in FEP patients with and without childhood trauma.

	All	N-CT	CT	Statistic	p-value
12 months					
Positive symptom remission	$N = 144$	$N = 71$	$N = 73$		
One month, N (%)	125 (86.8)	67 (94.4)	58 (79.5)	$\chi^2 = 6.99$	0.008
Three months, N (%)	113 (78.5)	63 (88.7)	50 (68.5)	$\chi^2 = 8.73$	0.003
Total months, mean (SD)	7.70 (4.3)	8.56 (3.7)	6.86 (4.7)	F = 5.89	0.016[a]
Negative symptom remission	$N = 134$	$N = 66$	$N = 68$		
One month, N (%)	90 (67.2)	46 (69.7)	44 (64.7)	$\chi^2 = 0.38$	0.539
Three months, N (%)	72 (53.7)	36 (54.5)	36 (52.9)	$\chi^2 = 0.04$	0.852
Total months, mean (SD)	3.64 (3.8)	4.05 (3.9)	3.25 (3.6)	F = 1.73	0.190
24 months					
Positive symptom remission	$N = 101$	$N = 54$	$N = 47$		
One month, N (%)	96 (95.0)	52 (96.3)	44 (93.6)	$\chi^2 = 0.03$	0.536
Three months, N (%)	93 (92.1)	51 (94.4)	42 (89.4)	$\chi^2 = 0.89$	0.345
Total months, mean (SD)	17.3 (7.1)	18.0 (6.8)	16.5 (7.4)	F = 1.12	0.293
Negative symptom remission	$N = 89$	$N = 48$	$N = 41$		
One month, N (%)	68 (76.4)	41 (85.4)	27 (65.9)	$\chi^2 = 3.67$	0.030
Three months, N (%)	61 (68.5)	34 (70.8)	27 (65.9)	$\chi^2 = 0.25$	0.614
Total months, mean (SD)	8.76 (7.7)	10.0 (7.9)	7.29 (7.3)	F = 3.21	0.096

FEP: first episode psychosis; N-CT: no childhood trauma; CT: childhood trauma.
[a] Result still significant when duration of untreated illness was included as covariate in the ANOVA (F = 4.21; $p = .042$).

Including antipsychotic medication as a covariate in the above ANOVAs, resulted in non-significant effects of childhood trauma on the total months in positive remission at 12 months (F = 2.64; $p = .107$) and negative remission and 24 months ($p = .52$).

3.3. Subscales of childhood trauma and symptom remission

Total trauma severity was correlated with fewer months of PSR at 12 months and fewer months of NSR at 24 months. Exploratory analyses with all five CT subscales showed that correlations between CT and total months of PSR at 12 months were driven by sexual abuse, physical and emotional neglect, whereas correlations between CT and NSR at 24 months were driven by emotional abuse (Table 3).

3.4. Dose response relationship between number of traumata and symptom remission

There was evidence for a dose-dependent relationship between the number of trauma categories fulfilled and the remission status (Table 4). Odds ratios for a status of 'no positive symptom remission' at 12 months of follow-up increased from 2.7 with one category of CT to 6.2 with two or more categories of CT ($\chi^2 = 9.54$; $p = .002$). Odds for a lack of NSR at 24 months of follow-up increased from 2.7 with one trauma category to 3.3 with two or more trauma categories ($\chi^2 = 4.47$; $p = .034$).

3.5. Childhood trauma, global functioning and symptom severity over two years

Considering only patients who had valid data at all time points, total trauma scores were not related to global functioning or symptom severity at baseline or 12 months (all $p > .13$), but showed significant associations with functioning (rho = −0.25; $p = .032$) and all symptom categories at 24 months of follow-up (positive: rho = 0.25; $p = .028$; negative: rho = 0.38; $p = .001$; depression: rho = 0.30; $p = .015$; Table 5). Only the association between CT and negative symptom severity at 24 months of follow up survived Bonferroni corrections for multiple comparisons ($p = .05/12 = 0.004$).

4. Discussion

The present study assessed the association of childhood trauma with symptom remission in FEP patients over two years following the onset of the disorder. Patients with a history of CT were less likely than N-CT patients to achieve remission of positive symptoms during the first year of follow-up and had fewer total months of positive symptom remission during this period. Over 24 months of follow-up, CT patients were less likely to achieve NSR. A greater number of childhood trauma categories was related with fewer months in positive and negative remission at these time points in a dose response fashion. Effects of CT on global functioning and positive and negative symptom severity

Table 3
Spearman correlations between childhood trauma and total months of positive and negative symptom remission.

	Total trauma		Physical neglect		Physical abuse		Emotional neglect		Emotional abuse		Sexual abuse	
	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Total months of remission												
12 months												
Positive symptoms (N = 144)	**−0.22**	**0.008**	**−0.19**	**0.026**	−0.13	0.115	**−0.17**	**0.039**	−0.15	0.072	**−0.23**	**0.007**
Negative symptoms (N = 134)	−0.14	0.108	−0.06	0.490	−0.08	0.356	−0.09	0.295	−0.14	0.104	−0.11	0.203
24 months												
Positive symptoms (N = 101)	−0.16	0.113	−0.08	0.424	−0.17	0.092	−0.03	0.762	−0.15	0.129	**−0.20**	**0.040**
Negative symptoms (N = 89)	**−0.22**	**0.039**	−0.14	0.182	−0.15	0.177	−0.20	0.066	**−0.22**	**0.034**	−0.06	0.604

CTQ: Childhood Trauma Questionnaire.
Bold fonts indicate statistical significance.

Table 4
Number of FEP patients achieving symptom remission for at least one month related to number of trauma diagnoses fulfilled.

	No remission	Remission	Odds ratio	Linear-by-linear association, p-value
12 months				
Positive symptoms				
No trauma type n (%)	4 (5.6)	67(94.4)	1[a]	$\chi^2 = 9.54$, p = .002
One trauma type n (%)	5 (13.9)	31 (86.1)	2.7	
Two to five trauma types n (%)	10 (27.0)	27 (73.0)	6.20	
Negative symptoms				
No trauma N (%)	20 (30.3)	46 (69.7)	1[a]	$\chi^2 = 0.31$, $p = .580$
One trauma N (%)	12(35.3)	22(64.7)	1.22	
Two to five traumas N (%)	12 (35.3)	22 (64.7)	3.74	
24 months				
Positive symptoms				
No trauma type n (%)	2 (3.7)	52(96.7)	1[a]	$\chi2 = 0.07$, $p = .789$
One trauma type n (%)	2 (8.7)	12 (91.3)	4.33	
Two to five trauma types n (%)	1 (4.2)	23 (95.8)	1.13	
Negative symptoms				
No trauma N (%)	7 (14.6)	41 (85.4)	1[a]	$\chi2 = 4.47$, p = .034
One trauma N (%)	6 (31.6)	13 (68.4)	2.70	
Two to five traumas N (%)	8 (36.4)	14 (63.6)	3.34	

FEP: first episode psychosis.
[a] Reference category.

were not observable at treatment onset and 12 months, but were pronounced at 24 months of follow-up. Exploratory analyses revealed that the impact of CT on PSR was driven by physical and emotional neglect, whereas poor NSR at 24 months was associated with emotional abuse.

Our findings support the notion that a history of CT has implications that go beyond the extensively reported elevated risk for onset of a psychotic disorder (Misiak et al., 2017; Varese et al., 2012), and additionally affects the course of the illness. Such research has found consistently higher symptom severity over time in CT victims following illness onset (Alameda et al., 2016; Alameda et al., 2017; Conus et al., 2010; Schalinski et al., 2015; Trotta et al., 2016; van Dam et al., 2015). However, to the best of our knowledge, the present study is the first to demonstrate CT effects on actual positive and negative symptom remission over 24 months of follow-up.

The relevance of these findings is highlighted by observations that poor symptom remission is associated with reduced functional outcome (Alvarez-Jimenez et al., 2012; Cassidy et al., 2010a; Jordan et al., 2014) and quality of life (Brissos et al., 2011; Emsley et al., 2007; Haro et al., 2014; Haynes et al., 2012; Heering et al., 2015; Kokacya et al., 2016; Madhivanan et al., 2017). In fact, it is the length of combined PSR and NSR which explains the largest proportion of variance in functioning at one and two years of follow-up (Jordan et al., 2014).

A possible reason for the paucity of previous studies finding CT effects on symptom remission might be the heterogeneous patient and age groups assessed and the lack of a clear definition of remission. In contrast, all patients in the current study were diagnosed with a consistently defined first episode of psychosis, had a limited age range of 14 to 35, and were treated in the same early intervention program (Iyer et al., 2015). Remission of both positive and negative symptoms was determined based on expert consensus guidelines for symptom severity (Andreasen et al., 2005) and thorough monthly symptom monitoring over two years following treatment onset (Jordan et al., 2014; Veru et al., 2016).

With respect to the length of remission, Andreasen et al. postulated that symptoms had to be absent for six months (Andreasen et al., 2005). However, there was no clear justification for this time criterion, and a subsequent study indicated that a three-month continuous remission criterion (as used in the current study) has equal predictive validity for functioning (Cassidy et al., 2010a). Exploratory analyses of our data using the six-month criterion did not reveal any significant results (data not shown). It is possible that the limited follow-up period of 24 months did not yield a large enough number of patients in remission for a sufficiently powered statistical analysis. We furthermore considered remission times of as short as one month and the number of total months in remission as dependent variables, increasing our chances to detect even subtle effects of CT exposure on symptom remission.

Interestingly, CT was not associated with positive and negative symptom severity and general functioning at baseline and 12 months of follow-up, possibly related to symptomatic and functional instability early during the illness course. In contrast, we observed distinct associations between CT and more severe positive and negative symptoms, depression and reduced functioning at 24 months of follow-up, suggesting that CT effects on the clinical picture of psychosis only become apparent after the acute effects of psychosis have been treated. We recently reported that associations between CT and the course of symptoms are highly sex specific (Pruessner et al., 2019).

Although our finding of a dose response relationship between CT and remission status at follow-up suggest a causal relationship, it is possible that the observed association is mediated by other variables. For example, it has been shown that patients with adverse childhood experiences show poor medication adherence (Tessier et al., 2017), a generally poor treatment response (Thomas et al., 2019) and, possibly related to both, receive higher doses of medication (Schneeberger et al., 2014). Particularly positive symptom reduction early in treatment has been associated with medication adherence (Cassidy et al., 2010b; Jordan et al., 2018). Poor medication adherence could thus explain the observed CT effect on PSR at one year of follow-up. In contrast, antipsychotic medication has little effects on negative symptoms (Fusar-Poli et al., 2015; Remington et al., 2016), suggesting that negative symptoms are less affected by possible CT effects on adherence with treatment. Indeed, we observed higher medication doses in CT compared to N-CT patients, which were identified as confounders in our analyses on the association between CT and symptom remission. While it is likely that higher medication doses are a consequence of poor remission, our findings suggest that they also have the potential to limit the impact of CT on clinical outcome, possibly by compensating for poor adherence and respsonse to treatment.

Another factor that could have mediated the association between CT and symptom remission is poor premorbid adjustment. Evidence for an association between CT and poor premorbid function stems from studies in high risk patients, early psychosis patients and schizophrenia

Table 5
Comparison of Spearman correlations between total trauma scores and clinical measures at different assessment times.

	GAF			SAPS			SANS			CDS		
	rho	*p*	*n*	*rho*	*p*	*n*	*rho*	*p*	*n*	*rho*	*p*	*n*
Time of assessment												
Baseline	0.02	0.843	*77*	−0.04	0.736	*77*	0.12	0.314	*73*	−0.03	0.803	*67*
12 months [a]	−0.06	0.611	*76*	0.16	0.179	*76*	0.18	0.131	*72*	0.04	0.761	*67*
24 months [a]	**−0.25**	**0.032**	*77*	**0.25**	**0.028**	*77*	**0.38**	**0.001**	*73*	**0.30**	**0.015**	*67*

GAF - Global assessment of functioning; SAPS - Scale for Assessment of Positive Symptoms; SANS - Scale for Assessment of Negative Symptoms; CDS - Calgary Depression Scale.
Bold fonts indicate statistical significance.
[a] Only patients with complete data on positive and negative symptomatic remission at all time points were included in the analysis.

patients (Alameda et al., 2015; Chan et al., 2019; Tikka et al., 2013). Poor premorbid adjustment may be an early sign of neurobiological alterations (Kilian et al., 2017), possibly as a consequence of CT. A recent study demonstrated that PSR at one year and NSR at two years of follow-up mediated between premorbid adjustment and functional outcome (Jordan et al., 2018). Furthermore, patients with a history of CT in the present study tended to experience more non-affective than affective forms of psychosis. Non-affective symptoms have been related to a worse clinical profile over time (Torrent et al., 2018), a finding that could be related to the associations observed in the present study.

It is possible that the reporting of early life adversity in the present study is biased by current psychopathology. However, observations of high accordance between subjective reports and clinical notes as well as stability of CT measures over time (Fisher et al., 2011), together with prospective studies (Kelleher et al., 2013; Okkels et al., 2017) and cumulative evidence supporting a dose-response relationship between CT and poor mental health outcomes (Misiak et al., 2017) have largely ruled out such reverse causation.

Our findings in CT subscales support previous studies, in which physical and emotional neglect have been associated with a more severe psychopathological profile (Garcia et al., 2016; Schalinski et al., 2015). Emotional abuse, on the other hand, has been associated with positive symptoms (van Dam et al., 2015) and psychopathology in general (Samplin et al., 2013), but not with negative symptoms particularly. It has also been associated with mood disorders (Ostefjells et al., 2017; Schulz et al., 2017) and schizotypy (Goodall et al., 2015), possibly mediated by heightened stress vulnerability and poor attachment (Goodall et al., 2015; Shapero et al., 2014). Our previous study in this data set suggests a strong gender effect, showing that the experience of emotional abuse was significantly more likely in male compared to female patients (Pruessner et al., 2019). The unexpected finding of an association between emotional abuse and poor negative symptom remission in the present study might thus be more meaningful when gender differences and stress vulnerability are considered.

There are several clinical implications of our findings. Given the observed association between childhood trauma and symptom remission as well as the long-term effects of poor symptomatic outcome on function and quality of life, therapeutic interventions in psychosis should not only attempt to increase remission times of positive and negative symptoms, but should ideally also target potentially maintaining factors for poor remission related to childhood trauma. It has actually been proposed that a history of CT can be considered as a new psychotic phenotype, which requires specific therapeutic interventions (Misiak et al., 2017). Thus efforts should be made to routinely identify a history of CT early in the course of the illness in patients entering FEP or high-risk programs and to integrate trauma-focused treatments into clinical service. Several therapeutic approaches have been proven effective to reduce the burden of the experienced trauma (Kienle et al., 2017; Lincoln et al., 2017; Schafer and Fisher, 2011; Schauer and Neuner, 2011; Swan et al., 2017) and have the potential to avert or at least limit problematic long-term consequences of CT on the course of the illness.

The initial years following psychosis onset are believed to constitute a critical period for intervention during which specialized treatments can offset poor symptomatic and functional outcomes (Birchwood et al., 1998; Lutgens et al., 2015). Indeed, recent data suggest that specialized intervention provided over five years compared to regular care has a positive impact on the length of PSR and NSR (Malla et al., 2017). Because of its important role for functioning and quality of life, special emphasis should be placed on early detection or prevention of negative symptoms (Jordan et al., 2018; Lyne et al., 2012; Melle et al., 2008; Rabinowitz et al., 2012).

Limitations of the study include the short follow-up period of two years in a rather young patient group and a decline in the number of patients with available data over time. Some symptom data had to be reconstructed based on clinical notes or through imputation to obtain 12 or 24-month remission ratings. We acknowledge the disadvantage of this approach compared to face-to face interviews, as it can only estimate symptom severity. Nevertheless, sensitivity analyses have confirmed our results for PSR, supporting our conclusion that a history of childhood trauma diminishes rates of symptomatic remission. With respect to the non-significant results of sensitivity analyses for NSR, it can be assumed that particularly patients with a continuously high negative symptom load had dropped out of follow-up at the FEP program. Analyses in this smaller study group might then not have had enough statistical power to evoke significant results. Other limitations include the risk of false positive test results due to multiple testing. Extended longitudinal study designs and the inclusion of larger patient groups would facilitate the investigation of CT effects on symptomatic remission of various duration and would allow more meaningful sensitivity analyses. Regular symptom assessments in a larger study group and over extended follow-up periods would furthermore permit to study the assessment of long-term functional outcome and quality of life using intra-individual study designs as well as long-term benefits of trauma-specific treatment on remission.

Finally, future research in this area should address potential mediating factors between CT and clinical outcome measures. Besides a closer inspection of premorbid adjustment and medication adherence, it is reasonable to assume that protective factors such as social support and neurobiological alterations play a mediating role between early life adversity and symptom progression in psychosis (Pruessner et al., 2017). A better understanding of these pathways might also offer additional avenues of intervention.

5. Conclusions

In conclusion, the present findings add to the comprehensive literature describing childhood trauma effects on mental health in adulthood. While previous studies have shown an increased risk for psychosis and persistence of symptoms associated with CT, the present findings additionally provide compelling evidence for CT effects on poor symptomatic remission and functional outcome over two years following illness onset. Future research needs to investigate clinical outcomes in psychosis over longer follow-up periods and gather information on the benefits of early identification and treatment of CT for the prevention or delay of poor remission and associated long-term toxic effects on functioning and quality of life.

CRediT authorship contribution statement

Marita Pruessner contributed to study design, data collection, analysis, interpretation and writing of the manuscript. Suzanne King contributed to recruitment of patients for childhood trauma assessment and to the interpretation of results. Franz Veru provided data for symptom remission. Inga Shalinski contributed to statistical analyses and interpretation of results. Nadia Vracotas and Sherezad Abadi contributed to data collection for childhood trauma and clinical symptoms. Ashok Malla contributed to recruitment of patients. Martin Lepage, Gerald Jordan, Srividya Iyer, Jai Shah and Ridha Joober contributed to interpretation of the findings and writing of the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

None.

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