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Decoding the impact of adverse childhood experiences on the progression of schizophrenia

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ABSTRACT

Adverse childhood experiences are frequently present in patients with mental disorders, including those with schizophrenia. Whereas an impact of childhood adversities on psychopathology and potential neuroendocrine/biological mediators has been reported for posttraumatic stress disorder, depression, and anxiety disorders, the relationships in schizophrenia remain to be clarified. The present study compared amount and types of adverse childhood experiences (screened by interview) between individuals at risk for psychosis (n = 29), early schizophrenia patients with 1–2 admissions (n = 34), chronic schizophrenia patients with multiple admissions (n = 24), and healthy comparison participants (n = 38). It was expected that at-risk individuals and early-stage as well as chronic patients report more childhood adversities than controls, and that adversity load predicts psychotic symptom severity and altered neuroendocrine regulation based on hair cortisol concentration. Results confirmed more childhood adversities in clinical groups than in controls, and relationships between total childhood adversities and increased positive symptom severity. Hair cortisol concentration did not differ between groups, but early abuse experiences predicted lower hair cortisol concentration, and the latter predicted severity of specific psychotic symptoms in the clinical sample. In conclusion, individuals at risk and with manifest schizophrenia experienced substantial childhood maltreatment, as reported for other diagnoses. The present findings suggest childhood adversities as sensitizing (environmental) factor in vulnerable individuals. Lower hair cortisol concentration may indicate lasting effects of past stress experiences on stress axis function in schizophrenia, which might modulate unfolding psychopathology.

1. Introduction

Numerous studies confirmed the impact of adverse childhood experiences (ACE[1]) on mental health and the development of psychiatric disorders (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Jaffee, 2017; Kerker et al., 2015; Pirkola et al., 2005; Taillieu, Brownridge, Sareen, & Afifi, 2016), and established relationships between ACE and symptom severity or unfavorable illness courses (Nanni, Uher, & Danese, 2012; Schalinski, Fischer, & Rockstroh, 2015a; Teicher & Samson, 2013). Whereas the majority of reports targeted depression and anxiety disorders (including posttraumatic stress disorder), recent studies also confirmed high prevalence of ACE in schizophrenia patients (e.g. Bonoldi et al., 2013; Pietrek *et al.*, 2013; Read, Fosse, Moskowitz, & Perry, 2014; Schalinski et al., 2017). Further findings suggest relationships between ACE and elevated general psychopathology, positive symptoms, or cognitive deficits (see Duhig et al., 2015; Longden, Sampson, & Read, 2016; Schalinski et al., 2015a, 2018; van Nierop et al., 2015). Moreover, ACE were found to predict lower functioning in individuals at risk for psychosis and/or individuals expressing attenuated psychotic symptoms (Addington et al., 2013; Boyda & McFeeters, 2015; Kraan *et al.*, 2015; Yung et al., 2015). Additionally, more ACE varied with increased psychotic symptoms in a general population sample (Janssen et al., 2004) or genetically high-risk individuals (Heins et al., 2011; see also reviews and meta-analysis by Mayo et al., 2017; Redman, Corcoran, Kimhy, & Malaspina, 2017; Varese et al., 2012). In sum, these findings suggest an impact of ACE on psychotic development in (genetically) vulnerable individuals.

In addition to the overall amount of ACE, specific types of ACE (such as emotional, physical, or sexual abuse or neglect) have been studied to decode the meaning of childhood experiences in psychotic symptom generation. Yet, results are diverse and inconclusive (Bailey et al., 2018). Several studies reported a particular impact of childhood abuse on the severity of positive symptoms, like hallucinations or delusions, but not negative symptoms in schizophrenia patients and vulnerable

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[1] ACE: adverse childhood experiences.

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individuals (Braehler et al., 2013; Heins et al., 2011; Rajkumar, 2015; Read, Agar, Argyle, & Aderhold, 2003; Schenkel, Spaulding, DiLillo, & Silverstein, 2005; Thompson et al., 2009). Other studies found an impact of both childhood abuse and neglect on positive symptoms (Abajobir et al., 2017; Schalinski et al., 2017; Üçok & Bıkmaz, 2007), on both positive and negative symptoms (Longden et al., 2016), and again others verified a specific relationship between physical neglect and negative symptoms (Vogel et al., 2011). Different relationships between childhood experiences and symptom severity in adult patients may in part result from factors potentially moderating ACE effects during the time between experience and symptom assessment, for instance, recent life events, personality traits (Pos et al., 2016) or cognitive functioning (Berthelot et al., 2015; see also review Jaffee, 2017).

ACE exert their effects on psychological function and dysfunction through their impact on the development of brain and neuroendocrine systems that are relevant for learning, memory and coping with stress (Andersen & Teicher, 2008; Pruessner, Cullen, Aas, & Walker, 2017; Walker, Mittal, & Tessner, 2008). Moreover, ACE-related long-term alteration of the stress response system is discussed as factor moderating the risk for psychiatric disorders (Read et al., 2014; Rietschel et al., 2016; White et al., 2017). Animal and human research indicate lasting effects of chronic stress and trauma on the hypothalamus-pituitary-adrenal (HPA[2]) axis (Baumeister, Lightman, & Pariante, 2014; Curley & Champagne, 2016; McCrory, de Brito, & Viding, 2010; White et al., 2017), indexed by blunted (salivary) awakening cortisol, elevated basal cortisol concentrations, attenuated stress evoked cortisol responses, and elevated hair cortisol concentration (HCC[3]; Andrade et al., 2016; Brenner et al., 2009; Girshkin, Matheson, Shepherd, & Green, 2014; Mondelli et al., 2010). Such indices of altered HPA axis function have been reported in chronic schizophrenia patients, first-episode schizophrenia patients, and individuals at risk for psychosis (e.g. Belvederi Mondelli et al., 2010; Murri et al., 2012; Pruessner et al., 2013, 2017; Walker et al., 2008), whereas evidence on their association with psychotic symptoms is inconsistent (Karanikas, Antoniadis, & Garyfallos, 2015). For hair cortisol concentration as index of long-term accumulated cortisol levels, relationships of high ACE and elevated hair cortisol levels were reported in women with stress-related disorders (Schalinski, Elbert, Steudte-Schmiedgen, & Kirschbaum, 2015b) and postpartum in mothers with the minor allele of the FKBP5 genotype (Koenig et al., 2018). Other studies reported lower hair cortisol concentration upon exposure to ACE in children/adolescents (White et al., 2017), in students (Kalmakis, Meyer, Chiodo, & Leung, 2015) or depressed patients (Hinkelmann et al., 2013). Recently, Steudte-Schmiedgen, Kirschbaum, Alexander, and Stalder (2016) suggested an initial increase of hair cortisol concentration upon traumatic experiences and a subsequent long-term attenuation. Regarding the meaning of hair cortisol concentration in clinical disorders, results differ depending on diagnoses and the relationship with symptoms. For instance, augmented hair cortisol concentration in first-episode patients (relative to healthy controls) was reported together with a relationship between general symptoms and hair segment changes over time (Andrade et al., 2016). In contrast, Streit et al. (2016) found elevated hair cortisol levels only in bipolar but not in schizophrenia patients, although hair cortisol concentration was related to manic symptoms in both groups[4]. Moreover, the relationship between ACE, hair cortisol concentration, and psychopathology remains to be clarified. It might be assumed that a higher ACE load affects HPA axis regulation, and that it is reflected by altered hair cortisol concentration.

The present study aimed at clarifying the impact of amount and type of ACE on presence and severity of psychotic symptoms and hair cortisol concentration by comparing individuals with subclinical and manifest schizophrenia symptoms. Three samples characterized by the severity of psychotic psychopathology were recruited: individuals defined as "at risk" (AR[5]) on the basis of prodromal psychotic symptoms, patients admitted for 1st or 2nd treatment for schizophrenia spectrum disorder (ICD-10 diagnoses F2) characterized as "early stage" (ES[6]), and chronic schizophrenia patients (CS) with at least 5 inpatient admissions. These clinical groups were compared to a sample of healthy comparison participants (HC) recruited from the community. We investigated the prevalence of ACE and relationships between ACE and hair cortisol concentrations as an index of long-term stress effects on HPA axis regulation (Russell, Koren, Rieder, & Van Uum, 2012; Stalder et al., 2017). In the clinical samples, we additionally examined the relationship between ACE, hair cortisol concentration and symptom severity. Investigations were based on the following hypotheses:

(1) The amount of ACE is higher in at-risk individuals and patients with manifest schizophrenia than in HC. As previous research did not indicate clear differences in ACE between at-risk individuals, first-episode, and chronic patients, and was inconclusive regarding the type of experience, no specific hypotheses for group and/or type differences were formulated.
(2) The amount of ACE varies with symptom severity (measured by Brief Psychiatric Rating Scale, BPRS,[7] sum score). In view of inconclusive evidence on the relationship between types of ACE and positive and negative symptoms, no specific hypotheses were formulated.
(3) ACE modulates hair cortisol concentration in psychotic patients and this varies with psychotic symptom severity. In view of diverse findings on reduced, normal or increased hair cortisol concentration in patients compared to controls, no hypothesis on the direction of association between the three measures ACE, hair cortisol concentration, and symptom severity was phrased.

2. Material and methods

2.1. Participants

In total, $N = 101$ participants were recruited at the outpatient clinic and at wards specialized for the treatment of psychoses of the local Center for Psychiatry. Eligible persons (see Fig. 1 for an overview of recruitment and sample sizes per stage of assessments and Table 1 for demographic and clinical characteristics of participants) were assigned to three groups, (1) $n = 29$ individuals diagnosed as at risk for psychosis (AR) by trained psychologists applying the Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al., 2008). Risk status was fulfilled if (a) attenuated psychotic symptoms (i.e. hallucinations, suspiciousness, unusual thought content and conceptual disorganization as items of the BPRS) were present at the current moment or within the last 2 weeks, and/or (b) past episodes (< 1 week) of transient distinct psychotic symptoms (brief limited intermittent psychotic symptoms, BLIPS) were reported, and/or (c) genetic disposition combined with prodromal symptoms according to DSM-III-R (e.g. magical thinking, unusual perceptual experiences, peculiar behavior; DSM-III criteria were chosen because prodromal symptoms were no longer included in DSM-IV) and unspecific risk factors (like depression, attention deficits, anxiety), or (d) only prodromal symptoms were present (see

[2] HPA: hypothalamus pituitary axis.
[3] HCC: hair cortisol concentration.
[4] these studies did not evaluate ACE.

[5] AR: individuals at risk for psychosis. The meaning of 'at risk for psychosis' varies with criteria/definition of risk, such as genetic risk (with ultra-high risk, UHR, defining individuals with affected first-degree relatives) or presence of subclinical, attenuated symptoms. The latter definition informed the present at-risk sample.
[6] ES: early-stage schizophrenia, CS: chronic schizophrenia, HC: healthy comparison participants.
[7] BPRS: Brief Psychiatric Rating Scale.

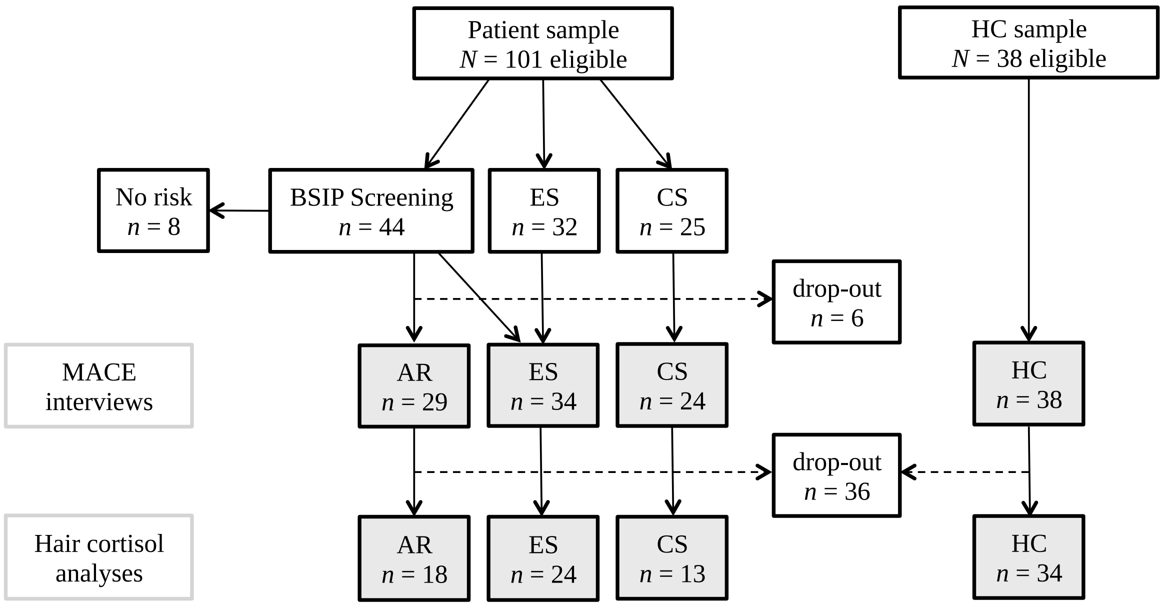

Fig. 1. Flowchart of sample composition. HC = healthy controls, AR = at-risk individuals, ES = early-stage schizophrenia patients, CS = chronic schizophrenia patients, BSIP = Basel Screening Instrument for Psychosis, MACE = Maltreatment and Abuse Chronology of Exposure. Samples included in statistical analyses are displayed in grey. *n* = 6 individuals dropped out prior to the assessments since they did not provide consent to the interview. *n* = 36 individuals dropped out before hair cortisol analyses due to either insufficient hair length (*n* = 15), lack of consent (*n* = 5), uncompleted hair sample analyses (*n* = 9) or exclusion of outliers (*n* = 7).

Table 1b for risk categories and comorbid psychopathology).

(2) *n* = 34 inpatients with diagnoses of schizophrenia spectrum disorders during their first or second admission were defined as early schizophrenia patients (ES). They were diagnosed by experienced psychiatrists/psychologists meeting diagnoses of paranoid-hallucinatory schizophrenia (ICD-10 code: F20.0, *n* = 22), acute psychotic episodes (F23.1, F23.2, *n* = 10), or delusional disorder (F22.0, *n* = 1). Comorbid diagnoses in ES patients were harmful cannabis use (*n* = 10; F12.1), harmful use of multiple drugs (*n* = 2; F19.1), cannabis dependence syndrome (*n* = 1; F12.2), harmful alcohol use (*n* = 1; F10.1), mixed personality disorder (n = 1; F61.0), post-traumatic stress disorder (*n* = 1; F43.1), and disturbance of activity and attention (*n* = 1; F90.0).

(3) *n* = 24 inpatients with a minimum of 5 admissions for schizophrenia spectrum disorders (*M* = 11.08, *SD* = 6.93) were defined as chronic schizophrenia (CS) patients. Patients met ICD diagnoses of F20.0, F20.1 or F20.4 (*n* = 21) or F25.0 or F25.1 (*n* = 3). Comorbid diagnoses in CS patients were harmful alcohol use (*n* = 4; F10.1), harmful use of multiple drugs (*n* = 2; F19.1), and harmful cannabis use (*n* = 1; F12.1).

All participants had been admitted to the hospital for acute symptoms but were in a post-acute, stable state at the time of assessment. For early-stage and chronic patients, the time between admission and assessment varied between 2 and 4 weeks. At-risk individuals were assessed within the 1st or 2nd week after admission, as they were most often released within 1–2 weeks. At the time of the assessments, *n* = 10 (of 29) AR, *n* = 32 (of 34) ES and all 24 CS patients were medicated with first or second generation antipsychotics (see Table 1 for chlorpromazine equivalents). Inpatients were invited to participate in the hospital's standard rehabilitation program, which includes 2–3/week individual psychotherapy sessions, group cognitive and social skill trainings, work therapy, and physical exercise. Except for individual psychotherapy, attendance was optional with most inpatients attending 1–3 treatment offers. Alcohol consumption is not allowed during inpatient treatment, while smoking is usually intense in medicated schizophrenia patients, as in our samples (see Table 1).

The three clinical groups (AR, ES, CS) did not differ in gender, years of school education nor IQ scores (measured by a German test for premorbid intelligence; Lehrl, 2005), and antipsychotic medication (only comparing medicated individuals). Chronic patients were older, had higher BPRS negative symptom scores and obtained lower functioning levels (GAF[8]) than early-stage patients and at-risk individuals, who did not differ in age, positive BPRS symptom scores, and global functioning (see Table 1).

N = 38 healthy controls (HC) were recruited among university students and the local community to be demographically comparable to the at-risk and schizophrenia patient samples. HC were screened with the Mini International Neuropsychiatric Interview (Ackenheil, Stotz-Ingenlath, Dietz-Bauer, & Vossen, 1999) for exclusion of any current or past psychiatric disorder. Patient samples and HC did not differ in gender distribution and years of school education, but HC attained higher IQ scores and were younger than the total clinical sample (see Table 1).

2.2. Measures and design

The study was approved by the Institutional Review Board of the local university. Participants provided written informed consent prior to the assessment, which included the interview on childhood adversities and hair sampling. Participants received 15 Euros upon completion of the assessment, which lasted about 1–2 h.

Adverse childhood experiences were assessed using the German version (Isele et al., 2014) of the Maltreatment and Abuse Chronology of Exposure (MACE[9]) scale (Teicher & Parigger, 2015). The MACE consists of 75 items that retrospectively screen 10 different types of childhood maltreatment, of which 2 are subsumed under the category ‘neglect’ (emotional and physical neglect) and 8 refer to experiences of ‘abuse’ (parental physical abuse, parental verbal abuse, parental nonverbal emotional abuse, sexual abuse, peer emotional violence, peer physical violence, witnessed violence towards parents and witnessed violence towards siblings). Severity of each experience is evaluated between 0 to 10, with the sum of all items (interpolated to account for the number of items per type) representing the severity per subscale.

[8] GAF: global assessment of functioning scale, DSM-IV.

[9] MACE: Maltreatment and Abuse Chronology of Exposure.

Table 1
Characteristics of the clinical samples and the healthy control group: demographic data, clinical variables, adverse childhood experiences, hair sample variables, and symptom severity.

	HC (n = 38)	AR (n = 29)	ES (n = 34)	CS (n = 24)	Group statistics	AR vs. ES	ES vs. CS	AR vs. CS	HC vs. AR	HC vs. ES	HC vs. CS
Gender (f/m)	14/24	6/23	12/22	5/19	χ^2 (3) = 3.48, p = .32						
Age, *M(SD)*	23.97 (4.40)	22.48 (4.22)	24.03 (4.79)	35.50 (9.08)	F(3,60.27) = 13.73, ***p* < .001**	p = .53, [−3.73 0.86]	***p* < .001**, [−15.36 −7.26]	***p* < .001**, [−16.83 −9.10]	p = .50, [−0.58 3.56]	p = 1.0, [−2.22 2.15]	***p* < .001**, [−15.27 −7.51]
Education, *M(SD)*	11.68 (1.32)	11.28 (1.46)	11.53 (1.52)	11.54 (1.35)	F(3121) = 0.46, p = .71						
IQ, *M(SD)*	110.00 (9.50)	101.76 (9.79)	102.24 (9.55)	105.50 (13.10)	F(3121) = 4.72, ***p* = .004**	p = .99, [−5.42 4.35]	p = .73, [−9.45 2.93]	p = .66, [−9.93 2.98]	***p* = .01**, [3.19 12.63]	***p* = .01**, [3.06 12.16]	p = .47, [−1.76 10.11]
Cig./day, *M(SD)*	2.39 (5.63)	5.83 (8.06)	8.06 (9.21)	18.46 (16.51)	F(3,57.17) = 9.14, ***p* < .001**	p = .74, [−6.30 2.03]	***p* = .04**, [−18.16 −2.87]	***p* = .01**, [−6.30 2.03]	p = .22, [−6.68 −0.18]	***p* = .02**, [−9.05 −2.01]	***p* = .001**, [−23.50 −8.97]
GAF, *M(SD)*	-	48.48 (8.68)	51.03 (7.86)	42.67 (9.85)	F(2,83) = 6.50, ***p* = .002**	p = .46, [−6.68 1.56]	***p* = .004**, [3.34 13.05]	p = .07, [.83 11.13]			
CPZ, *M(SD)*	-	297.00 (228.39)	378.56 (361.46)	617.58 (532.97)	F(2,63) = 3.05, p = .05						
ACE variables											
MACE total, *M(SD)*	1.56 (1.00)	3.02 (1.64)	2.72 (1.57)	2.97 (1.46)	F(3121) = 8.04, ***p* < .001**	p = .89, [−0.71 1.19]	p = .92, [−1.21 0.76]	p = 1.0, [−1.03 0.98]	***p* = .001**, [−2.14 −0.64]	***p* = .003**, [−2.01 −0.42]	***p* = .001**, [−2.23 −0.60]
Abuse, *M(SD)*	1.68 (1.12)	2.99 (1.54)	2.95 (1.61)	3.07 (1.54)	F(3121) = 7.31, ***p* < .001**	p = 1.0, [−0.81 1.02]	p = .99, [−1.18 0.91]	p = 1.0, [−1.11 0.96]	***p* = .002**, [−2.10 −0.59]	***p* = .002**, [−2.11 −0.46]	***p* = .003**, [−2.33 −0.55]
Neglect, *M(SD)*	1.08 (1.15)	3.14 (2.64)	1.79 (1.81)	2.60 (1.79)	F(3121) = 7.56, ***p* < .001**	p = .11, [−0.64 2.06]	p = .34, [−1.76 0.76]	p = .82, [−1.31 1.72]	***p* = .002**, [−2.73 −0.46]	p = .21, [−1.85 0.01]	***p* = .004**, [−2.49 −0.32]
Hair sample variables											
HCC in pg/mg, *M(SD)*	6.12 (3.86)	6.68 (2.77)	6.63 (3.48)	6.06 (3.13)	F(3,82) = 0.18, p = .91						
Hair washes/week, *M(SD)*	5.40 (2.06)	4.98 (2.12)	4.42 (2.74)	3.91 (1.53)	F(3,94) = 2.06, p = .11						
Semi-permanent hair coloration, %	22.6	10.5	26.1	30.8	χ^2 (3) = 2.42, p = .49						
Symptom severity											
BPRS Sum, *M(SD)*	-	42.10 (7.47)	44.21 (7.57)	48.58 (9.67)	F(2,83) = 3.58, ***p* = .03**	p = .42, [−6.64 1.34]	p = .28, [−8.21 1.30]	***p* = .03**, [−10.71 −1.39]			
BPRS PS, *M(SD)*	-	8.71 (2.40)	8.76 (3.36)	9.58 (3.28)	F(2,83) = 0.66, p = .52						
BPRS NS, *M(SD)*	-	7.46 (2.59)	7.59 (3.04)	10.50 (3.87)	F(2,83) = 7.64, ***p* = .001**	p = .98, [−1.49 1.27]	p = .98, [−4.81 −1.03]	***p* = .01**, [−4.97 −1.21]			

Note. M(SD) = mean (standard deviation). Age in years, Education = years of school education, IQ = score according to the German standard test, MWT-B; Lehrl, 2005, Cig./day = number of cigarettes per day, GAF = Global Assessment of Functioning, CPZ = chlorpromazine equivalent (for n = 10 ARP, n = 32 ES and all CS), ACE = adverse childhood experiences, MACE = Maltreatment and Abuse Chronology of Exposure, HCC = hair cortisol concentration, BPRS = Brief Psychiatric Rating Scale (PS, positive symptoms and NS, negative symptoms), HC = healthy control subjects, AR = at-risk individuals, ES = early-stage schizophrenia patients, CS = chronic schizophrenia patients. Level of significance was set at $p \leq 0.05$. If homogeneity of variance was not given, Welch-tests were reported. Statistics for hair cortisol were computed with the natural log-transformed data and the covariate hair washing frequency. Non-significant group differences were not followed-up by specific comparisons between samples. Games-Howell post hoc tests were applied. 95% bootstrapped confidence intervals are reported for post hoc tests in square brackets.

Table 1b
Risk categories defining at-risk individuals and their comorbid diagnoses.

	Number of AR individuals, $n = 29$
Risk category	
a) APS	$n = 20$
b) BLIPS	$n = 7$
c) Genetic disposition & prodromal signs	$n = 2$
d) only prodromal signs	$n = 6$
Combination of categories a-c	$n = 5$
Comorbid diagnoses (ICD-10)	
Affective disorders (F30, F31, F32, F33)	$n = 22$
Psychoactive substance abuse (F10, F12, F19)	$n = 6$
Anxiety or stress-related disorders (F40, F41, F42, F43)	$n = 6$
No comorbid disorders	
> 1 comorbid diagnoses	$n = 2$ $n = 7$

Note. AR = at-risk individuals, APS = attenuated psychotic symptoms, BLIPS = brief limited intermittent psychotic symptoms, ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision.

The sum of all subscales and their severity scores add up to the total ACE score. Severity scores were determined separately for abuse and neglect types as the sum of 8 abuse and 2 neglect subscales. The abuse, neglect and the total score were divided by the included respective subscales, resulting in the applied abuse, neglect, and MACE total scores ranging from 0 to 10. ACE age and duration can be determined by noting the age of experience (0–18 years) for each item/attested experience (in the present analysis this measure was used only for probing the importance of early experiences).

Symptom severity was rated for each at-risk individual and each schizophrenia patient by the responsible psychologist or psychiatrist using the Brief Psychiatric Rating Scale (BPRS; Lukoff, Nuechterlein, & Ventura, 1986). Presence and severity of each of 24 symptoms is rated on 7-point scales and ratings were summed up separately for positive and negative symptoms (following Ventura, Nuechterlein, Subotnik, Gutkind, & Gilbert, 2000), and for all symptoms as measure of general severity.

Hair cortisol concentration (HCC) was determined from hair strands (of at least 3 cm length) that were cut from two different posterior vertex locations in close proximity to the participant's scalp. Hair samples were stored at room temperature protected from daylight in separate pieces of aluminium foil. In the laboratory, hair strands were cut into samples of 3 cm length for further analyses. Assuming a hair growth of about 1 cm per month (see also Wennig, 2000, and Stalder et al., 2017 for factors that determine and modify HCC measures) accumulated cortisol levels for the past 3 months were analyzed. See Fig. 1 for the number of analyzed hair samples per group and respective drop-out rates due to insufficient hair length, individual rejection or missing data. 4–10 mg hair extracts were washed with 2.5 ml isopropanol and glucocorticoids were retrieved with 1800 ml methanol at 45°C for 18 h. In the resuspended extracts, cortisol concentration was measured by a commercial immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany). For a detailed protocol of cleaning, processing and analyses of the hair samples see Kirschbaum, Tietze, Skoluda, and Dettenborn (2009). A natural log-transformation served to reduce positive skewness of HCC (pg/mg). In addition, $n = 7$ participants with a difference of more than 2 standard deviations from the mean were excluded as outliers prior to further statistical analyses.

2.3. Statistical hypothesis testing

Statistical tests were accomplished using the software IBM SPSS Statistics 25.0. The level of significance was set at $p \leq 0.05$. Normal distribution was examined with the Kolmogorov-Smirnov test. As normal distribution of residuals was not verified for all models, bootstrapping was applied to reduce bias.

As further assumptions for parametric testing were fulfilled, differences in ACE between groups per hypothesis (1) were examined by repeated measures analyses of variance with the between-subject factor Group (comparing AR, ES, CS, and HC) and the within-subject factor Type (abuse and neglect). In separate univariate analyses of variance, (1) total number of experiences, and (2) the accumulated number of abuse and neglect experiences were compared between groups. A significant main effect of Group was verified in post-hoc tests (Games-Howell) for specific group differences.

Addressing hypothesis (2), Pearson's correlations tested relationships between ACE and symptom severity (separately for BPRS sum score, positive and negative symptoms score). Symptom severity correlated with age, since CS patients achieved both the highest age and the highest symptom scores ($r = 0.30, p = .006$). Addressing hypothesis (3), HCC was compared between groups by means of an analysis of covariance (ANCOVA), including hair washing frequency as covariate (see Dettenborn, Tietze, Kirschbaum, & Stalder, 2012; Stalder et al., 2017; after verifying that HCC did not vary with age, $r = -0.07$, $p = .50$, and gender distribution, $r = -0.15, p = .18$). The relationship between ACE, HCC, and symptom scores was examined regressing overall load and subtypes on HCC, and HCC on BPRS symptom scores across at-risk individuals and schizophrenia patient groups.

3. Results

3.1. ACE distribution

Fig. 2 illustrates that at-risk individuals and schizophrenia patients (ES and CS) reported more total ACE than HC. The group differences were evident for both abuse and neglect (see Table 1 for mean values). A main effect Group ($F(3121) = 8.41, p < .001$) confirmed higher total ACE in the three clinical groups compared to HC. The main effect Type ($F(1121) = 14.07, p < .001$) verified more abuse than neglect across all groups (for simple effects, see group statistics in Table 1). A significant Group x Type interaction ($F(3121) = 4.49$, $p = .01$) resulted from similar neglect experiences in ES and HC, in contrast to more neglect experiences in at-risk individuals and CS than in HC (see Table 1).

As groups differed in age and, hence, during the time elapsed between childhood experiences and retrospective ACE assessment, participants may have experienced further stressful events (e.g. Matz, Pietrek, & Rockstroh, 2010 for psychosis, and Stalder et al., 2017 for HCC), a potential impact of age was evaluated by Pearson's correlations. While there was no significant relationship between total ACE and age ($r = 0.13$, $p = .16$), more ACE varied with lower IQ as a trend ($r = -0.16, p = .07$). Moreover, an analysis of covariance with age and IQ as covariates showed similar results as reported above for total ACE ($F(3119) = 6.06$, $p = .001$), abuse ($F(3119) = 6.22$, $p = .001$), and neglect ($F(3119) = 5.48$, $p = .001$[10]).

3.2. Relationship between ACE and symptom severity

Pearson's correlations (Table 2) confirmed that more total ACE, more abuse, and more neglect experiences were associated with higher symptom severity (BPRS sum). Evaluating positive and negative symptoms separately supported significant relationships between (more) abuse and (more) neglect experiences and (more) positive symptoms, whereas no relationships were confirmed for negative symptoms. The relationship between total ACE and positive symptoms was prominent in AR ($r = 0.40, p = .01$) and CS ($r = 0.44, p = .03$), but not in ES ($r = 0.12, p = .51$). Yet, correlation coefficients did not differ significantly between groups.

[10] It should be noted that conclusions from such covariates are limited (Miller & Chapman, 2001).

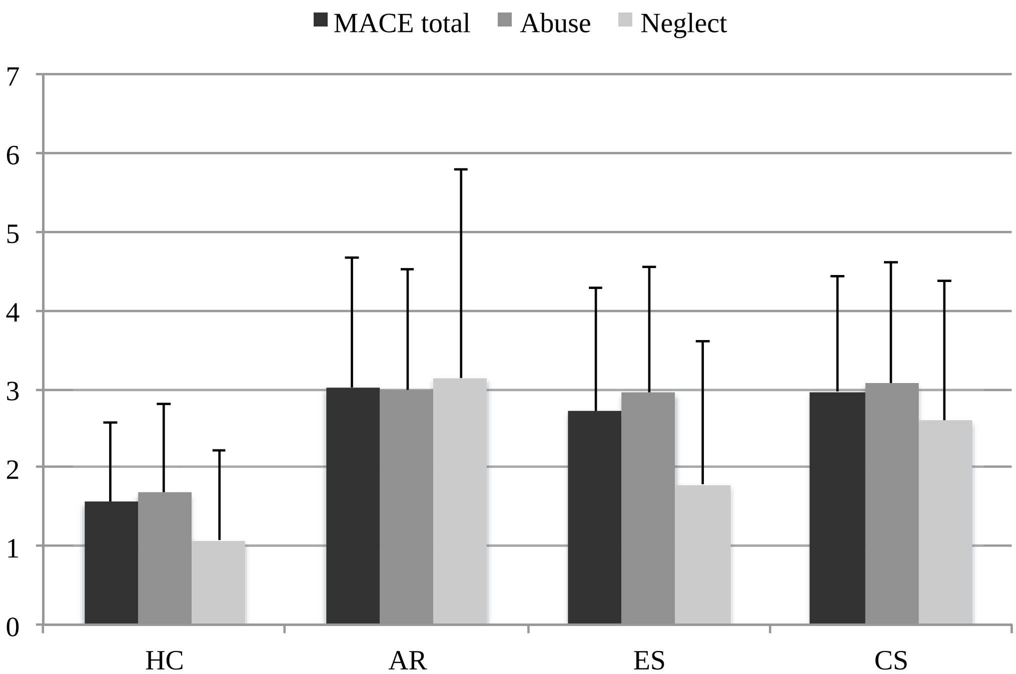

Fig. 2. Adverse childhood experiences displayed as overall experience load (MACE total), abuse and neglect separately for the four groups per means ± standard deviations. MACE = Maltreatment and Abuse Chronology of Exposure. MACE scores were adjusted for the number of included subtypes. HC = healthy controls, ARP = at-risk individuals, ES = early-stage schizophrenia patients, CS = chronic schizophrenia patients. All comparisons between the clinical samples and the HC group were significant, except for the neglect score of the ES group. There were no significant differences among the clinical samples themselves.

Table 2
Pearson's correlations between ACE and symptom severity across all clinical samples.

	BPRS sum	BPRS PS	BPRS NS
MACE total	***r* = 0.44, *p* = .001**, CI [.17 0.64]	***r* = 0.36, *p* = .007**, CI [.13 0.61]	*r* = −0.08, *p* = .56, CI [−0.33 0.18]
Abuse	***r* = 0.44, *p* = .001**, CI [.18 0.65]	***r* = 0.34, *p* = .01**, CI [.11 0.57]	*r* = −0.12, *p* = .40, CI [−0.37 0.16]
Neglect	***r* = 0.29, *p* = .03**, CI [.02 0.55]	***r* = 0.32, *p* = .02**, CI [.07 0.56]	*r* = 0.05, *p* = .73, CI [−0.17 0.29]

Note. ACE = adverse childhood experiences, BPRS = Brief Psychiatric Rating Scale, PS = positive symptoms, NS = negative symptoms. Clinical samples include at-risk individuals, early-stage, and chronic schizophrenia patients. Level of significance was set at $p \leq 0.05$. 95% bootstrapped confidence intervals are reported.

3.3. *Relationships between hair cortisol concentration, ACE and symptom severity*

The ANCOVA did not verify HCC differences between groups after controlling for hair washing frequency ($F(2,81) = 0.40$, $p = .76$; see Table 1 for the estimated marginal means and standard errors of the original HCC values (pg/mg) per group). HCC neither varied with total experience load, nor with abuse or neglect (see Table 3), nor with BPRS sum, positive or negative symptom scores. An exploratory analysis of abuse and neglect experiences prior to the age of 11, showed that both types together predicted HCC with 21% explained variance (see Table 3), although only early abuse, but not neglect, varied significantly with lower HCC. Moreover, exploratory analyses of relationships between HCC and distinct symptoms, in particular those considered relevant for at-risk diagnosis, showed that higher scores of suspiciousness and conceptual disorganization predicted lower HCC ($p \leq 0.007$ after Bonferroni correction for multiple comparisons).

Table 3
Regression analyses with 1) ACE regressed on HCC, and 2) HCC regressed on symptoms.

	R^2	*F*-statistic	*β*	*p*
1) ACE ⟶ HCC				
MACE total	.10	*F*(2,54) = 2.96	−0.20	.13
Multiple regression ACE types ⟶ HCC				
Abuse and neglect	.11	*F*(3,54) = 2.00		.13
Abuse			−0.22	.30
Neglect			.02	.92
Multiple regression *early* ACE types ⟶ HCC				
Early abuse and neglect	.21	*F*(3,54) = 4.64		**.01**
Early abuse			−0.31	**.02**
Early neglect			−0.16	.31
2) HCC ⟶ symptoms				
Simple regressions on BPRS (sub-)scales				
BPRS sum	.04	*F*(2,54) = 1.04	−0.20	.15
BPRS PS	.06	*F*(2,54) = 1.58	−0.24	.05
BPRS NS	.004	*F*(2,54) = 0.09	.05	.72
Psychotic subscales in BSIP:				
Hallucinations	.002	*F*(2,54) = 0.06	−0.05	.75
Suspiciousness	.15	*F*(2,54) = 4.64	−0.38	**.003**
Unusual thought content	.09	*F*(2,54) = 2.50	−0.31	.01
Conceptual disorganisation	.13	*F*(2,54) = 3.97	−0.35	**.005**

Note. ACE = adverse childhood experiences, HCC = hair cortisol concentration, MACE = Maltreatment and Abuse Chronology of Exposure, BPRS = Brief Psychiatric Rating Scale, PS = positive symptoms, NS = negative symptoms, BSIP = Basel Screening Instrument for Psychosis. Bootstrapped *p*-values are reported and tests including hair cortisol were controlled for hair washing frequency. After a Bonferroni correction for 7 multiple comparisons, level of significance was set at $p \leq 0.007$ for the regression between HCC and symptom severity. The upper half (1) of the table displays a simple regression of the ACE total score on hair cortisol and two multiple regressions of abuse/neglect and early abuse/early neglect on hair cortisol concentration. The lower half (2) shows several simple regressions of hair cortisol concentration regressed on BPRS symptom scores and subscales.

4. Discussion

Evidence for the impact of childhood maltreatment on mental health in individuals suffering from psychological disorder and in potentially vulnerable individuals has been accumulated in recent years. Yet, insufficient or inconclusive evidence in schizophrenia asks for further clarification of the role of adverse childhood experiences in the emergence of psychopathology in (genetically) vulnerable individuals. The present study aimed at clarifying this impact by addressing overall amount and specific types of ACE (abuse and neglect) and symptom severity in individuals at different stages of a psychotic illness (at risk, early and chronic stage), and by examining altered stress-axis function, indexed by HCC, as potential moderator of ACE on emerging psychopathology.

Results confirmed the previously reported high amount of childhood maltreatment in schizophrenia patients, and also in individuals with attenuated psychotic symptoms showing signs of being at risk for a conversion into psychosis (e.g. Mayo et al., 2017). It is tempting to conclude that childhood adversities foster the emergence of manifest psychosis in vulnerable individuals. However, an impact of childhood maltreatment on psychotic development can be inferred only from individuals who convert to psychosis within 12 – 24 months, and only about one-third of individuals diagnosed as at risk are expected to meet these criteria of conversion (Fusar-Poli et al., 2012). It has to be assumed that the present at-risk sample included individuals who converted to manifest psychosis, individuals who developed another severe psychiatric disorder within the year after the assessment, and individuals who showed transient psychotic symptoms but did not receive a diagnosis of psychosis on the long run. Clear results with sufficient statistical power would have required longitudinal assessments over 1–2 years in sufficiently large samples. The lack of both, a larger sample of at-risk individuals and sufficient follow-up, clearly limit the strength of the present results.

The presence of comorbid disorders in at-risk individuals might support their risk or prodromal state. Yet, psychotic symptoms have been found in adversity-exposed members of the general population (Janssen et al., 2004). Moreover, similar relationships between childhood maltreatment and non-specific symptoms (including psychotic symptoms) in patients with diagnoses other than schizophrenia (e.g. Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013; Misiak et al., 2017; Pietrek *et al.*, 2013; Read et al., 2014; Weber et al., 2008) suggest that ACE do not foster specific disorders but moderate the emergence of mental illnesses in generally vulnerable individuals.

The present study showed more abuse and neglect experiences across all samples, without marked dominance of one or the other type (as in Üçok & Bıkmaz, 2007). This underscores that not only severe traumata impact development and/or severity of psychiatric disorders. When compared between samples, at-risk individuals and chronic patients reported more neglect experiences than patients at early stage of illness. Present results may suggest that it is the overall experience load or the accumulation of abuse and neglect experiences that influence the emergence of psychopathology. Similar prominence of abuse and neglect experiences has previously been found, particularly in studies which used similar screening instruments as the present study (Prokopez et al., 2018; Simpson *et al.*, 2018). Thus, a potential influence of the assessment method on present results cannot be ruled out, which limits firm conclusions about the role of distinct types of adversity in schizophrenia.

Severity of childhood maltreatment predicted symptom severity independent of stage of illness. Given that positive symptom severity did not differ significantly between the three clinical groups (see Table 1), the similar relationships, too, support the assumption that ACE may sensitize for the development of psychopathology in vulnerable individuals (van Nierop et al., 2015). An impact of early experiences on the course of illness can only be verified by longitudinal assessment. The present relationships across samples at different stages of illness suggest a sensitizing effect of childhood adversities rather than an impact on a severe course of disorder. A relationship between severe childhood maltreatment and positive symptoms, as demonstrated in the present assessment, has been repeatedly reported (e.g. Daalman et al., 2012; Hacioglu Yildirim et al., 2014; Sar et al., 2010; Schalinski et al., 2015a/b, b, 2017; Thompson et al., 2009; Üçok & Bıkmaz, 2007). Yet, reports on the relationship between childhood maltreatment and symptom characteristics are inconsistent, and may vary with the assessment instrument and the sample (acute or chronic states are characterized by different symptom accentuation), and by the time gap between childhood experience and assessment of symptoms that may have blurred the relationship between positive/negative symptoms and specific experiences. Thus, the potential relationship between childhood adversities and symptom severity needs further clarification.

Previous results of elevated HCC (stable over 3 months) in drug-naïve first-episode patients (Andrade et al., 2016) were not supported by present inconspicuous HCC in at-risk individuals and schizophrenia patients. Streit et al. (2016) reported higher HCC in bipolar but also confirmed unaltered HCC in schizophrenia patients (compared to controls) and no HCC changes over 6 months despite a decrease of perceived stress. Thus, HCC may serve as a relatively stable cortisol index.

Still, the exploratory inspection indicated that intense early abuse experiences were associated with lower HCC in at-risk individuals and schizophrenia patients. Evidence on the relationship between childhood maltreatment, HCC and psychotic psychopathology is mixed and still rare (Andrade *et al.*, 2016 vs. Streit et al., 2016; Steudte-Schmiedgen et al., 2016). This might be due to various basic and stress-related variables that modify HCC (see Abell et al., 2016; Stalder et al., 2017). For instance, higher-than-normal HCC was often found in individuals who experienced childhood maltreatment but also more recent life events experiences or chronic stress (Stalder et al., 2017). The latter was not screened in the present sample. As previous studies indicated a sensitizing effect of childhood maltreatment on later life events (Matz et al., 2010), one might speculate that prodromal/attenuated symptoms and hospital admissions meet criteria of chronic stress. Indeed, Streit et al. (2016) found higher HCC in psychotic patients upon admission than in remitted outpatients. However, Koenig et al. (2018) reported that the association between childhood maltreatment and HCC in women postpartum differed depending on the respective FKBP5 genotype. The present study did not consider genetic factors and therefore we cannot draw conclusions about potential gene-environment interactions that might have influenced HCC.

Recent trauma has been found to vary with lower HCC in students and depressive patients (Hinkelmann et al., 2013; Kalmakis et al., 2015) and White et al. (2017) verified a relationship between more childhood maltreatment and reduced HCC in children and adolescents at age 9–16 years, and a gradual reduction of HCC with increasing age. Moreover, lower-than-normal HCC has been reported for patients with anxiety disorders including PTSD (Stalder et al., 2017; Steudte-Schmiedgen et al., 2016). Thus, present results show that ACE might be a factor modulating HCC in at-risk individuals and patients with manifest psychosis.

There is agreement, that chronic stress early in life, particularly maltreatment experience during sensitive periods of neuroendocrine development, alters long-term HPA axis function (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Kuhlmann, Chiang, Horn, & Bower, 2017; Trickett, Noll, Susman, Shenk, & Putnam, 2010). Long-term modification upon chronic stress is considered maladaptive (Stalder et al., 2017), as it may sensitize HPA reactivity to ongoing or anew stress experiences later in life, particularly in individuals vulnerable for mental disorder including schizophrenia (Lardinois, Lataster, Mengelers, van Os, & Myin-Germeys, 2011; Myin-Germeys, Delespaul, & van Os, 2005; Pruessner et al., 2017). With caution in view of insufficient control of basic determinants of HCC the present negative relationships between early maltreatment and lower HCC and between lower HCC and psychotic symptoms (such as suspiciousness and conceptual disorganization) support HPA dysregulation following early stress. If substantiated in further studies, this link should strengthen the hypothesized functional impact of severe (early) maltreatment - potentially by way of altered HPA axis regulation - on the development of psychopathology in (genetically) vulnerable individuals.

4.1. Limitations

Further limitations have to be noted: (1) The present cross-sectional study design does not allow conclusions about the development and course of disorder. Similar amounts of ACE and similar psychotic symptoms across samples, characterized by different stages of illness, need to be complemented by longitudinal assessment for causal conclusions. (2) The reliability of retrospective self-reports of childhood maltreatment in adulthood has been questioned, as the retrieval of past events may be blurred with elapsing time (e.g. Conus, Cotton, Schimmelmann, McGorry, & Lambert, 2010). It has also been assumed that self-reports of psychotic patients are modulated by acute, positive symptoms. Yet, reliability of retrospective self-reports has been verified in psychotic patients (Fisher et al., 2011). Moreover, good psychometric properties of the highly structured MACE have been confirmed (Isele et al., 2014; Teicher & Parigger, 2015). While potential memory distortion of retrospective self-reports can never be completely ruled out, a major impact on the present results is not assumed. (3) Whereas amount and type of childhood maltreatment did not correlate with age in the present data set, age might influence reported ACE and their relationship with symptom severity, as age is related to the time between adverse experience and unfolding of manifest psychosis. Such an influence should have become evident in a different amount of reported ACE between groups, which differed in age. Yet, neither self-reported total ACE dose nor its relationship with symptom severity clearly differed between groups. (4) In the present study, age differed between groups, but did not vary with HCC. Inconsistent results may have resulted from basic factors that differed between studies, such as age or hair treatment. Whereas the influence of hair-washing frequency was controlled for, we could not control for every basic factor that might modulate HCC, which clearly limits the interpretation of present results.

4.2. Conclusion

The present results confirm reports of more adverse childhood experiences in at-risk individuals as well as early-stage and chronic schizophrenia inpatients compared to healthy controls. Moreover, positive correlations between adverse childhood experiences and positive symptom severity support the hypothesis that maltreatment during childhood moderates later psychotic symptom manifestation. The significant relationship between higher reports of early abuse and lower hair cortisol concentration, as well as lower hair cortisol concentration and more severe psychotic symptoms hints at a possible long-term attenuation of the HPA axis function resulting from early experiences. Hence, low cortisol levels leading to increased stress sensitivity might play an important role for the emergence of psychotic symptoms. Consequently, the assignment to at-risk state could benefit from examining an individual's history of (early) experiences in combination with assessing hair cortisol concentration, also adding to a better understanding of psychosis development.

Conflict of interest

None.

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