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The relationship between self-reported childhood adversities, adulthood psychopathology and psychological stress markers in patients with schizophrenia

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Abstract

Background: Childhood adversity is a well-established risk factor for the development of schizophrenia. In particular, there is evidence that childhood adversity increases the occurrence of positive symptoms, possibly through glucocorticoid influences on dopaminergic neurotransmission.

Aims: To compare levels of childhood trauma in schizophrenia patients vs. healthy control persons, and to study the association between childhood adversity and the symptomatology of adulthood schizophrenia, as well as subjective and biological markers of psychological stress.

Methods: Thirty-seven patients fulfilling ICD-10 criteria for schizophrenia and 39 healthy control persons filled out the comprehensive Childhood Abuse and Trauma Scale (CATS). Data were analyzed after a data-driven dichotomization into two groups of either high or low CATS score in patients and controls, respectively. The psychopathology of the patients was measured by the Positive and Negative Syndrome Scale (PANSS) and analyzed by a five-factor PANSS model. Measures of perceived stress (Perceived Stress Scale) and hypothalamic-pituitary-adrenal (HPA)-axis activity (9 AM plasma cortisol and daytime salivary cortisol output) were recorded.

Results: As expected, patients had significantly higher total CATS scores than the control persons (>3-fold, $P < 0.001$), reflecting significantly higher scores across all subscales of the CATS. In patients, the total PANSS score did not significantly differ between the high and the low CATS score group ($P = 0.2$). However, there was a statistically significant higher level of positive symptoms in the high CATS group ($P = 0.014$), and no difference in other psychopathological domains. Correspondingly, when using the CATS score as a continuous variable, a strong association with positive PANSS scores was found ($P = 0.009$). The high CATS score group showed higher levels of perceived stress ($P = 0.02$), but there was no difference between the high vs. low CATS group in HPA-axis activity.

Conclusion: Although causal inferences cannot be made from this cross-sectional study, the study adds support to the suggestion that childhood adversity specifically increases the occurrence of positive symptoms in adulthood schizophrenia in a manner that appears to leave HPA-axis activity unaltered.

1. Introduction

Numerous large-scale and cross cultural studies have shown that a history of childhood maltreatment increases the probability of developing a psychiatric disorder in later life. This relationship has also been established in psychotic illnesses [1–6]. Recent evidence has converged on an odds ratio between 2.72 and 3.3, suggesting that patients [6] with

Conflicts of interest: Within the last three years, UK has been a consultant for AstraZeneca. None of the other authors report any conflicts of interest.

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psychosis are almost three times as likely to have been exposed to childhood adversities as controls [2,3,7–10]. This relationship between childhood adversities and the development of psychosis seems stable and valid, even when controlling for other general demographic and clinical confounders (e.g. comorbid psychopathology, family history of psychiatric disorder) [7,8,11–13], indicating that childhood adversities causally increases the risk for the development of psychotic experiences.

More specifically, several large studies have found an association between childhood adversities and the presence of positive symptoms (defined as delusions, hallucinations, disorganized thinking and catatonia) in adult schizophrenia [3,7,14–17], as well as in healthy siblings of patients with schizophrenia [18]. This is supported by studies indicating that even in people who do not meet diagnostic criteria for a psychiatric disorder, individuals with a history of childhood maltreatment are far more prone to hallucinatory experiences than others [11,19–22]. Some studies have shown that patients with schizophrenia and a history of childhood adversities are more likely to have poorer functional outcomes [22] and a more severe course of illness [3,16,23–25] than patients with schizophrenia and no history of childhood adversities.

When investigating a possible specific effect of type of adversity, some researchers find a strong association between CPA or CSA and auditory hallucinations (AH) [10,15,23,26,27]. In contrast, while both Varese et al. [7] and Trauelsen et al. [12] concluded that childhood adversities clearly increase the risk of psychosis, there was no evidence that any specific type of trauma is a stronger predictor of psychosis than any other [7,12].

The possible neurobiological connection between childhood adversity and adulthood psychotic symptomatology is unknown. A recent preclinical study suggested a mechanistic link between the exposure to childhood and adolescent stress and psychotic illnesses, in which glucocorticoids exert an epigenetic control of mesocortical dopaminergic projections, yielding an adult phenotype more susceptible to psychosis [28]. In humans, a greater number of childhood adversities were found to be associated with a larger striatal dopamine release upon an amphetamine challenge [29]. These findings are consistent with a suggested stress-diathesis model of schizophrenia, in which the HPA-axis activity and its feedback influences on subcortical areas of the brain mediate the connection between life stress and psychosis [30,31].

In conclusion, childhood adversities seem to play an influential part in the appearance, distribution and severity of symptomatology in schizophrenia in adults. The present study aimed at investigating if the severity of positive schizophrenic symptoms depends on the patients' history of adversity, and whether patients with low vs. high levels of childhood adversities differ in measures of psychological stress and HPA-axis activity.

2. Methods

2.1. General study outline

The present study was based on data from a cohort originally established to investigate the relation between psychopathology, stress and markers related to somatic aging in schizophrenia [32]. Recruitment took place from September 2008 through May 2011. Patients were recruited by referral from doctors at the Psychiatric Centre Copenhagen, which provides mental health services to the citizens of the central, northern and northwestern areas of Copenhagen. Physicians at the center were informed of the study, and received regular reminders to refer patients. Both inpatients as well as patients from the affiliated outpatient clinics were recruited.

2.2. Participants

The inclusion criterion for patients was an ICD-10 diagnosis of either schizophrenia or acute schizophreniform psychosis, confirmed by a structured interview at referral. Exclusion criteria were: 1) somatic disease and somatic medication. A non-regular use of e.g. painkillers or asthma medication was allowed, 2) abuse of alcohol, marijuana or other drugs, 3) coercion of any kind, 4) severely disorganized thinking, making it impossible to obtain an informed consent, 5) use of dietary supplements, and 6) pregnancy or breast-feeding. Of 45 patients referred to the study and accepting to participate, 40 were included. In the excluded patients, the diagnosis of schizophrenia was considered uncertain after the inclusion interview (N = 4), or a standard biochemical screening revealed a medical disorder (N = 1).

Healthy control persons were recruited from the blood donation corps at Rigshospitalet by personal contact, as they were scheduled for donating blood. Exclusion criteria for the healthy controls were: 1) any psychiatric or somatic disease 2) abuse of alcohol, marijuana or other drugs 3) use of any medication including dietary supplements and 4) first degree family members with psychiatric disease. A total of 175 healthy persons meeting none of the exclusion criteria were asked to participate, and of these, 40 accepted to participate. They underwent the same examinations as the patients, except for the PANSS rating.

For the present study, data on childhood adversities were obtained for 37 patients and 39 controls, and all analyses are based on these individuals.

2.3. Measures

2.3.1. Childhood adversities

Childhood adversities were measured using the Child Abuse and Trauma Scale (CATS). The questionnaire measures the individual's current and subjective perception of the degree of stress or trauma present in his/her childhood, based on the idea that "the meaning a child makes of experiences influences how the experience affects the child" [33]. CATS is a self-report questionnaire, presented to the

participants as a home environment questionnaire. It consists of 38 questions related to the individuals' childhood or adolescent experiences of sexual maltreatment, physical maltreatment and punishment, psychological maltreatment, physical or emotional neglect, and negative home environment (e.g. parental substance abuse or fighting). The frequency of each experience is rated on a 5-point Likert scale, ranging from 0 = "never" to 4 = "always". The total CATS score is derived by summing item frequency scores and dividing by the total number of answered items [33]. The measure contains three subscales: negative home environment/neglect (NEG), sexual abuse (SA), and punishment (PUN) [33]. For the present study and following the work of Kent and Waller (1998), a subscale addressing emotional abuse (EMO) was included [34].

2.3.2. Psychopathology

A SCAN-interview (Schedule in Clinical Assessment in Neuropsychiatry) [35] was applied to ensure that the diagnostic inclusion criteria were met and that no present or lifetime psychiatric morbidity was present in the healthy control persons. Medical doctors with previous clinical experience in psychiatry performed all the SCAN ratings. The severity of psychopathology was measured with the Positive and Negative Syndrome Scale (PANSS) [36]. Regular co-ratings between the primary investigator and a certified expert PANSS-rater were performed, yielding an intraclass correlation coefficient of 0.91 for positive items, 0.76 for negative items, 0.79 for general items and 0.83 for all items, indicating very good agreement across all subscales.

Several factor-analytic studies of the PANSS have suggested that a five-factor model captures the dimensions with a better validity than the original PANSS subscales. For the present study, the five-factor model suggested by van der Gaag et al. was applied [37,38]. The five factors are referred to as positive symptom cluster (POS), negative symptom cluster (NEG), disorganization symptom cluster (DIS), excitement symptom cluster (EXC), and emotional distress symptom cluster (EMO).

2.3.3. Psychological stress and HPA-axis activity

The level of perceived stress was assessed with the Perceived Stress Scale 10-item (PSS) [39]. Plasma cortisol was measured in a 9 AM fasting state blood sample as part of the standard biochemical screening. Samples for salivary cortisol were obtained by the "Salivette" system immediately upon awakening, at 15, 30, 45 and 60 minutes after awakening, at 6 PM and at 11 PM, as previously described [32]. Briefly, samples were made either in the participant's own home and mailed to the laboratory (controls and out-patients) or at the ward (in-patients). Upon receipt at the laboratory, the Salivette tubes were centrifugated at 1590×*g* for 5–10 minutes to extract the saliva. Samples were stored at −80 °C until analysis. Saliva was assayed for cortisol by an electrochemiluminescence immunoassay, using a commercially available kit (Roche Diagnostics GmbH, Mannheim, Germany). The lower detection limit of the assay was 1 nmol/L. The inter- and intra-assay coefficients of variation of the assay were 7.1% and 4.0%, respectively, according to the manufacturer. All samples from each participant were analyzed in the same batch, but control and patient samples were analyzed on separate occasions. Therefore, we refrained from making direct comparisons between patients and controls. The area under the curve with respect to the ground level for all samples (AUCg) was calculated for each participant by the trapezoidal rule [40], which incorporates cortisol values and the exact times between samples to estimate whole-day "exposure" to unbound cortisol. Before computations, extreme values in each group for each time point (outside the 99th percentile) were excluded (30 out of a total of 658 determinations). For series of samples with more than one sample missing, the AUC was not computed. If only one sample was missing, values were replaced by the mean of the two adjacent values, or, if the missing value were either the awakening or 11 PM sample, by the mean of the full sample for that time point. We were able to compute AUCg for 28 patients and 36 controls.

2.4. Statistical analysis

All data are presented as means (±standard deviation) or median (interquartile range, IQR), if not otherwise stated. Normal distributed data were analyzed with independent samples t-tests or repeated measures analysis of variance (ANOVA), as relevant. Non-normally distributed data were analyzed with Mann–Whitney test or Spearman's test, as relevant. For categorical data, chi-squared tests were used. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM Corporation, NY, USA). Statistical significance was defined as $P < 0.05$. All statistical tests were two sided.

2.5. Ethics

All participants gave a written informed consent before inclusion. The study protocol complied with the Declaration of Helsinki, and was approved by the regional committee on research ethics (H-D-2008-064) and the National Data Protection Agency (2008-41-2052).

3. Results

3.1. Childhood adversity in schizophrenia patients vs. controls

Basic data and CATS scores of patients and controls are presented in Table 1. All patients met the ICD-10 diagnostic criteria for schizophrenia (paranoid type (F20.0) = 55%; undifferentiated type (F20.3) = 28%; hebephrenic type (F20.1) = 12%, unspecified type (F20.9) = 5%). Patients had a >3-fold higher total CATS score compared to the healthy control persons (Mann–Whitney $U = 243.0$,

Table 1

	Patients (N = 37)	Controls (N = 39)	*P*-value
Demographics			
Gender (M/F)	17/20	20/19	0.642
Age	32.3 ± 10.7	31.7 ± 9.7	0.798
CATS scores			
Total	1.13 (0.55–1.82)	0.34 (0.21–058)	<0.001
Sexual abuse	0.17 ± (0.00–0.50)	0.00 (0.00–0.00)	0.001
Punishment	1.60 (0.80–2.20)	0.80 (0.40–1.20)	0.001
Neglect	1.50 (0.61–2.46)	0.36 (0.14–0.64)	<0.001
Emotional abuse	1.00 (0.64–2.29)	0.43 (0.29–0.57)	<0.001

Basic data obtained on healthy controls and schizophrenia patients. Numbers are in mean (standard deviation) or median (IQR). CATS = Child Abuse and Trauma Scale.

$P < 0.001$). The significantly higher score was repeated across all subscales ($P < 0.001$ in all subscales) (Table 1).

3.2. Psychopathology in schizophrenia patients with high vs. low CATS score

Dichotomization of patients into two groups depending on CATS scores was performed by using the median of the CATS scores in the patient group (Table 2). The two groups did not differ significantly in basic demographics (gender and age), or in various measures of disease course (duration of illness, duration of antipsychotic medication, number of admissions, and defined daily doses of present antipsychotic medication). The total PANSS score of the high vs. low CATS groups was not significantly different ($t = 1.301$, $dF = 35$, $P = 0.202$). However, the high CATS group had a significantly higher amount of positive symptoms than the low CATS group ($t = 2.594$, $dF = 35$, $P = 0.014$). There was a similar non-significant trend with symptoms of emotional distress ($t = 1.843$, $dF = 35$, $P = 0.074$). The association between CATS group and positive symptoms persisted when using the original PANSS positive subscale ($t = 2.480$, $dF = 35$, $P = 0.018$), and when analyzing the association with the total CATS score as a continuous variable (Spearman's rho = 0.42, $P = 0.009$) (Fig. 1).

In an exploratory analysis, it was investigated if the CATS score was correlated to the three key domains "delusions" (PANSS item 1, P1), "hallucinations" (P2) and "conceptual disorganization" (P3) in the PANSS positive category. There was a significant difference in delusions between the two groups (high CATS group: 4.37 ± 1.01) vs. low CATS group: 3.44 ± 1.10 ($t = 2.666$, $dF = 35$, $P = 0.012$), but no significant difference in hallucinations ($P = 0.8$) or conceptual disorganization ($P = 0.3$) between the two groups.

3.3. Psychological stress and HPA-axis activity in schizophrenia patients with high vs. low CATS score

Levels of perceived stress as measured by PSS scores were higher in the high vs. the low CATS group of schizophrenia patients (25.1 ± 5.5 vs. 21.1 ± 5.9 points, $t = 2.147$, $dF = 35$, $P = 0.039$). There was no significant difference between the high CATS and the low CATS patients in 9 AM plasma cortisol levels. In a repeated measures ANOVA of salivary cortisol output, we found a significant effect of time ($F_{(6156)} = 24.855$, $P < 0.001$), reflecting that in both groups, cortisol concentrations displayed the expected diurnal pattern (peak values at 30 minutes after awakening and nadir at 11 PM) (Fig. 2). However, we found no effect of CATS group status ($F_{(1,24)} = 0.014$, $P = 0.907$) or a time × group interaction ($F_{(6156)} = 1.204$, $P = 0.307$). Likewise, we found no difference between the groups when analyzing the data as AUCg ($t = 0.851$, $dF = 26$, $P = 0.402$).

Table 2

	High CATS (N = 19)	Low CATS (N = 18)	*P*-value
Demographic and clinical characteristics			
Gender (M/F)	7/12	10/8	0.461
Age (years)	31.9 ± 9.1	32.7 ± 12.5	0.818
Duration of illness (months)	72 (26–192)	86 (34–186)	0.504
Number of admissions	2 (1–7)	3 (1.5–5)	0.500
Duration of antipsychotic medication (months)	24 (1.5–72)	24 (12–76)	0.253
Defined daily doses of present antipsychotic medication	1.7 (0.5–2.3)	1.4 (0.9–2.2)	0.726
CATS total score	1.74 (1.42–2.16)	0.55 (0.3–0.75)	<0.001
Psychopathology (PANSS scores)			
POS	25.32 ± 5.49	20.44 ± 5.93	0.014
NEG	21.95 ± 7.29	22.56 ± 7.10	0.799
DIS	28.89 ± 5.86	28.17 ± 5.36	0.696
EXC	20.84 ± 5.01	18.56 ± 3.36	0.114
EMO	26.37 ± 4.18	23.11 ± 6.40	0.074
Total	90.58 ± 16.00	83.94 ± 14.97	0.202

Basic data and psychopathology of patients with schizophrenia and high vs. low levels of childhood adversity, respectively. Data are presented as median (interquartile range) or mean (±SD). CATS = Child Abuse and Trauma Scale. PANSS: Positive and Negative Syndrome Scale. POS: positive symptom cluster, NEG: negative symptom cluster, DIS: disorganization symptom cluster, EXC: excitement symptom cluster, EMO: emotional distress symptom cluster.

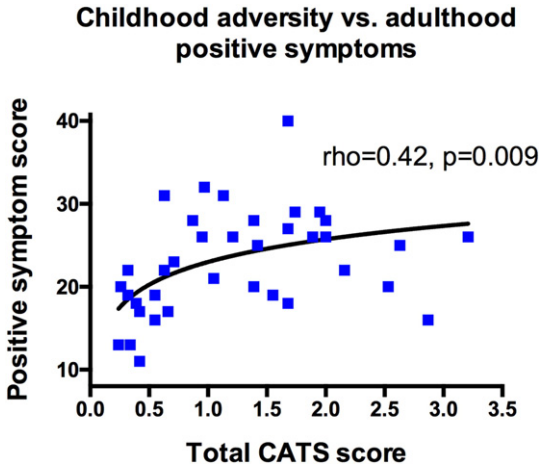

Fig. 1. The relationship between self-reported childhood adversities, as measured by the Childhood Abuse and Trauma Scale (CATS) scores, and Positive and Negative Syndrome Scale (PANSS) positive symptom cluster scores in adults with schizophrenia.

4. Discussion

In this study, the occurrence of self-reported experiences of childhood adversities was explored in a group of 37 patients with a diagnosis of schizophrenia or schizophreniform psychosis and compared to a group of 39 healthy controls. In accordance with earlier research [1,3,5], the patients reported significantly higher amounts of childhood adversities than the healthy controls. This applied to the total amount of adversities and across subscales targeting sexual abuse, physical abuse, emotional abuse and neglect.

Hence, our data support the idea of a relationship between childhood adversities and schizophrenia. Similar results have led some researchers to suggest the relationship to be causal, with a dose-respond effect [7,15]. However, other researchers draw attention to the fact that the idea of a causal relationship, as intuitive as it may be, can be challenged by the notion of a possible adverse causality [9,41]. Adverse causality refers to the hypothesis that (possibly subclinical) symptoms of psychosis could be present in the child before the exposure to maltreatment, possibly weakening the child's ability to make healthy judgments of the perpetrator and avoid dangerous situations, hereby placing the child in greater risk of experiencing childhood maltreatment [9,42]. Another hypothesis is that co-founding factors, such as low IQ or extreme poverty, leads to both the later expression of psychosis as well as an increased likelihood of exposure to early life adversity. This would mean that the actual adversity in itself does not impact on the later development of psychosis. The theory of adverse causality or important co-founding factors seems to be challenged by the fact that the strong relationship between childhood adversities and psychosis is repeated even when controlling for various possible confounding factors, suggesting that the adversities in themselves do affect the development of psychotic symptoms [8,9,43].

The present study also explored the association between childhood adversities and the distribution and severity of schizophrenic symptoms within the patient group. While we found no significant differences between the groups in overall PANSS scores, there was a significant relationship between the amount of adversity and the amount of positive symptoms (Fig. 1). There was a trend toward an effect on emotional distress symptoms as well. When performing secondary analysis of the relationship between individual positive symptoms and CATS score, the strongest correlation was found between a high CATS score and delusions. As opposed to what was expected, there was only a weak relationship with hallucinations and conceptual disorganization, suggesting that in this cohort, the higher level of positive symptoms in patients with high levels of childhood adversities is mainly driven by an increased occurrence of delusions. However, these secondary analyses should be interpreted with caution due to the small number of participants.

The data on childhood adversities were collected using self-report forms concerning childhood adversities. There has been vivid discussion concerning adult retrospective reports of childhood experiences [44]. However, the past predominant skepticism has been replaced by an emerging research into the topic, finding that within retrospective self-report of childhood adversities, false positive reports are absent, but there are high rates of false negative responses. This is found to be independent of psychiatric state and reporting errors. Although those subject to abuse tend to provide unreliable reports of their abuse history, reporting errors were statistically independent of the respondents' psychiatric status [45]. Similar findings suggest that self-administered questionnaires and structured interviews yield similar results when investigating prevalence of childhood adversities in both patients and normal popula-

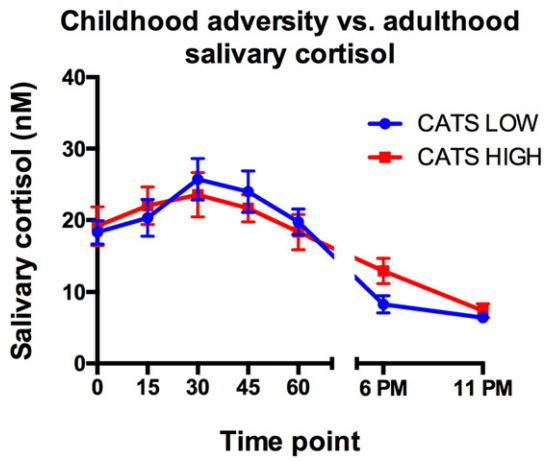

Fig. 2. The relationship between self-reported childhood adversity group (high vs. low), as measured by the Childhood Abuse and Trauma Scale (CATS) scores and salivary cortisol concentrations at 0, 15, 30, 45 and 60 minutes after awakening; at 6 PM, and at 11 PM, in patients wih schizophrenia. There are no significant differences between the groups at any time point. Error bars: SEM.

tions [44]. Comparisons with prospective measures confirm this [8,46,47]. Studies that determine childhood adversities through interviews, self-report questionnaires and fact checking (e.g. authorities reports, police reports, child protective services etc.) claim to find equal reports of childhood adversities among psychotic patients [5,7,10]. Fisher et al. examined the reliability and comparability of first-presentation psychosis patients' reports of childhood abuse. They find that the retrospective information is stable over time, congruent with instruments measuring e.g. parental bonding, and not associated with current severity of psychotic or depressed mood symptoms [8]. In the original validation of the CATS scale, the total CATS score were found to be .75 (+/− .42) and .73 (+/− .41) in a group of college students [33]. This suggests that our group of healthy controls is comparable to the original validation group, although with slightly lower scores.

The present study does not allow for conclusions on what underlies the association between childhood adversity and adulthood positive symptoms in patients with schizophrenia. A suggested psychological explanation is that childhood trauma induce a susceptibility to dissociative states, which may persist into adulthood and interfere with normal interpretation of perceptual experiences and cause experiences of disintegration and depersonalization, thereby rendering the individual more prone to develop positive psychotic symptoms [15,48–50]. A possible biological – and not counter exclusive – connection between childhood adversity and adulthood symptomatology is a dysregulation of the HPA-axis, which may subsequently influence dopaminergic neurotransmission, yielding the individual more susceptible to psychosis [30,32]. The HPA-axis is activated in response to stressful events, and several studies have shown that adults, who have experienced a high amount of childhood adversities, show hyperreactivity and persistent sensitization of the HPA stress response, as well as a reduction of hippocampal volume and function, thus limiting hippocampal negative feedback inhibition of the HPA-axis activity [51–53]. Since adults with schizophrenia similarly have an altered HPA stress response and HPA axis hyperactivity, it is adjacent to hypothesize this as one possible mediator between stress and the development of psychiatric illnesses including psychotic disorders [51–53]. Using the Childhood Trauma Questionnaire to identify schizophrenia patients with and without moderate childhood trauma (N = 7 in each group), Braehler et al. found a reduced salivary cortisol output in patients with childhood trauma [54]. We cannot rule out that the use of different childhood trauma scales may explain the discrepancy with our study, in which no difference between the groups was found. It is also important to emphasize that we measure "baseline", unstimulated HPA-axis activity, whereas differences among the groups may perhaps reveal themselves under experimental stimulation of HPA-axis activity (e.g. with psychosocial stressors or pharmacological means).

Some limitations of the study should be mentioned. 1) The cross-sectional comparison of patients and controls does not allow for inferences on the mechanistic relationship between schizophrenia and childhood adversities, and confounding factors which were not determined in the study could contribute to this finding. 2) All patients were medicated, and we cannot rule out that this could influence associations between e.g. childhood adversity and HPA-axis activity. 2) The sample size is relatively low, and this may explain the null finding with regards to the association between CATS score and psychometric variables. 3) Finally, as discussed above, we only measured baseline, "unstimulated" activity of the HPA-axis.

Although causal inferences cannot be made from this cross-sectional study, the study adds support to the hypothesis that childhood adversities specifically increase the occurrence of positive symptoms in adulthood schizophrenia. Acknowledging the amount of childhood adversities in patient populations forces clinicians to pay greater attention to the psychological and developmental history of the patients [2,15]. It demands a more comprehensive focus on the relationship between past experiences of adversities and the present form and content of symptoms in schizophrenia. In future research, this relationship should be additionally explored, hopefully also focusing on which individual and relational protective factors can explain that not all children exposed to childhood maltreatment develop psychopathology. Furthermore, the integration of environmental factors and individual development in an epigenetic approach gives promises of new ways of understanding, preventing and treating long term effects of childhood adversities.

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