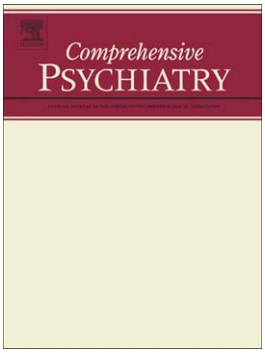


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# Sex-differences in the effect of childhood trauma on the clinical expression of early psychosis

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**CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

**ABSTRACT**

Childhood trauma, a risk factor of psychosis, is associated the clinical expression of the illness (greater severity of psychotic symptoms; poorer cognitive performance). We aimed to explore whether there are sex differences in this relationship. We studied 79 individuals with a psychotic disorder (PD) with <3 years of illness and 59 healthy subjects (HS). All participants were administered the MATRICS Cognitive Consensus Cognitive Battery (MCCB) to assess cognition. Depressive, positive and negative psychotic symptoms, and global functioning were also assessed. History of childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ). Patients reported a greater history of childhood trauma on all CTQ domains (emotional, physical and sexual abuse, and physical and emotional neglect). A poorer cognitive performance was also observed in PD when compared to HS. No sex differences were found in the CTQ scores. In the relationship between childhood trauma and psychopathological symptoms, significant correlations were found between CTQ scores and positive and negative psychotic symptoms, depressive symptoms and poorer functionality, but only in women. Childhood trauma was associated with poorer social cognition in both men and women. Of all CTQ dimensions, emotional neglect and physical neglect were more clearly associated with a more severe psychopathological and cognitive profile. Our results suggest that childhood trauma, particularly emotional and physical neglect, is associated with the clinical expression of psychosis and that there are sex differences in this relationship.

Keywords: Sex differences; Gender differences; Childhood trauma; Early psychosis; Cognition; Social cognition; Depression.

## 1. INTRODUCTION

Schizophrenia is a complex, multidimensional psychotic syndrome based on positive symptoms (delusions and hallucinations), negative symptoms (motivational impairment), mood symptoms (depression, mania, anxiety) and cognitive impairment [1]. Although heritability is an important factor related to the onset of psychotic disorders (PDs), environmental factors also play a role. Schizophrenia diagnosis is associated with growing up in an urbanized area, minority group position, cannabis use and developmental trauma [1]. Childhood maltreatment (including physical, sexual, and emotional abuse as well as physical and emotional neglect) is a risk factor for developing a PD [2]. Longitudinal studies in high-risk populations suggest a greater role of sexual abuse when exploring the risk of developing psychosis [3,4]. Childhood maltreatment may have a negative impact on the developing brain, as there is evidence that early life stress is associated with reduced hippocampal volumes in adults with child abuse or neglect history [5]. The traumagenic neurodevelopmental model of psychosis [6] incorporates biological, psychological, and social factors in an account that suggests that the neurodevelopmental abnormalities that underpin the heightened sensitivity to stressors widely accepted as a prominent feature of schizophrenia are shaped by early traumatic experiences. These trauma-induced neurobiological abnormalities may be related to various aspects of schizophrenia, such as oversensitivity to stress, cognitive impairments, and pathways to negative and positive psychotic symptoms [6,7].

People suffering from PD and a history of childhood trauma show a more severe clinical expression [8] with more auditory hallucinations and delusions [2] when compared with those without childhood trauma. The type of maltreatment has been related to specific symptoms of psychosis. Most studies have reported an association between sexual abuse and auditory hallucinations [9–11]. Other studies have also reported a relationship between physical or emotional abuse and paranoia [9,12] and emotional or physical neglect and visual hallucinations

[11]. However, a relationship between childhood maltreatment and negative psychotic symptoms has not been found [12,13].

In relation to cognition, only a few studies have explored whether childhood trauma may have some impact on the cognitive performance of subjects with a psychotic disorder. This is an area of interest because cognitive alterations that include impairment in memory and learning, working memory, executive functions, attention, processing speed [14] and social cognition[15] are already present in the early stages of psychosis [16] and are related to a poorer functional outcome [15]. To our knowledge, there are only two studies exploring the association between childhood trauma and cognition in psychotic disorders. In one study that included 138 patients with a first psychotic episode and 138 healthy controls, a history of childhood trauma was associated with a significant decrease in cognitive function (general cognition, verbal intelligence, language, attention, concentration and mental speed), predominantly in male patients with affective psychosis [17]. In that study, childhood trauma was assessed with the Childhood Experience of Care and Abuse Questionnaire, but different dimensions of childhood trauma (e.g., abuse vs neglect) were not considered. In another study including 239 patients with a schizophrenia-spectrum disorder and 167 patients with a bipolar disorder, physical abuse, sexual abuse and physical neglect were significantly associated with reduced scores on working memory and executive function [18]. One limitation of these two studies was that they did not assess social cognition, a cognitive domain that is known to be affected in both high-risk subjects and psychotic patients [15,16] and that can be affected in victims of childhood trauma, as children who have been maltreated tend to display negatively biased social-cognitive processing styles [19]. The MATRICS Consensus Cognitive Battery (MCCB), a recently developed cognitive battery to solve the lack of an accepted standard for measuring cognitive change in schizophrenia, has included the assessment of social cognition. The managing emotions component of the Mayer-Salovey-Caruso Emotional Intelligence Test was selected for its relatively stronger relationship to functional status [20].

Another limitation of previous studies exploring the relationship between childhood trauma and the clinical profile of subjects of psychosis is that they do not address whether there are sex differences in this relationship. This is a particularly important issue because some studies in non-psychotic populations have suggested that women, rather than men, develop more frequently posttraumatic stress disorder after childhood trauma [21] and tend to internalize their emotional pain [22]. In a previous study [23] that addressed whether there are sex differences in the prevalence of childhood sexual and physical abuse among people with psychosis in comparison with healthy controls, the reports of childhood physical abuse were found to be associated with later psychosis, particularly in women. However, other studies have reported no such sex differences [13]. There also sex differences in the clinical presentation and outcome of psychotic disorders. Women have a later age of onset [24], better social functioning [25] and superior mentalizing abilities [26]. Some previous studies conducted in subjects with a psychotic disorder have reported sex differences in cognitive abilities, with a poorer executive function and verbal memory in men [25,27]. However, other studies have failed to report such sex differences [28]. Concerning psychotic symptoms, several studies have found that men have more negative symptoms, while positive symptoms were not significantly different [29,30]. Other studies have reported sex differences in prodromal symptoms of psychosis [31]. It is important to address whether there are sex differences in the relationship between childhood trauma and clinical outcomes in psychoses, as knowledge of this issue may benefit the development of sex-specific therapies that may help patients recover from the negative effects of childhood trauma.

The aim of our study was to evaluate whether there are sex differences in the relationship between childhood trauma and clinical variables (cognitive abilities, severity of positive psychotic symptoms, negative symptoms and depressive symptoms, substance use) in a sample of young subjects with a psychotic disorder at early stages of the disease. As a secondary aim of our study, we conducted an exploratory analysis with a dimensional approach concerning the different subtypes of childhood trauma (abuse, neglect) and different clinical

symptoms (positive and negative psychotic symptoms, depressive symptoms, neurocognition, social cognition).

## 2. MATERIALS AND METHODS

### 2.1. Participants

We studied 79 individuals with early psychosis (aged 18-35 years) who were attending the Early Intervention Service from Reus (Hospital Universitari Institut Pere Mata, Spain). We also included a control group of 58 healthy subjects (HS) who were recruited from the community through advertisements and were screened to rule out past or current history of psychiatric disorder. Patient recruitment was conducted by consecutive sampling at the Early Intervention Service with data collection between June 2011 and June 2013. Early psychosis patients were subjects with a PD less than 3 years from the onset of the illness. Exclusion criteria were: pregnancy, mental retardation, severe head injury or neurological disease, active glucocorticoid treatment, active substance dependence (other than tobacco or cannabis), language difficulties or visual impairment that limited the administration of the cognitive battery.

Ethical approval was obtained from the local Ethics Committee. After a complete description of the study was given to the subjects, written informed consent was obtained.

### 2.2. Clinical Assessment

#### *2.2.1. Psychopathological measures*

All subjects were assessed with the Schedules for Clinical Assessment in Neuropsychiatry. OPCRIT checklist v.4.0. was used to generate DSM-IV diagnoses for psychotic disorders (schizophreniform disorder, schizophrenia, bipolar disorder, psychotic depression, unspecified psychotic disorder).

The Positive and Negative Syndrome Scale (PANSS) [32] was administered to explore positive, negative and general psychopathological symptoms. The PANSS is a 30-item heteroadministered scale. Each item is rated from 1 to 7, representing increasing levels of symptom severity. It has 3 subscales used for rating positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items). The scores for these scales are obtained by the addition of ratings across component items. Therefore, the potential ranges are 7 to 49 for the positive and negative scales and 16 to 112 for the general psychopathology scale.

The Calgary Depression Scale for Schizophrenia (CDSS) [33] was administered to explore depressive symptoms. The CDSS is a 9-item heteroadministered scale with a global range score between 0 and 27 that was specifically developed to assess the level of depression in schizophrenia.

The Global Assessment of Functioning (GAF) was used to evaluate the level of social and occupational functioning of PD patients. The GAF is a heteroadministered numeric scale (1 through 100) that serves well as a global indicator of symptom distress and social dysfunction [34]. Higher scores reflect better functioning.

The psychometric scales were administered on the same day as the cognitive assessment.

*2.2.2. Cognitive assessment*

The MCCB was administered to explore neuropsychological functioning [20]. This instrument contains 10 tests to measure cognitive performance in 7 cognitive domains: speed processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Table S1 from electronic supplementary materials). A composite score is obtained that combines the individual scores of the 10 tests and scores them on a normative scale to derive a T-score, where the mean is 50 and a standard deviation is

10 for the composite. Normative data for the MCCB have been obtained in Spain [35]. These data suggest that significant age, gender, and education effects are comparable to those effects described for the original standardized English version in the U.S. These findings support the robustness of the MCCB for use in different countries. All neuropsychological assessments were performed in the morning, with starting times between 9 h and 12 h. Subjects with a PD were assessed when they were clinically stable, and cognitive testing in first episodes of psychosis was performed when the acute episode had remitted.

*2.2.3. Childhood trauma*

Childhood trauma was assessed with the Spanish version of the 28-item Childhood Trauma Questionnaire [36]. This 28-item self-reported questionnaire assesses 5 types of childhood trauma (sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect) and includes one response bias scale (the minimization and denial scale) developed to detect the underreporting of maltreatment. Each item is rated between 1 and 5. Two items from the physical neglect subscale and five items from the emotional neglect subscale are reverse-coded. Each childhood trauma subscale is composed of 5 items (subscales scores range between 5 and 25). Total CTQ scores are obtained by adding all 5 subscales (total scores range between 25 and 75).



**2.3. Statistical analysis**

The SPSS version 20.0 software (SPSS Inc., Chicago, Illinois, USA) was used to carry out the statistical analyses.

2.3.1. Exploratory analyses

Spearman correlation was used to explore the association between continuous or ordinal variables. A chi-square test was used to compare categorical between groups. ANCOVA was performed to compare continuous data between sex and diagnostic groups (HS vs PD) while

testing for a sex by group interaction effect. We explored the distribution of dependent variables and used logarithmic (ln) transformation to normalize skewed variables before their inclusion in the ANCOVA. Significance was set at $p<0.05$ (two-tailed).

We also conducted a sex-stratified exploratory analysis of the relationship between distinct CTQ dimensions and clinical variables (substance use, psychometric scales and MCCB cognitive domains). Exploratory analyses were not adjusted for multiple comparisons because the correction for multiple testing is not strictly necessary for analyses that are exploratory in nature [37].

2.3.2. Hypothesis testing: are there sex differences in the relationship between childhood trauma and clinical variables in psychotic patients?

To explore the association between childhood trauma (CTQ scores) and clinical variables (substance use, psychometric scales and MCCB cognitive domains) while adjusting for covariates and testing interactions among CTQ, sex and diagnosis (HS vs PD), we conducted multiple linear regression analyses. An independent equation was conducted for each clinical variable that was considered the dependent variable. In the case of the MCCB cognitive domains, T-scores (adjusted for age, gender and education status) were used. CTQ scores were included in the equation as an independent variable. Other independent variables were female sex, PD diagnosis, smoking, cannabis use and antipsychotic treatment. Interactions among female sex, diagnostic group and CTQ scores were tested to explore whether the relationship between childhood trauma and each clinical variable differs by sex and diagnosis. This would happen if the three-way interaction (e.g., CTQ x female sex x PD diagnosis) was significant. We also tested two-way interactions (e.g., CTQ x female sex, CTQ x PD diagnosis, female sex x PD diagnosis) in the equation. The non-significant three-way interaction and any subsequent non-significant two-way interactions were dropped from the final model. Multiple linear regression analyses were adjusted for false discovery rate using the Benjamini-Hochberg procedure [38].

All dependent variables in linear regression analyses were tested for normal distribution. A log transformation (ln) was used to reduce skewness of positively skewed variables. For those variables including zero values, a ln (x+1) transformation was applied. The independence assumption was explored with residual plots. Independent variables (but not interaction terms) were tested for multicollinearity with the tolerance statistic. Tolerance values $\leq 0.2$ were considered indicative of multicollinearity.

#### 2.3.3. Reliability analysis of psychometric scales

We conducted a reliability analysis with Cronbach's alpha that was used as an internal consistency estimate of the reliability of the psychometric scales (PANSS subscales, CDSS, CTQ). This analysis was conducted in male and female patients separately, and both alpha values were compared with the Fisher-Bonett test.

## 3. RESULTS

### 3.1. Exploratory analyses

The sex percentages for both groups were as follows: HS (30 men= 51.7%; 28 women= 48.3%) and PD (48 men= 60.7%, 31 women= 39.2%). The socio-demographic, substance use and childhood trauma variables of the sample are summarized in Table 1. PD diagnosis was associated with a lower education status, more tobacco and cannabis consumption, and a greater history of childhood trauma, with greater scores on all CTQ domains and higher global scores. There were no sex differences in CTQ scores in the HS or PD groups. A sex by PD interaction was found for cannabis consumption (greater consumption was found in men, particularly in men with a PD).

In relation to clinical symptoms (Table 2), men reported more positive psychotic symptoms. No sex differences were found in negative symptoms, general psychopathology, depressive symptoms or functionality.

Cognitive measures in the HS and PD subjects are described in Table 3. PD patients showed a poorer cognitive performance in all cognitive domains. In relation to sex differences, male sex was associated with a better performance in reasoning and problem solving, and female sex was associated with social cognition. However, these results were not significant when considering the T-score adjusted for age, gender and education status. Two significant sex by PD diagnosis interactions were found in processing speed and attention and vigilance. As can be seen in Table 3, male HS show better processing speed and attention/vigilance, whereas the male advantage is not found in PD patients.

Correlations between childhood trauma and clinical variables in PD patients are reported in Table 4. In relation to substance use, childhood trauma was associated with increased alcohol intake in men, whereas the opposite relationship was found in women. Psychopathological measures were associated with childhood trauma only in women. A greater severity in positive and negative psychotic symptoms, general psychopathology, depressive symptoms and impaired functioning was observed in women with higher CTQ scores, particularly with emotional neglect. Emotional abuse was also associated with positive psychotic symptoms in women.

### 3.2. Hypothesis testing

The results of the multiple linear regression analyses (Table 5) suggest that CTQ scores are associated with poorer social cognition, greater severity in the PANSS general psychopathology scale and poorer functioning, with no sex interactions. In terms of alcohol consumption, a sex interaction effect was observed with CTQ scores (which were associated with less alcohol intake in women and greater alcohol intake in men).

PD diagnosis was associated with more tobacco and cannabis consumption and a poorer cognitive performance in all MCCB tasks. Female sex was associated with a poorer

performance in processing speed and attention and vigilance, with a significant female sex by PD interaction for both domains (meaning that although female sex was associated with a poorer cognitive performance in HS, the opposite relationship was found in PD patients). Female PD patients had lower scores on the PANSS positive and general subscales.

However, after testing for the false discovery rate with a Benjamini-Hochberg procedure, of all results regarding female sex, only the negative association with the attention and vigilance domain maintained its significance. In terms of childhood trauma, the negative relationship between CTQ scores and social cognition was also significant at the 0.05 false discovery rate. This relationship is also shown in Figure 1.

### 3.3. Reliability analysis of psychometric scales

In the reliability analysis conducted in male and female PD patients, the Cronbach's alphas were as follows: PANSS positive (0.80 vs 0.60, p= 0.027), PANSS negative (0.93 vs 0.92, p= 0.310), PANSS general psychopathology (0.62 vs 0.80, p= 0.142), CDS (0.87 vs 0.87, p= 0.466) and CTQ (0.83 vs 0.85, p= 0.644). All scales showed a good internal consistency without significant sex differences, with the exception of the PANSS positive subscale (a poorer reliability was observed in female patients).

## 4. DISCUSSION

In accordance with the scientific literature, PD patients reported a greater history of childhood trauma when compared to HS [10]. No sex differences were found in the prevalence of childhood trauma in either HS or PD patients, which contrasts with previous studies reporting more physical abuse in women [23]. However, although the prevalence of childhood trauma was similar between men and women with a PD, which could imply that traumatic experiences during childhood may be important for the development of the psychotic illness in both sexes,

exploratory analyses suggest that there are sex differences in the relationship between childhood trauma and particular symptoms or behaviors, including the following: association with depressive symptoms, positive and negative symptoms and poorer social functioning only in women, and greater alcohol intake in men. In relation to cognitive symptoms, we did not find sex differences in the relationship. Of all MCCB cognitive domains, only social cognition was associated with childhood trauma, without sex differences in the relationship.

In line with previous research studies, our results support the association between childhood maltreatment and positive symptoms [8,9]. The association between childhood trauma history and greater risk of positive, negative and depressive symptoms in women is in line with previous studies suggesting that there are gender differences in the effects of childhood trauma on well-being, as women tend to internalize their emotional pain [22]. It is also in line with previous studies reporting an association between childhood trauma and psychosis in women [23,39]. Moreover, sex differences have also been reported in relation to the effect of early life trauma on hypothalamic-pituitary-adrenal activity [40]. In this latter study, women showed an increased activation of the hypothalamic-pituitary-adrenal axis in response to a CRH challenge, which may suggest a different gender susceptibility to psychopathology following childhood trauma. HPA axis abnormalities (increased baseline cortisol levels [41] and increased cortisol secretion after awakening [42]) are biomarkers that have been linked to the risk of developing a psychotic disorder in high-risk populations. A sensitized dopaminergic response to stress has been demonstrated in both antipsychotic-naïve individuals with schizophrenia and people at risk of psychosis [43]. Other studies also suggest that there are sex differences in the neural impact of exposure to maltreatment during childhood. Both males and females with a history of childhood trauma show lower prefrontal-hippocampal connectivity. However, females also show lower connectivity in the prefrontal-amygdala pathway. Herringa et al. (2013) suggest that this “double hit” in females may partially explain the greater risk for anxiety and depression after childhood trauma. Although speculative, it is plausible that there are sex differences regarding the biological effects of childhood trauma (HPA axis, brain circuitry),

which could explain the significant association between CTQ scores and psychopathological symptoms (depression, positive and negative symptoms) in women.

In our study, people with a PD demonstrated poorer cognitive performance when compared to HS, which fits well with the known cognitive impairment of psychosis [45]. Healthy men outperformed women in several cognitive tasks, mainly speed of processing and attention/vigilance. This finding is in line with previous studies [35] that have used the MCCB, reporting better performance in some neurocognitive domains (attention/vigilance, reasoning and problem solving and working memory) in men, although women performed better in social cognition. In contrast, a different profile was observed for psychotic patients, as women had a better cognitive profile in tasks related to processing speed and verbal learning. These results are in accordance with previous reports showing a female advantage in processing speed and verbal memory [30,46] in patients with schizophrenia. However, there are contradictory findings in the literature, as some studies have reported more cognitive impairment in male subjects with schizophrenia [27,47], whereas others that include first episodes of psychosis have not reported sex differences [28,48]

In contrast with previous studies reporting that early psychosis patients with a history of childhood trauma show a poorer cognitive performance in neurocognitive domains, including language, attention, concentration, working memory and processing speed [17,18], we only found social cognition to be affected by a history of childhood trauma. Social cognition, a process by which people select, interpret, remember, and use social information to make judgments and decisions that are necessary to understand others is affected in subjects with schizophrenia and who are at risk for psychosis [16]. Cognitive models suggest that emotional processes act singly or in combination with cognitive biases in vulnerable individuals to increase the risk of developing psychosis [49]. Early traumatic experiences may have an effect on the development of emotional disturbance and negative schematic beliefs about the self and others, which may make some individuals more vulnerable to psychosis. Psychotic patients more frequently show a ‘jumping to conclusions’ reasoning style [50] and do not have

accessible alternative explanations for their experiences [51]. These cognitive biases are key elements in the social cognition deficits that may traduce a poorer emotional recall in the Mayer-Salovey-Caruso Emotional Intelligence Test.

Among the different childhood trauma dimensions (abuse vs neglect), we found that neglect had a clearer relationship with certain clinical symptoms (impairment in social cognition) in both genders and with depression and positive and negative symptoms in women. Our results underscore different roles for abuse and neglect in the association with clinical symptoms. Other studies that have considered abuse and neglect as separate childhood trauma dimensions have also found differences in the relationship with psychopathology: abuse has been linked to positive symptoms [13], whereas neglect has been associated with general psychopathology [13] and negative symptoms [52]. Our results regarding the association between neglect and psychotic and general symptoms are in accordance with these studies [13,52], although they did not report sex differences, as in our sample. Some studies have found that neglect and emotional abuse are even more strongly related to psychosis than physical and sexual abuse [53–55]. It is recognized that unlike sexual and physical abuse, in the case of emotional neglect, the perpetrator is almost invariably the primary caregiver and attachment figure for the child. Neglect is characterized by a lack of parent-child interaction. The experience of maltreatment by emotional neglect is chronic and can be more harmful and have more devastating effects than sexual abuse. Maltreatment associated with attachment problems would have implications for core predictors associated with the development of psychosis characterized by problematic emotional and interpersonal adaptation, heightened sensitivity to interpersonal stress (e.g., criticism and emotional over-involvement), poor pro-social coping and help-seeking, social withdrawal and avoidant and/or conflicted coping styles, and impoverished reflective function and affect regulation [56]. Our findings regarding potential sex differences in the relationship between abuse and neglect and clinical symptoms are exploratory in nature and may help the generation of hypotheses for future larger studies that are needed to confirm these differences.

Both genetic and environmental factors contribute to the onset of psychosis. Previous studies conducted in people at high genetic risk for schizophrenia suggest that genes interact with childhood trauma to induce the emergence of positive psychotic symptoms [57]. Having one or more biological parents with a history of psychotic disorder has been associated with both an increased risk of exposure to abuse [58,59] and the development of symptoms and psychotic disorders [60–63]. Previous studies suggest that reverse causation is unlikely to explain the association between childhood trauma and psychosis and that this association remains strong and significant when controlling for genetic risk [64].

Our study has several clinical implications in terms of the evaluation and treatment of psychosis. Given the importance of psychosocial adversity in general and the types of abuse in children in particular, the assessment of childhood trauma should be included in the assessment protocols and treatment planning in patients with psychosis. As has been recognized, cognitive behavioral therapy (CBT) has proven effective in treating psychosis following trauma, and it is relatively quick and easy to train practitioners in its use [65]. Morrison's integrative cognitive approach to hallucinations and delusions [66] suggests that these two conditions may represent different points on a spectrum of responses to trauma mediated by shared mechanisms such as dissociation, attributional style, or interpretations of intrusions. In Morrison's model, the experience of trauma can lead to negative beliefs about the self, the world, and others. These beliefs, specifically formed as a consequence of trauma, are associated with psychotic experiences [67]. CBT therapy can help patients with psychosis recognize the relationship among past trauma, current thought processes and their psychotic experiences. Specific techniques such as imagery re-scripting [68,69] in the cognitive-behavioral treatment of psychosis have been proposed. In relation to sex differences, because childhood trauma is associated with alcohol intake in male patients and with the severity of depressive and psychotic symptoms in female patients, this knowledge may help clinicians screen for a history of childhood trauma in vulnerable patients (men with alcohol abuse, women with depressive symptoms or persistent positive or negative symptoms). Addressing the history of childhood trauma in these patients may accelerate recovery from certain pathological conditions (e.g.,

alcohol intake in men, depression in women) that might be difficult to treat using standard treatment without considering a trauma-based approach.

Several limitations of our study need to be addressed. First, no causal relationship between childhood trauma and psychopathology or cognitive impairment can be inferred, due to the cross-sectional design. Second, childhood maltreatment was retrospectively assessed with a self-report instrument; thus, a recall bias may exist. However, the CTQ has demonstrated high reliability and validity [36,70], and studies using self-reported measures of childhood trauma in psychotic patients indicate that such reports are reliable [71]. Third, we did not assess the age at occurrence of the trauma or the subject's relationship to the perpetrator, as this information is not included in the CTQ assessment. The CTQ does not allow the assessment of longitudinal changes (e.g., repeated exposure) of traumatic experiences during childhood, but these changes could be important for psychosis risk, as "behavioral sensitization" is thought to play a role in how stressful experiences may increase the risk of psychosis [72]. Finally, our study sample was relatively small, which may result in a lack of statistical power for detecting small effects regarding the relationship among sex, childhood trauma and clinical variables. The small sample size also suggests that one should be cautious in interpreting the reliability analysis of psychometric scales conducted in PD patients, as larger samples (N>100) are usually needed for this type of analysis.

In conclusion, our study underscores that childhood trauma, particularly emotional and physical neglect, is associated with the clinical expression of psychosis, with poorer social cognition in both genders and with greater positive and negative psychotic symptoms and depressive symptoms in women. These findings support the existence of a distinct vulnerability to the effects of childhood trauma in women and men. If replicated in longitudinal studies, this knowledge would be useful for developing sex-specific interventions for childhood trauma survivors to prevent later psychopathological problems.

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Figure 1. Scatter plot of the relationship between childhood trauma and social cognition in 79 individuals with early psychosis.

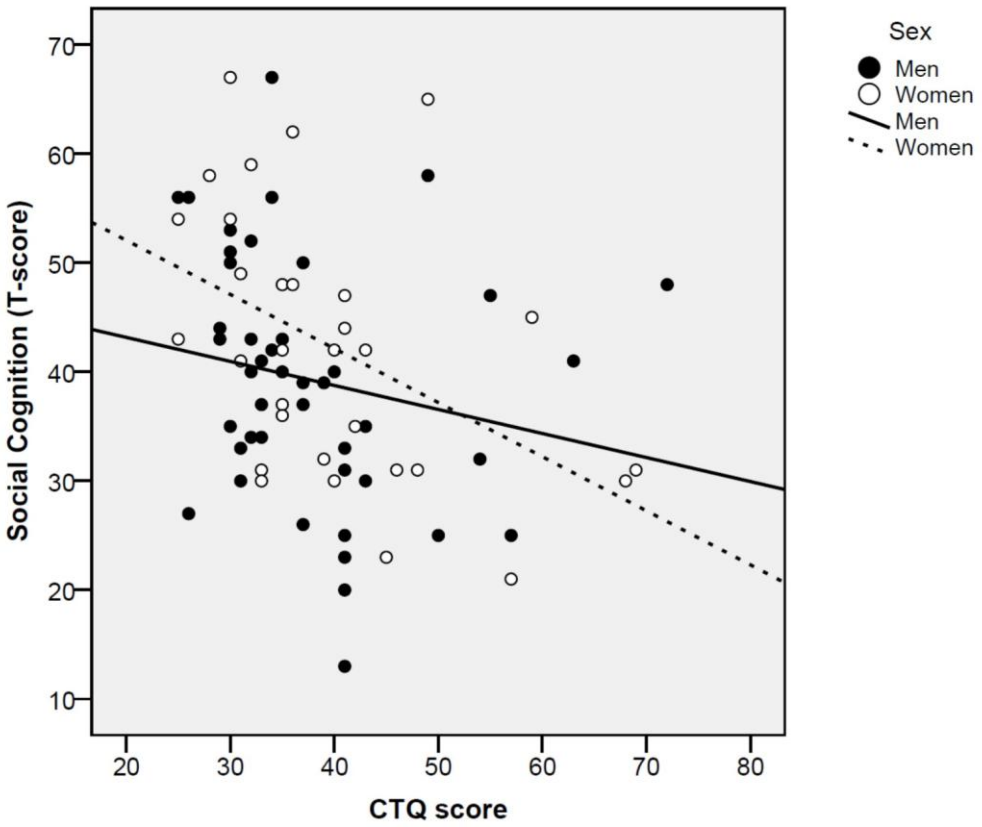

Table 1. Socio-demographic, substance use and childhood trauma variables in 58 healthy subjects and 79 patients with a psychotic disorder. Sex-differences by diagnostic group.

| | Male HS N=30 | Female HS N=28 | Male PD N=48 | Female PD N=31 | P values† Sex | PD | Sex by PD interaction |
|---|---|---|---|---|---|---|---|
| **Sociodemographic** | | | | | | | |
| Age (years), mean (SD) | 24.0 (4.8) | 23.9 (4.2) | 24.4 (4.5) | 26.8 (5.9) | 0.150 | 0.135 | 0.113 |
| Education (years), mean (SD) | 13.1 (2.7) | 14.0 (2.9) | 11.1 (3.0) | 11.9 (2.6) | 0.094 | <0.001 | 0.936 |
| *Substance use* | | | | | | | |
| Smoking (dichotomic), N (%) | 9 (30%) | 4 (14.3%) | 36 (75%) | 21 (67.7%) | | | |
| Smoking (cigarrettes/day), median (range) | 0 (0-20) | 0 (0-15) | 10 (0-40) | 6 (0-25) | 0.082 | <0.001 | 0.347 |
| Cannabis use (dichotomic), N (%) | 2 (6.7%) | 0 (0%) | 21 (43.8%) | 7 (22.6%) | | | |
| Cannabis (joints/day), median (range) | 0 (0-3) | 0 (0) | 0 (0-17) | 0 (0-5) | 0.014 | <0.001 | 0.039 |
| Alcohol intake (dichotomic), N (%) | 1 (3.3%) | 0 (0%) | 7 (14.6%) | 2 (6.5%) | | | |
| Alcohol intake (standard units/day), median (range) | 0 (0-2) | 0 (0) | 0 (0-15) | 0 (0-3) | 0.160 | 0.103 | 0.245 |
| **CTQ scores** | | | | | | | |
| Emotional abuse, median (range) | 7 (5-18) | 6 (5-11) | 7 (5-25) | 8 (5-21) | 0.691 | <0.001 | 0.062 |
| Physical abuse, median (range) | 5 (5-14) | 5 (5-8) | 5 (5-16) | 5 (5-12) | 0.347 | 0.002 | 0.418 |
| Sexual abuse, median (range) | 5 (5-9) | 5 (5-6) | 5 (5-14) | 5 (5-15) | 0.427 | 0.003 | 0.105 |
| Emotional negligence, median (range) | 7 (5-15) | 6.5 (5-18) | 9 (5-22) | 10 (5-25) | 0.916 | <0.001 | 0.227 |
| Physical negligence, median (range) | 5 (5-10) | 5 (5-8) | 6.5 (5-13) | 6 (5-14) | 0.732 | <0.001 | 0.135 |
| Minimization/Denial, median (range) | 11 (7-15) | 12 (7-15) | 10 (4-15) | 10 (3-15) | 0.921 | <0.001 | 0.388 |
| Total CTQ score, median (range) | 30 (25-48) | 28 (25-50) | 35 (25-72) | 37 (25-69) | 0.645 | <0.001 | 0.135 |

Abbreviations: HS= Healthy subjects; PD= Psychotic disorder; CTQ= Childhood Trauma Questionnaire.

†An ANCOVA analysis was conducted for all continuous variables. CTQ scores were log transformed (ln) to reduce skewness. P values for the effects of sex, PD and the interaction sex by PD are shown. In some variables (e.g. CTQ scores for physical abuse or sexual abuse), although median values are identical, the PD group has a greater proportion of patients with higher scores (over the median) when compared to HS. For this reason, there are significant differences between HS and PD groups.

Table 2. Sex-differences in psychopathological and treatment variables in patients with a psychotic disorder.

| | **Men N=48** | **Women N=31** | **P value** |
|---|---|---|---|
| **Psychometric scales** | | | |
| PANSS-Positive | 10 (7-24) | 9 (7-17) | 0.039 |
| PANSS-Negative | 14 (7-39) | 14 (7-28) | 0.480 |
| PANSS-General | 26(16-55) | 23 (16-41) | 0.115 |
| CDSS | 1 (0-15) | 1 (0-14) | 0.979 |
| GAF | 64 (12.5) | 66.6 (12.1) | 0.370 |
| *Treatment* | | | |
| Antipsychotic treatment (equivalents of chlorpromazine, mg/day) | 461.0 (507.8) | 318.3 (260.9) | 0.153 |
| Benzodiazepines (equivalents of diazepam, mg/day) | 3.3 (8.7) | 1.6 (5.0) | 0.332 |
| Biperiden (mg/day) | 0.7 (1.5) | 0.2 (0.8) | 0.046 |

Abbreviation: PANSS= Positive and Negative Syndrome Scale; CDSS= Calgary Depression Scale for Schizophrenia; GAF= Global Assessment of Functioning.
Data are mean (SD) or median (range).

Table 3. Cognitive measures in 58 healthy subjects and 79 patients with a psychotic disorder.

| | Male HS N=30 | Female HS N=28 | Male PD N=48 | Female PD N=31 | P values† | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sex | PD | Sex by PD interaction |
| **MCCB Tests (Raw data)** | | | | | | | |
| TMT-A (seconds) | 22.3 (6.2) | 26.7 (9.5) | 40.6 (22.7) | 33.1 (7.8) | 0.573 | <0.001 | 0.024 |
| BACS-SC | 62.7 (11.2) | 62.9 (8.9) | 44.4 (14.4) | 47.5 (9.5) | 0.431 | <0.001 | 0.477 |
| HVLT-R | 27.7 (3.8) | 27.6 (3.5) | 21.1 (4.8) | 23.4 (4.5) | 0.156 | <0.001 | 0.113 |
| WMS-III-SS | 16.7 (2.5) | 15.8 (3.2) | 13.6 (3.7) | 13.9 (3.1) | 0.616 | <0.001 | 0.298 |
| LNS | 14.4 (2.6) | 14.0 (3.3) | 12.0 (2.8) | 11.8 (1.9) | 0.468 | <0.001 | 0.852 |
| NAB Mazes | 23.1 (3.4) | 21.14 (3.4) | 18.8 (5.4) | 16.9 (5.8) | 0.021 | <0.001 | 0.991 |
| BVMT-R | 27.4 (6.2) | 26.9 (5.6) | 20.3 (7.5) | 19.7 (5.9) | 0.602 | <0.001 | 0.985 |
| Fluency- animal naming | 26.0 (6.3) | 22.9 (4.5) | 18.2 (4.7) | 17.2 (5.4) | 0.025 | <0.001 | 0.246 |
| MSCEIT-ME | 93.0 (8.8) | 96.2 (8.9) | 84.8 (10.2) | 88.7 (10.6) | 0.042 | <0.001 | 0.842 |
| CPT-IP | 2.8 (0.6) | 2.4 (0.5) | 1.9 (0.7) | 2.1 (0.6) | 0.178 | <0.001 | 0.009 |
| **MCCB Domains T-scores (adjusted for age, gender and education status)** | | | | | | | |
| Speed of processing | 54.6 (10.5) | 47.1 (8.0) | 34.0 (14.2) | 35.9 (10.4) | 0.165 | <0.001 | 0.022 |
| Attention/vigilance | 47.4 (9.1) | 40.5 (7.0) | 36.2 (9.2) | 39.6 (9.1) | 0.252 | <0.001 | 0.001 |
| Working memory | 43.5 (7.5) | 43.4 (9.2) | 34.9 (9.7) | 39.2 (8.6) | 0.185 | <0.001 | 0.171 |
| Verbal learning | 50.8 (8.9) | 47.7 (8.3) | 40.8 (7.7) | 42.3 (8.4) | 0.594 | <0.001 | 0.121 |
| Visual learning | 47.8 (10.5) | 46.1 (9.1) | 37.1 (12.7) | 36.8 (10.3) | 0.277 | <0.001 | 0.699 |
| Reasoning and problem solving | 50.7 (7.9) | 47.1 (7.9) | 42.5 (9.4) | 42.3 (10.0) | 0.234 | <0.001 | 0.275 |
| Social Cognition | 48.3 (9.9) | 50.7 (9.0) | 39.2 (11.4) | 42.2 (12.2) | 0.163 | <0.001 | 0.877 |
| Composite score (overall) | 47.8 (8.4) | 43.4 (9.0) | 31.8 (10.4) | 32.1 (10.9) | 0.246 | <0.001 | 0.173 |

Data are mean (SD).

Abbreviation: HS= Healthy subjects; PD= Psychotic disorder; MCCB= MATRICS Consensus Cognitive Battery; TMT-A= Trail Making Test, Part A; BACS-SC= Brief Assessment of Cognition in Schizophrenia-Symbol Coding; HVLT-R= Hopkins Verbal Learning Test-Revised; WMS-III-SS= WMS-III Spatial Span; LNS= University of Maryland Letter-Number Span; NAB= Neuropsychological Assessment Battery; BVMT-R= Brief Visuospatial Memory

Test-Revised; MSCEIT-ME= Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions; CPT-IP= Continuous Performance Test- Identical Pairs.

[†]An ANCOVA analysis was conducted for all cognitive variables. P values for the effects of sex, PD and the interaction sex by PD are shown.

Table 4. Correlations between childhood trauma dimensions and clinical variables in 79 patients with a psychotic disorder. Sex-stratified analysis.

| | **Men N=48** | | | | | | **Women N=31** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **EA** | **PA** | **SA** | **EN** | **PN** | **CTQ** | **EA** | **PA** | **SA** | **EN** | **PN** | **CTQ** |
| **Subastance use** | | | | | | | | | | | | |
| Smoking (cigarrettes/day) | 0.010 | 0.064 | 0.003 | 0.096 | 0.042 | 0.107 | 0.326 | 0.132 | -0.088 | 0.112 | 0.209 | 0.248 |
| Cannabis (joints/day) | 0.140 | -0.004 | 0.154 | -0.072 | 0.179 | 0.102 | 0.309 | 0.224 | -0.162 | 0.144 | 0.201 | 0.228 |
| Alcohol (standard units/day) | 0.018 | 0.171 | 0.120 | 0.277 | 0.356* | 0.331* | -0.178 | -0.153 | -0.165 | -0.384* | -0.302 | -0.384* |
| **Psychometric scales** | | | | | | | | | | | | |
| PANSS-Positive | 0.127 | 0.134 | 0.252 | 0.059 | -0.080 | 0.046 | 0.471** | 0.147 | 0.195 | 0.498** | 0.269 | 0.425* |
| PANSS-Negative | -0.172 | 0.215 | 0.174 | 0.124 | 0.146 | 0.157 | 0.212 | 0.061 | -0.149 | 0.378* | 0.379* | 0.226 |
| PANSS-General | 0.148 | 0.288* | 0.219 | 0.197 | -0.002 | 0.237 | 0.344 | 0.352 | 0.007 | 0.403* | 0.206 | 0.367* |
| CDS | -0.017 | 0.064 | -0.140 | 0.103 | 0.116 | 0.120 | 0.126 | 0.365* | 0.297 | 0.481** | 0.230 | 0.405* |
| GAF | -0.046 | -0.257 | -0.115 | -0.181 | -0.145 | -0.208 | -0.319 | -0.314 | -0.073 | -0.497* | -0.326 | -0.391* |
| **MCCB T-scores (adjusted for age, gender and education status)** | | | | | | | | | | | | |
| Speed of processing | 0.171 | -0.106 | 0.257 | -0.112 | -0.072 | 0.005 | -0.009 | -0.223 | -0.122 | 0.051 | 0.142 | 0.004 |
| Attention/vigilance | 0.063 | -0.129 | 0.233 | -0.101 | -0.205 | -0.069 | 0.100 | -0.217 | 0.094 | -0.042 | -0.026 | 0.033 |
| Working memory | 0.130 | -0.055 | 0.023 | -0.099 | -0.165 | -0.044 | 0.145 | -0.048 | 0.137 | 0.119 | 0.074 | 0.104 |
| Verbal learning | 0.147 | -0.068 | -0.094 | -0.153 | -0.038 | -0.057 | -0.153 | -0.331 | -0.068 | -0.205 | -0.328 | -0.294 |
| Visual learning | 0.049 | 0.001 | 0.004 | -0.142 | -0.030 | -0.044 | 0.170 | -0.219 | 0.073 | -0.049 | -0.119 | 0.006 |
| Reasoning and problem solving | 0.084 | -0.169 | 0.161 | -0.158 | -0.229 | -0.107 | 0.135 | -0.001 | 0.052 | 0.281 | 0.315 | 0.205 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Social cognition | 0.081 | -0.198 | 0.046 | -0.423** | -0.378* | -0.365* | -0.162 | -0.059 | -0.263 | -0.546** | -0.561** | -0.483** |
| Composite (overall) | 0.029 | -0.287 | 0.059 | -0.116 | -0.166 | -0.130 | 0.027 | -0.251 | -0.011 | -0.090 | -0.123 | -0.095 |

*p<0.05 **p<0.01

Abbreviations: EA= Emotional abuse; PA= Physical abuse; SA= Sexual abuse; EN= Emotional neglect; PN= Physical neglect; CTQ= Childhood trauma questionnaire (total score); PANSS= Positive and Negative Syndrome Scale; CDS= Calgary Depression Scale; GAF= Global Assessment of Functioning.

Table 5. Results of the multiple linear regression analyses exploring the association between CTQ scores, sex and clinical outcomes in terms of substance use, PANSS scores and cognitive abilities.

| | Regression statistics | | | Independent variables[I] | | | |
|---|---|---|---|---|---|---|---|
| Dependent variable | Adjusted $R^2$ | F | P value | Female sex | PD diagnosis | CTQ | Interactions |
| **Substance use**[†] | | | | | | | |
| Smoking (cigarettes/day) | 0.209 | 11.74 | <0.001 | -0.146 (p=0.061) | 0.387 (p<0.001*) | 0.069 (p= 0.424) | NSI |
| Cannabis (joints/day) | 0.184 | 7.45 | <0.001 | -0.024 (p= 0.843) | 0.435 (p<0.001*) | 0.057 (p= 0.515) | Female sex by PD (β= -0.294, p= 0.032) |
| Alcohol (standard units/day) | 0.054 | 2.96 | 0.022 | 0.506 (p=0.110) | 0.127 (p= 0.174) | 0.256 (p= 0.036) | Female sex by CTQ (β= -0.677, p= 0.037) |
| **Cognitive abilities (MCCB domains)**[‡] | | | | | | | |
| Speed of processing | 0.345 | 11.23 | <0.001 | -0.271 (p= 0.011) | -0.660 (p<0.001*) | -0.043 (p= 0.581) | Female sex by PD (β= 0.293, p= 0.018) |
| Attention and vigilance | 0.171 | 4.95 | <0.001 | -0.370 (p= 0.002*) | -0.440 (p= 0.001*) | -0.001 (p= 0.987) | Female sex by PD (β= 0.411, p= 0.004) |
| Working memory | 0.132 | 4.46 | <0.001 | 0.111 (p= 0.183) | -0.341 (p= 0.002*) | 0.116 (p= 0.193) | NSI |
| Verbal learning | 0.180 | 5.94 | <0.001 | -0.031 (p= 0.703) | -0.334 (p= 0.001*) | -0.109 (p=0.211) | NSI |
| Visual learning | 0.205 | 6.79 | <0.001 | 0.001 (p= 0.987) | -0.413 (p<0.001*) | -0.042 (p= 0.620) | NSI |
| Reasoning and problem solving | 0.098 | 3.44 | 0.004 | -0.088 (p= 0.305) | -0.340 (p= 0.002*) | 0.061 (p= 0.505) | NSI |
| Social cognition | 0.205 | 6.68 | <0.001 | 0.155 (p= 0.059) | -0.301 (p= 0.004*) | -0.273 (p= 0.002*) | NSI |
| Composite (global score) | 0.340 | 11.93 | <0.001 | -0.066 (p= 0.384) | -0.502 (p<0.001*) | -0.090 (p=0.263) | NSI |
| **Psychometric scales**[§] | | | | | | | |
| PANSS positive[#] | 0.087 | 3.22 | 0.009 | -0.138 (p= 0.130) | NA | 0.173 (p= 0.057) | NSI |
| PANSS negative | 0.159 | 3.92 | 0.003 | -0.119 (p= 0.286) | NA | 0.134 (p= 0.208) | NSI |
| PANSS general | 0.139 | 3.50 | 0.007 | -0.273 (p= 0.017) | NA | 0.281 (p= 0.010) | NSI |
| CDSS[#] | 0.079 | 1.04 | 0.400 | -0.031 (p= 0.795) | NA | 0.217 (p= 0.060) | NSI |
| GAF | 0.200 | 4.17 | 0.001 | 0.115 (p= 0.306) | NA | -0.272 (p= 0.012) | NSI |

Abbreviation: PD= Psychotic disorder; CTQ= Childhood Trauma Questionnaire; MCCB= Matrics Consensus Cognitive Battery; PANSS= Positive and Negative Syndrome Scale; CDSS= Calgary Depression Scale for Schizophrenia; GAF= Global Assessment of Functioning; NSI= Not significant interactions; NA= Not assessed.

[|]Standardized beta coefficients are shown.

[#]Variables were log transformed (ln) for reducing skewness. For CDSS scores, a ln (x+1) transformation was applied.

[†]Independent variables of the linear regression analyses exploring substance use were: female sex, PD diagnosis, CTQ and antipsychotic treatment dosing. We also tested two-way and three-way interactions between female sex, PD diagnosis and CTQ.

[‡]Independent variables of the linear regression analyses exploring MCCB cognitive domains (age, gender and education status adjusted T-scores) were: female sex, PD diagnosis, CTQ, smoking, cannabis use and antipsychotic treatment dosing. We also tested two-way and three-way interactions between female sex, PD diagnosis and CTQ.

[§]Independent variables of the linear regression analyses exploring psychometric scales were: female sex, CTQ, smoking, cannabis use and antipsychotic treatment dosing. We also tested the potential interaction female sex by CTQ. As psychometric scales were only administered to patients, PD diagnosis was not included as an independent variable in these linear regression analyses.

[*]Significant p values at the 0.05 false discovery rate (Benjamini-Hochberg adjustment).