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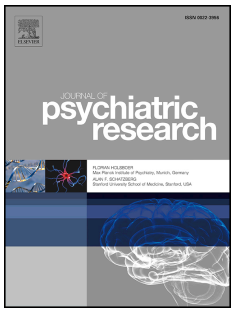

Trauma and psychosis: The mediating role of premorbid adjustment and recent stressful events in a 3-year longitudinal study

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TRAUMA AND PSYCHOSIS: THE MEDIATING ROLE OF PREMORBID ADJUSTMENT AND RECENT STRESSFUL EVENTS IN A 3-YEAR LONGITUDINAL STUDY

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Abstract

Background: Some of the most-studied environmental factors that can contribute to the development of psychosis are the adversities experienced at an early age. Among these, childhood interpersonal trauma (CIT) has been considered especially influential in the onset of the disease. The aim of the study was to explore the relationship between CIT and the first episode of psychosis (FEP), as well as the relationship between CIT and clinical and functional outcomes 3 years after illness onset.

Methods: A total of 278 patients with a FEP and 52 healthy controls were studied. Logistic regression analysis was carried out to examine the explained variation by CIT at the beginning of psychosis. Recent stressful events and premorbid adjustment related to CIT, were introduced in path analyses to determine their mediating effects between CIT and the disease and its clinical and functional results.

Results: Mediation analyses showed that CIT was indirectly associated with belonging to the FEP group through recent stressful events (Effect = 0.981; SE = 0.323; CI = 0.485 to 1.761). Premorbid academic adjustment in late adolescence mediated the relationship between CIT and clinical and functional outcomes, specifically in the measurements of the Scales for Assessment of Positive and Negative Symptoms, in the Brief Psychiatric Rating Scale, and in the Disability Assessment Scale.

Conclusions: These findings suggest that early traumatic experiences play an important role in the FEP. Early intervention that promotes good academic adjustment during adolescence and/or avoids retraumatisation could positively impact both the onset and the course of psychotic illness.

TRAUMA AND PSYCHOSIS: THE MEDIATING ROLE OF PREMORBID ADJUSTMENT AND RECENT STRESSFUL EVENTS IN A 3-YEAR LONGITUDINAL STUDY

1. Introduction

Psychotic disorders are mental illnesses caused by the combination of genetic susceptibility and different environmental factors (Bernardo et al., 2017, Pelayo-Teran et al., 2012, van Os et al., 2010). Some of the most widely-studied environmental factors include childhood traumatic experiences. Different studies have found that a history of early life trauma has been related to the emergence of psychotic disorders (Matheson et al., 2013, Morgan and Fisher, 2007, Trotta et al., 2015), and the meta-analysis undertaken by Varese et al. indicated that up to 33% of the incidence of psychosis could be due to childhood traumatic experiences (Varese et al., 2012). There seems to be evidence that childhood interpersonal trauma (CIT) may be a particularly strong risk factor for psychosis (Arseneault et al., 2011, Fisher et al., 2010). Sexual abuse, physical abuse, and physical and emotional neglect are different forms of CIT. What all these traumas have in common is the involvement of another person, that is, they have been perpetrated by other individuals who are frequently part of the child's closest environment, such as their family members, carers or educators.

Among the known consequences of trauma, different studies have shown that childhood adversities can lead to impaired premorbid adjustment (Trauelsen et al., 2016, Stain et al., 2014), understood as the psychosocial functioning of the individual before the onset of a disease (Cannon-Spoor et al., 1982). Several investigations have found a negative association between CIT and premorbid adjustment in samples of patients with a first episode of psychosis (FEP) (Kilian et al., 2017, Hegelstad et al., 2021). This potential

connection is essential, since many aspects of premorbid adjustment have been well documented in the literature as having an influence on the illness, affecting such important issues as the duration of untreated psychosis (Larsen et al., 2000), the age of illness onset (Vyas et al., 2007), and the severity of symptoms when it manifests (Grau et al., 2016).

In addition to childhood trauma, some authors have been concerned about the effects that recent stressful events, that is, those that occurred before the onset of illness, have on psychosis (Arranz et al., 2018, Ayesa-Arriola et al., 2020, Morgan et al., 2014). These events have been defined as situations or events that cause a positive or negative change in personal circumstances and/or involve an element of threat (Beards et al., 2013). The conclusions of these studies identified the presence of a synergistic effect between childhood trauma and recent stressful events (RSEs) for the development of psychosis (Morgan et al., 2014) and the existence of a synergistic influence of trauma and RSEs on the cognitive function of FEP patients (Ayesa-Arriola et al., 2020).

Although there seems to be a clear association between trauma and psychosis, the same cannot be said for how trauma is related to clinical and functional outcomes. A recently published systematic review reported that data on the effects of trauma on the severity, prognosis, and course of the FEP are inconclusive (Vila-Badia et al., 2021).

Aims of the study

To shed some light on the subject, our objective was to explore the relationship between CIT and psychosis and its evolution in the 3 years since the onset of the illness. The study addressed the possible mediating effect of other variables such as RSEs or premorbid adjustment, which have already been shown to have an effect on the disease (Grau et al., 2016, Morgan et al., 2014). This general aim was divided into three specific objectives:

- The first objective was to confirm whether CIT is significantly associated, directly or indirectly through RSEs, with belonging to the FEP group.
- The second objective was to confirm whether CIT is significantly related to relapses over the 3 years since the FEP and whether premorbid adjustment and/or RSEs mediate this relationship.
- The third objective was to confirm whether CIT is significantly related to clinical and functional outcomes at 3 years of disease duration and whether premorbid adjustment and/or RSEs act as mediators in this relationship.

We hypothesised that the presence of CIT will have a negative influence on the disease, being directly or indirectly associated through RSEs, with the emergence of psychosis. We hypothesised that the presence of CIT will be related to relapses, with the premorbid adjustment and RSEs acting as mediators in this relationship. Finally, we hypothesised that the presence of CIT will be related to worse clinical and functional outcomes at 3 years of follow-up and that premorbid adjustment and RSEs will play a mediating role.

2. Methods

2.1 Study design and population

The data used in this study were obtained from a large epidemiological cohort of patients with a FEP who were treated as part of a longitudinal intervention programme called *Programa Asistencial a las Fases Iniciales de Psicosis* (Support Programme for Early-stage Psychosis (PAFIP)) (clinical trial identifier NCT02526030). This programme was implemented at the outpatient clinic and the inpatient unit at the Marqués de Valdecilla University Hospital, Santander, Spain. The study complied with international standards for research ethics and was approved by the local ethics committee, namely, the *Comité de ética de la investigación con medicamentos de Cantabria, CEIm de Cantabria*

(Cantabria Research Ethics Committee for Studies involving Drugs). A detailed description of the PAFIP methodology can be found in previous publications (Crespo-Facorro et al., 2007, Pelayo-Teran et al., 2008).

All patients who were included in this study were evaluated between 2001 and 2017. They met the following inclusion criteria: (a) aged between 15 and 60 years old; (b) lived in the catchment area; (c) were patients with a FEP; (d) had not received antipsychotic treatment lasting more than 6 weeks; and (e) met DSM-IV criteria for schizophrenia, schizophreniform disorder, brief psychotic disorder, not otherwise specified psychosis, schizoaffective disorder, or delusional disorder. Patients were excluded for any of the following reasons: (a) having an intellectual disability, brain injury or neurological disease, and/or (b) meeting the DSM-IV criteria for drug dependence (except nicotine dependence).

A total of 278 patients who met the PAFIP inclusion criteria were selected for the study. Out of the 278 patients assessed at baseline, 250 (89.9%) were re-evaluated at 3 years follow-up. Attrition within the analysis sample seemed random; that is, the participation on reassessments was not associated with sex, age, diagnosis, symptoms or traumatic antecedents (data available upon request). In addition, a group of 52 healthy volunteers (29 men, age range 15 to 50 years old) recruited from the community through advertisements between 2003 and 2007 was included with the purpose of answering the first objective of this study. The volunteers had no current or past history of psychiatric neurological or general medical illnesses, including substance abuse, according to an abbreviated version of the Comprehensive Assessment of Symptom and History (CASH) (Andreasen et al., 1992). All patients and controls (or their parents, if they were minors) gave their written informed consent to participate in this study.

2.2 Assessments

Sociodemographic data. The sociodemographic information of patients was recorded at admission. The data considered in the study were: sex, age, years of education, socioeconomic status derived from parental occupations ('low-skilled worker' vs 'others'), place of residence ('urban location' vs 'rural location'), family history of psychosis ('yes' vs 'no'), employment status ('employed' vs 'unemployed'), and current cannabis use as a dichotomous measure ('yes' vs 'no').

Clinical measures. The clinical variables considered in the study were: hospitalisation at intake ('yes' vs 'no'); age of onset of the disease; diagnosis of schizophrenia confirmed using the Structured Clinical Interview for DSM-IV (SCID-I); duration of untreated illness (DUI), defined as the time from the first non-specific symptoms related to psychosis to the start of adequate treatment with antipsychotic medication; duration of untreated psychosis (DUP), defined as the time from the first continuous psychotic symptoms to the start of appropriate treatment with antipsychotic medication; general psychopathology evaluated by adding the scores of all the items of the Brief Psychiatric Rating Scale (BPRS) (Flemenbaum and Zimmermann, 1973); psychotic symptoms assessed using the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for Assessment of Positive Symptom (SAPS) (Andreasen, 1984); symptoms of depression as assessed by the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993); and functionality as evaluated using the Disability Assessment Scale (DAS), Spanish version (Mañá S et al., 1998), and the Global Assessment of Functioning (GAF) (DSM-IV-TR, 2002). Relapses, understood as worsening in functionality or in severity of symptoms after clinical improvement, were

also considered. Relapses were assessed using clinical qualification instruments (details can be seen in Caseiro O. et al.) (Caseiro et al., 2012).

Trauma evaluation. Traumatic events in childhood were assessed using the Childhood Traumatic Events Scale (CTES) (Pennebaker and Susman, 1988). The CTES is a brief survey of six types of trauma experienced before the age of 17 (death of a close friend or family member; parental divorce; sexual abuse; physical abuse; illness/accident; or other). Since the objective of this study was the investigation of CIT, only sexual abuse, physical abuse and other trauma scores were considered when they were perpetrated by other persons (e.g., bullying or parental neglect) and it was considered that an individual had suffered CIT when they presented one or several of these three traumas. Recent stressful events (RSEs) were assessed with the Recent Traumatic Events Scale (RTES) (Pennebaker and Susman, 1988). The RTES collects information on traumatic events that occurred in the 3 years prior to the onset of the disease or to the interview in the case of healthy controls (adding work-related trauma to the CTES types of trauma). The information collected on this scale was categorised into two variables, a dichotomous one that indicated whether the patients had experienced any RSEs, and a quantitative one that indicated the perception of severity of the trauma (RSEp), which was calculated based on the traumas experienced by each individual. In both scales, the evaluation was carried out using a seven-point Likert scale where 1 = nothing traumatic; 4 = somewhat traumatic; and 7 = extremely traumatic.

Assessment of premorbid adjustment. Premorbid functioning was measured using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), which assesses school adaptation and socialisation during different periods from childhood to adulthood. Direct scores range from 1 to 6, with higher scores indicating more disability. The scores

received for each item in a section are added together and expressed as the total score divided by the possible score (which depends on the number of questions answered). The PAS differentiates between four periods: childhood (up to 11 years old); early adolescence (12-15 years old); late adolescence (16-18 years old); and adulthood (19 years old and over). The PAS also has a general section that contains elements designed to estimate the highest level of functioning that the subject reached before becoming ill.

2.3 Statistical analysis

The statistical package for social sciences (SPSS), version 27.0 (IBM, 2020) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to assess the normality of the distribution. The cross-sectional analyses of the sociodemographic and clinical variables (primary analyses) were carried out by the use of the chi-square test to compare categorical variables, and the Mann-Whitney U test was used for continuous variables. When the analysis revealed significant effects between groups, additional post-hoc analyses (Bonferroni correction) were applied. Significant variables in the primary analyses were entered into a logistic regression analysis that examined the proportion of variance explained by the model (with respect to FEP group membership). Through mediation analysis, the relationship between CIT and membership in the FEP group mediated by RSEp was explored. The indirect relationship between CIT and disease outcomes was tested through RSEp and premorbid adjustment using baseline clinical variables as covariates. All mediation analyses were performed by the SPSS macro Process (Hayes, 2017) (model 4). This resulted in a 95% bootstrap bias-corrected confidence interval, based on 5000 bootstrapping samples to determine the indirect effects.

3. Results

3.1. Relationship between CIT and the first episode of psychosis

This study took into account data from 278 patients with a FEP aged 30.6 (9.7), of whom 151 were men (54.3%), and 52 healthy controls aged 28.2 (7.8), of whom 29 were men (55.8%). **Table 1** shows the differences between them.

The significant variables which had emerged from our primary analyses (RSEp, employment status and family history of psychosis) and CIT variable (based on our hypothesis) were entered into a regression model. The objective was to analyse the effect of these variables on the FEP. CIT did not have statistical significance (B = -0.199; p = 0.813) and the variable that better explained the FEP was RSEp (B = -0.253; p <0.001) (See **Table 2**). Given the relationship between both variables (rho = 0.155; p =0.005), mediation analysis was performed to find out whether CIT was indirectly related to the disease through RSEp. The results of this analysis were statistically significant, which indicated that CIT indirectly influenced the emergence of the FEP through RSEp (Effect = 0.981; SE = 0.323; CI = 0.485 to 1.761) (See **Figure 1**).

The differences between FEP patients who had experienced a CIT and those who had not, are listed in **Table 3**. Patients with CIT have a younger age of onset of the disease (u=4441; p=0.015), have a higher score for RSEp (u=5217; p=0.044), and have worse academic premorbid adjustment (APA), both in early (u=4518.5; p=0.010) and late adolescence (u=2966; p=0.002). Due to the large number of variables analysed, Bonferroni correction was applied to the level 0.0027 (0.05/18). After Bonferroni correction only APA in late adolescence was significant.

3.2. Relationship between CIT and long-term outcomes

We examined whether CIT had any influence on disease outcomes. First, the relationship between CIT and the second episode of psychosis (SEP), that is, the first relapse after recovery, was analysed. For these analyses, all relapses experienced by patients within 3 years after FEP were considered. Out of the 278 patients included in the study, 115 (41.4%) showed at least one relapse during the follow-up period. The CIT did not show a significant association with the SEP, neither directly nor indirectly through the variables under study (RSEp or premorbid adjustment). Second, the relationship between CIT and clinical and functional symptoms after 3 years of FEP was analysed. No direct or indirect relationships through RSEp were observed. However, we found that APA in late adolescence acted as a mediator between CIT and clinical and functional outcomes, specifically in the clinical variables BPRS (Effect -0.818; SE 0.466; CI -1.908 to -0.086), SAPS (Effect -0.323; SE 0.165; CI -0.698 to -0.055), SANS (Effect -0.420; SE 0.232; CI -0.942 to -0.054) and DAS functionality variable (Effect -0.120; SE 0.049; CI -0.203 to -0.009) (See **Figure 2**).

4. Discussion

This study analysed the relationship between CIT and psychosis, both in connection with the onset of the disease and with long-term results. Our main finding was that CIT was indirectly related to the FEP through RSEp. However, once the disease emerged, RSEp did not show any influence in the evolution; however, APA did in late adolescence.

4.1. Influence of CIT in the onset of a psychotic disorder

Our results are in line with those obtained in other studies which analysed the relationship with childhood trauma and psychosis, although they did not analyse the mediating role of RSEs. As argued by Morgan et al., childhood adversity could be one of the first steps on the road to psychosis (Morgan et al., 2014). This idea has been reinforced by studies that

suggest that childhood trauma makes subjects more sensitive to later adversity, which is experienced with greater distress and in turn could result in an increased expression of psychosis (Lataster et al., 2012, Holtzman et al., 2013). In this vein, Lardinois et al. observed that a history of CIT in patients with psychosis was associated with greater reactivity to stress later in life (Lardinois et al., 2011). For this reason, these authors suggested the existence of an underlying process of behavioural sensitisation. This would explain Pearlin's affirmation that stressors are not isolated events but could be connected with each other, and that exposure to one stressor over time could lead to exposure to other secondary stressors (Pearlin et al., 1981, Pearlin, 2010). These facts could be framed in the theory of the 'double hit' of the pathogenesis of psychosis. This theory proposes that the disease may involve early exposure to any adverse factor that produces latent vulnerability, which makes individuals more susceptible to future stressful events that in turn contribute to the development of psychosis (Feinberg, 1982, Maynard et al., 2001). According to this model, CIT would be the 'first hit' that could have an impact on the development of the central nervous system; specifically, it could induce alterations in the development of the hypothalamic-pituitary-adrenal axis and the dopaminergic system (Andersen, 2003, Gunnar and Donzella, 2002, Walker, 1994). This could make the adult brain more vulnerable to a 'second hit' (the RSE), which would precipitate the disease. However, in addition to biological mechanisms, there are theories that implicate psychological mechanisms in the transition from childhood trauma to the onset of a psychotic disorder. The review by Misiak et al., pointed out different psychological mechanisms such as cognitive schemas, stress or affective regulation, attachment and dissociative processes (Misiak et al., 2017). Furthermore, Howes and Murray indicated that the different mechanisms can act together (Howes and Murray, 2014). These authors developed a model in which biological and psychological aspects were combined to

explain the relationship between childhood trauma and psychosis. The model postulates that early trauma can disrupt development and sensitize the dopaminergic system and at the same time bias the cognitive schema, causing the individual to see the world as threatening. Both mechanisms would perform together and would feed off each other: cognitive biases will lead to an increase in stress and this will lead to an increase in dopamine dysregulation, which in turn will lead to more stress and biased interpretations of the context (Howes and Murray, 2014).

4.2. Mediating variables between CIT and psychotic disorder outcomes

One of our objectives was to confirm whether there was a relationship between CIT and the outcomes of patients with a FEP, focusing on two aspects: the first relapse (or SEP) and the symptoms evaluated after 3 years of the FEP. The hypothesis that CIT was related to the SEP was not fulfilled. Neither direct association nor indirect association was observed through those variables that were related to CIT. However, CIT was found to be indirectly related to the severity symptoms of the disease 3 years since onset. This relationship occurred with the APA in late adolescence as a mediator.

These results support previous findings in which significant relationships were observed between trauma and symptoms, and between premorbid adjustment and symptoms, respectively. Different studies have observed that trauma is related to the persistence and severity of psychotic symptoms (Alameda et al., 2016, Alameda et al., 2017, Schalinski et al., 2015, Trotta et al., 2016, van Dam et al., 2015). It has also been found that CIT, in addition to leading to poor remission, leads to poor functional outcomes 2 years after the FEP (Pruessner et al., 2021). Even poorer remission of symptoms has been observed 5 years after the FEP in patients who had suffered exposure to childhood adversity (Ajnakina et al., 2018). Regarding the relationship of premorbid adjustment to symptoms,

it seems that there is agreement that poor premorbid adjustment can have negative effects both at the onset and during the course of the disease. In Chang's study, the best premorbid adjustment was associated with more positive symptom remission during the first year after the FEP (Chang et al., 2013). Furthermore, in a systematic review of 75 studies it was observed that poor premorbid adjustment was among the most replicated predictors of poorer clinical, functional, cognitive and biological outcomes in patients with a FEP (Diaz-Caneja et al., 2015).

Most of the studies that have included both trauma and premorbid adjustment among their study variables have found associations between both, although these findings have been uneven. Some studies confirmed a relationship between trauma and social premorbid adjustment (Hegelstad et al., 2021, Haahr et al., 2018); other studies found CIT to be related both to the social dimension and to the academic dimension of premorbid adjustment (Stain et al., 2014), while others showed no difference in the relationship between both dimensions (Tikka et al., 2013). In our study, patients with CIT showed poorer APA in both early and late adolescence. However, a mediating effect between CIT and symptoms was only seen among those who had poorer APA in late adolescence. These results are consistent with the chronological exposure to each of the events since, in the case of early adolescence, we cannot rule out the possibility that difficulties in premorbid academic adaptation preceded the trauma; on the contrary, we can ensure that all CIT cases preceded poor academic adjustment in late adolescence. Hegelstad et al. jointly addressed CIT and premorbid adjustment in relation to the evolution of psychosis. Their results showed that CIT and premorbid adjustment, both independently and interacting with each other, predicted remission of symptoms at 2 years (Hegelstad et al., 2021). They introduced CIT as a moderator in the relationship between premorbid adjustment and remission and obtained positive results.

The main strength of this study is its 3 years longitudinal design, which enabled us to assess whether CIT has both direct and indirect impact on how psychosis evolves over time. However, the study also has some limitations. The main one is that the assessment of trauma, of premorbid adjustment at different stages of life, and of the recent stressful events were performed retrospectively. This may have been affected by memory bias, although previous studies suggest good reliability in this type of evaluations (Fisher et al., 2009, Brill et al., 2008). Another limitation that could bias the results of the study is related with the control group. This is a group with considerably fewer participants than the patient group. In addition, this group may not be representative of the general population since its members were not randomly recruited, but instead volunteered for the study. Finally, it is also a limitation that the potential role of pharmacological treatments cannot be explored.

To conclude, childhood interpersonal trauma was found to be related with belonging to the FEP group and with the outcomes and symptoms as the disease evolved. These findings are of great importance since, once the existence of the trauma is known, a preventive intervention could be carried out in two ways: by addressing the psychological mechanisms involved in the transition towards a new traumatization through psychological interventions and/or by promoting good academic adjustment during adolescence. These strategies may contribute to cushion the impact of trauma on the disease.

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Conflict of interest

The authors have no conflict of interest to declare.

References

Addington, D., Addington, J. & Maticka-Tyndale, E. 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry Suppl*, 39-44.

Ajnakina, O., Trotta, A., Forti, M. D., Stilo, S. A., Kolliakou, A., Gardner-Sood, P., Lopez-Morinigo, J., Gaughran, F., David, A. S., Dazzan, P., Pariante, C., Mondelli, V., Murray, R. M. & Fisher, H. L. 2018. Different types of childhood adversity and 5-year outcomes in a longitudinal cohort of first-episode psychosis patients. *Psychiatry Res,* 269**,** 199-206.

Alameda, L., Golay, P., Baumann, P. S., Ferrari, C., Do, K. Q. & Conus, P. 2016. Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. *J Clin Psychiatry,* 77**,** e612-8.

Alameda, L., Golay, P., Baumann, P. S., Progin, P., Mebdouhi, N., Elowe, J., Ferrari, C., Do, K. Q. & Conus, P. 2017. Mild Depressive Symptoms Mediate the Impact of Childhood Trauma on Long-Term Functional Outcome in Early Psychosis Patients. *Schizophr Bull,* 43**,** 1027-1035.

Andersen, S. L. 2003. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev,* 27**,** 3-18.

Andreasen, N. 1983. Scale for the Assessment of Negative Symptoms (SANS). *Iowa City: University of Iowa*.

Andreasen, N. 1984. Scale for the Assessment of Positive Symptoms (SAPS). *Iowa City: University of Iowa*.

Andreasen, N. C., Flaum, M. & Arndt, S. 1992. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. *Archives of general psychiatry,* 49**,** 615-623.

Arranz, S., Monferrer, N., Jose Algora, M., Cabezas, A., Sole, M., Vilella, E., Labad, J. & Sanchez-Gistau, V. 2018. The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis. *Schizophr Res,* 201**,** 352-359.

Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E. & Caspi, A. 2011. Childhood trauma and children's emerging psychotic symptoms: A genetically sensitive longitudinal cohort study. *Am J Psychiatry,* 168**,** 65-72.

Ayesa-Arriola, R., Setien-Suero, E., Marques-Feixa, L., Neergaard, K., Butjosa, A., Vazquez-Bourgon, J., Fananas, L. & Crespo-Facorro, B. 2020. The synergetic effect of childhood trauma and recent stressful events in psychosis: associated neurocognitive dysfunction. *Acta Psychiatr Scand,* 141**,** 43-51.

Beards, S., Gayer-Anderson, C., Borges, S., Dewey, M. E., Fisher, H. L. & Morgan, C. 2013. Life events and psychosis: a review and meta-analysis. *Schizophr Bull,* 39**,** 740-7.

Bernardo, M., Bioque, M., Cabrera, B., Lobo, A., Gonzalez-Pinto, A., Pina, L., Corripio, I., Sanjuan, J., Mane, A., Castro-Fornieles, J., Vieta, E., Arango, C., Mezquida, G., Gasso, P., Parellada, M., Saiz-Ruiz, J., Cuesta, M. J., Mas, S. & GROUP, P. E. 2017. Modelling gene-environment interaction in first episodes of psychosis. *Schizophr Res,* 189**,** 181-189.

Brill, N., Reichenberg, A., Weiser, M. & Rabinowitz, J. 2008. Validity of the premorbid adjustment scale. *Schizophr Bull,* 34**,** 981-3.

Cannon-Spoor, H. E., Potkin, S. G. & Wyatt, R. J. 1982. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull,* 8**,** 470-84.

Caseiro, O., Perez-Iglesias, R., Mata, I., Martinez-Garcia, O., Pelayo-Teran, J. M., Tabares-Seisdedos, R., Ortiz-Garcia de la Foz, V., Vazquez-Barquero, J. L. & Crespo-Facorro, B. 2012. Predicting relapse after a first episode of non-affective psychosis: a three-year follow-up study. *J Psychiatr Res,* 46**,** 1099-105.

Crespo-Facorro, B., Pelayo-Teran, J. M., Perez-Iglesias, R., Ramirez-Bonilla, M., Martinez-Garcia, O., Pardo-Garcia, G. & Vazquez-Barquero, J. L. 2007. Predictors of acute

treatment response in patients with a first episode of non-affective psychosis: sociodemographics, premorbid and clinical variables. *J Psychiatr Res,* 41**,** 659-66.

Chang, W. C., Ming Hui, C. L., Yan Wong, G. H., Wa Chan, S. K., Ming Lee, E. H. & Hai Chen, E. Y. 2013. Symptomatic remission and cognitive impairment in first-episode schizophrenia: a prospective 3-year follow-up study. *J Clin Psychiatry,* 74**,** e1046-53.

Diaz-Caneja, C. M., Pina-Camacho, L., Rodriguez-Quiroga, A., Fraguas, D., Parellada, M. & Arango, C. 2015. Predictors of outcome in early-onset psychosis: a systematic review. *NPJ Schizophr,* 1**,** 14005.

DSM-IV-TR 2002. *American Psychiatric Association. Diagnostic an statistical manual of mental disorders (4th ed.).* Washington, DC.

Feinberg, I. 1982. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res,* 17**,** 319-34.

Fisher, H., Morgan, C., Dazzan, P., Craig, T. K., Morgan, K., Hutchinson, G., Jones, P. B., Doody, G. A., Pariante, C., McGuffin, P., Murray, R. M., Leff, J. & Fearon, P. 2009. Gender differences in the association between childhood abuse and psychosis. *Br J Psychiatry,* 194**,** 319-25.

Fisher, H. L., Jones, P. B., Fearon, P., Craig, T. K., Dazzan, P., Morgan, K., Hutchinson, G., Doody, G. A., McGuffin, P., Leff, J., Murray, R. M. & Morgan, C. 2010. The varying impact of type, timing and frequency of exposure to childhood adversity on its association with adult psychotic disorder. *Psychol Med,* 40**,** 1967-78.

Flemenbaum, A. & Zimmermann, R. L. 1973. Inter- and intra-rater reliability of the Brief Psychiatric Rating Scale. *Psychol Rep,* 32**,** 783-92.

Grau, N., Rubio-Abadal, E., Usall, J., Barajas, A., Butjosa, A., Dolz, M., Banos, I., Sanchez, B., Rodriguez, M. J., Pelaez, T., Sammut, S., Carlson, J., Huerta-Ramos, E., Group, G. & Ochoa, S. 2016. Influence of cognition, premorbid adjustment and psychotic symptoms on psycho-social functioning in first-episode psychosis. *Psychiatry Res,* 242**,** 157-162.

Gunnar, M. R. & Donzella, B. 2002. Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology,* 27**,** 199-220.

Haahr, U. H., Larsen, T. K., Simonsen, E., Rund, B. R., Joa, I., Rossberg, J. I., Johannessen, J. O., Langeveld, J., Evensen, J., Trauelsen, A. M. H., Vaglum, P., Opjordsmoen, S., Hegelstad, W. T. V., Friis, S., McGlashan, T. & Melle, I. 2018. Relation between premorbid adjustment, duration of untreated psychosis and close interpersonal trauma in first-episode psychosis. *Early Interv Psychiatry,* 12**,** 316-323.

Hayes, A. F. 2017. *Introduction to Mediation, Moderation, and Conditional Process Analysis, Second Edition: A Regression-Based Approach*, Guilford Publications.

Hegelstad, W. T. V., Berg, A. O., Bjornestad, J., Gismervik, K., Johannessen, J. O., Melle, I., Stain, H. J. & Joa, I. 2021. Childhood interpersonal trauma and premorbid social adjustment as predictors of symptom remission in first episode psychosis. *Schizophr Res,* 232**,** 87-94.

Holtzman, C. W., Trotman, H. D., Goulding, S. M., Ryan, A. T., Macdonald, A. N., Shapiro, D. I., Brasfield, J. L. & Walker, E. F. 2013. Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience,* 249**,** 172-91.

Howes, O. D. & Murray, R. M. 2014. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet,* 383**,** 1677-1687.

IBM, C. 2020. IBM SPSS Statistics for Windows, Version 27.0. *Armonk, NY: IBM Corp*.

Kilian, S., Burns, J. K., Seedat, S., Asmal, L., Chiliza, B., Du Plessis, S., Olivier, M. R., Kidd, M. & Emsley, R. 2017. Factors Moderating the Relationship Between Childhood Trauma and Premorbid Adjustment in First-Episode Schizophrenia. *PLoS One,* 12**,** e0170178.

Lardinois, M., Lataster, T., Mengelers, R., Van Os, J. & Myin-Germeys, I. 2011. Childhood trauma and increased stress sensitivity in psychosis. *Acta Psychiatr Scand,* 123**,** 28-35.

Larsen, T. K., Moe, L. C., Vibe-Hansen, L. & Johannessen, J. O. 2000. Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. *Schizophr Res,* 45**,** 1-9.

Lataster, J., Myin-Germeys, I., Lieb, R., Wittchen, H. U. & van Os, J. 2012. Adversity and psychosis: a 10-year prospective study investigating synergism between early and recent adversity in psychosis. *Acta Psychiatr Scand,* 125**,** 388-99.

Mañá S, Ivorra J & M., G. 1998. Adaptación y fiabilidad de la entrevista para la evaluación de la discapacidad social en pacientes psiquiátricos (OMS). *Revista de Psiquiatría de la Facultad de Medicina de Barcelona,* 25**,** 6.

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R. & Carr, V. J. 2013. Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychol Med,* 43**,** 225-38.

Maynard, T. M., Sikich, L., Lieberman, J. A. & LaMantia, A. S. 2001. Neural development, cell-cell signaling, and the "two-hit" hypothesis of schizophrenia. *Schizophr Bull,* 27**,** 457-76.

Misiak, B., Krefft, M., Bielawski, T., Moustafa, A. A., Sasiadek, M. M. & Frydecka, D. 2017. Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neurosci Biobehav Rev,* 75**,** 393-406.

Morgan, C. & Fisher, H. 2007. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma--a critical review. *Schizophr Bull,* 33**,** 3-10.

Morgan, C., Reininghaus, U., Fearon, P., Hutchinson, G., Morgan, K., Dazzan, P., Boydell, J., Kirkbride, J. B., Doody, G. A., Jones, P. B., Murray, R. M. & Craig, T. 2014. Modelling the interplay between childhood and adult adversity in pathways to psychosis: initial evidence from the AESOP study. *Psychol Med,* 44**,** 407-19.

Pearlin, L. I. 2010. The life course and the stress process: some conceptual comparisons. *J Gerontol B Psychol Sci Soc Sci,* 65B**,** 207-15.

Pearlin, L. I., Lieberman, M. A., Menaghan, E. G. & Mullan, J. T. 1981. The stress process. *J Health Soc Behav,* 22**,** 337-56.

Pelayo-Teran, J. M., Perez-Iglesias, R., Ramirez-Bonilla, M., Gonzalez-Blanch, C., Martinez-Garcia, O., Pardo-Garcia, G., Rodriguez-Sanchez, J. M., Roiz-Santianez, R., Tordesillas-Gutierrez, D., Mata, I., Vazquez-Barquero, J. L. & Crespo-Facorro, B. 2008. Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the Clinical Programme on Early Phases of Psychosis. *Early Interv Psychiatry,* 2**,** 178-87.

Pelayo-Teran, J. M., Suarez-Pinilla, P., Chadi, N. & Crespo-Facorro, B. 2012. Gene-environment interactions underlying the effect of cannabis in first episode psychosis. *Curr Pharm Des,* 18**,** 5024-35.

Pennebaker, J. W. & Susman, J. R. 1988. Disclosure of traumas and psychosomatic processes. *Soc Sci Med,* 26**,** 327-32.

Pruessner, M., King, S., Veru, F., Schalinski, I., Vracotas, N., Abadi, S., Jordan, G., Lepage, M., Iyer, S., Malla, A. K., Shah, J. & Joober, R. 2021. Impact of childhood trauma on positive and negative symptom remission in first episode psychosis. *Schizophr Res,* 231**,** 82-89.

Schalinski, I., Fischer, Y. & Rockstroh, B. 2015. Impact of childhood adversities on the short-term course of illness in psychotic spectrum disorders. *Psychiatry Res,* 228**,** 633-40.

Stain, H. J., Bronnick, K., Hegelstad, W. T., Joa, I., Johannessen, J. O., Langeveld, J., Mawn, L. & Larsen, T. K. 2014. Impact of interpersonal trauma on the social functioning of adults with first-episode psychosis. *Schizophr Bull,* 40**,** 1491-8.

Tikka, M., Luutonen, S., Ilonen, T., Tuominen, L., Kotimaki, M., Hankala, J. & Salokangas, R. K. 2013. Childhood trauma and premorbid adjustment among individuals at clinical high risk for psychosis and normal control subjects. *Early Interv Psychiatry,* 7**,** 51-7.

Trauelsen, A. M., Bendall, S., Jansen, J. E., Nielsen, H. G., Pedersen, M. B., Trier, C. H., Haahr, U. H. & Simonsen, E. 2016. Childhood adversities: Social support, premorbid functioning

and social outcome in first-episode psychosis and a matched case-control group. *Aust N Z J Psychiatry,* 50**,** 770-82.

Trotta, A., Murray, R. M., David, A. S., Kolliakou, A., O'Connor, J., Di Forti, M., Dazzan, P., Mondelli, V., Morgan, C. & Fisher, H. L. 2016. Impact of Different Childhood Adversities on 1-Year Outcomes of Psychotic Disorder in the Genetics and Psychosis Study. *Schizophr Bull,* 42**,** 464-75.

Trotta, A., Murray, R. M. & Fisher, H. L. 2015. The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychol Med,* 45**,** 2481-98.

van Dam, D. S., van Nierop, M., Viechtbauer, W., Velthorst, E., van Winkel, R., Genetic, R., Outcome of Psychosis, i., Bruggeman, R., Cahn, W., de Haan, L., Kahn, R. S., Meijer, C. J., Myin-Germeys, I., van Os, J. & Wiersma, D. 2015. Childhood abuse and neglect in relation to the presence and persistence of psychotic and depressive symptomatology. *Psychol Med,* 45**,** 1363-77.

van Os, J., Kenis, G. & Rutten, B. P. 2010. The environment and schizophrenia. *Nature,* 468**,** 203-12.

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J. & Bentall, R. P. 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull,* 38**,** 661-71.

Vila-Badia, R., Butjosa, A., Del Cacho, N., Serra-Arumi, C., Esteban-Sanjusto, M., Ochoa, S. & Usall, J. 2021. Types, prevalence and gender differences of childhood trauma in first-episode psychosis. What is the evidence that childhood trauma is related to symptoms and functional outcomes in first episode psychosis? A systematic review. *Schizophr Res,* 228**,** 159-179.

Vyas, N. S., Hadjulis, M., Vourdas, A., Byrne, P. & Frangou, S. 2007. The Maudsley early onset schizophrenia study. Predictors of psychosocial outcome at 4-year follow-up. *Eur Child Adolesc Psychiatry,* 16**,** 465-70.

Walker, E. F. 1994. Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophr Bull,* 20**,** 453-80.

Table 1. Comparison of FEP patients and healthy controls on demographic characteristics and traumatic events

	FEP Patients	Healthy controls		
Demographic characteristics	N=278	N=52	Statistic	p value
Sex (male)	54.3%	55.8%	x^2=0.037	0.847
Low socio-economic status (yes)	52.5%	40.4%	x^2=2.352	0.125
Urbanicity (yes)	68%	69.2%	x^2=0.031	0.860
Unemployed (yes)	37.1%	0	x^2=14.033	**<0.001**
Family history (yes)	25.9%	0	x^2=17.226	**<0.001**
Cannabis (yes)	37.1%	29.2%	x^2=1.106	0.293
Age (years)	30.6 (9.7)	28.2 (7.8)	u=6471	0.231
Years of education	10.6 (3.3)	10.7 (2.3)	u=6293	0.514
Childhood trauma				
Sexual trauma	6.8%	3.8%	x^2= 0.657	0.418
Physical trauma	10.1%	1.9%	x^2=3.629	0.057
Other interpersonal trauma	9%	5.8%	x^2=0.586	0.444
Any childhood interpersonal trauma (CIT)	20.5%	9.6%	x=3.404	0.065
Recent stressful events				
Recent stressful events	63%	21%	x^2=31.702	**<0.001**
Recent stressful events (perception)	4.1 (2.4)	1.7 (2.1)	u=3438	**<0.001**

Table 2. Regression model to belong to the FEP group.

	B	S.E.	Wald	df	Sig.	Exp(B)
Unemployed	-18,689	3388,859	0,000	1	0,996	0,000
Family history	-18,562	3929,807	0,000	1	0,996	0,000
CIT	-0,199	0,841	0,056	1	0,813	0,819
RSEp	-0,253	0,070	12,981	1	<0,001	0,776
Constant	-0,574	0,286	4,024	1	0,045	0,563

FEP: First episode of psychosis; CIT: Childhood interpersonal trauma; RSEp: Recent stressful events (perception)

Table 3. Differences between patients with and without childhood interpersonal trauma

	Childhood interpersonal trauma	No Childhood interpersonal trauma		
Demographic characteristics	N=57	N=221	Statistic	p value
Sex (male)	50.90%	55.20%	x^2=0.342	0.559
Family history of psychosis (yes)	28.10%	25.30%	x^2=0.176	0.675
Cannabis (yes)	43.90%	35.30%	x^2=1.425	0.233
Hospitalization at intake (yes)	70.20%	70.60%	x^2=0.004	0.951
Diagnosis (schizophrenia)	54.40%	49.30%	x^2=0.465	0.495
Age at illness onset (years)	26.27 (6.55)	30.32 (9.89)	u=4441	**0.015**
Duration of Untreated Illness	16.70 (22.20)	18.43 (23.88)	u=5021.5	0.486
Duration of Untreated Psychosis	6.18 (8.85)	10.17 (16.36)	u=4896	0.123
Recent Stressful Events				
Recent Stressful Events (perception)	4.94 (1.56)	3.94 (2.57)	u=5217	**0.044**
Functionality variables				
Disability Assessment Scale	1.42 (1.47)	1.47 (1.55)	u=5700.5	0.967
Global Assessment of Functioning	60.05 (31.72)	50.87 (30.67)	u=2728.5	0.110
Baseline clinical variables				
Calgary Depression Scale for Schizophrenia	2.56 (3.28)	2.29 (3.20)	u=5808.5	0.399
Brief Psychiatric Rating Scale	66.61 (16.02)	63.39 (15.38)	u=5490.5	0.176
Scale for Assessment of Positive Symptoms	14.25 (4.86)	13.72 (4.67)	u=6224	0.890
Scale for Assessment of Negative Symptoms	7.66 (5.89)	6.69 (6.37)	u=5293	0.124
Premorbid adjustment				
Childhood social	0.13 (0.18)	0.12 (0.15)	u=5736	0.675
Childhood academic	0.33 (0.19)	0.27 (0.17)	u=5025.5	0.074
Early adolescence social	0.12 (0.15)	0.12 (0.16)	u=5829.5	0.989
Early adolescence academic	0.46 (0.23)	0.38 (0.23)	u=4518.5	**0.010**
Late adolescence social	0.14 (0.19)	0.12 (0.18)	u=5561.5	0.460
Late adolescence academic	0.55 (0.25)	0.42 (0.26)	u=2966	**0.002**
Adulthood	0.18 (0.25)	0.15 (0.22)	u=4379.5	0.456
General	0.36 (0.24)	0.29 (0.20)	u=4382	0.059

Figure 1. Mediation model diagram with unstandardized coefficients of direct and indirect effects of CIT on Group (FEP or control) by RSEp.

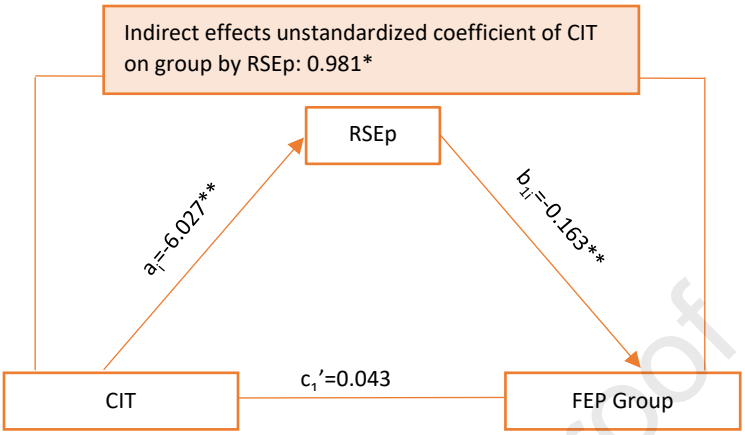
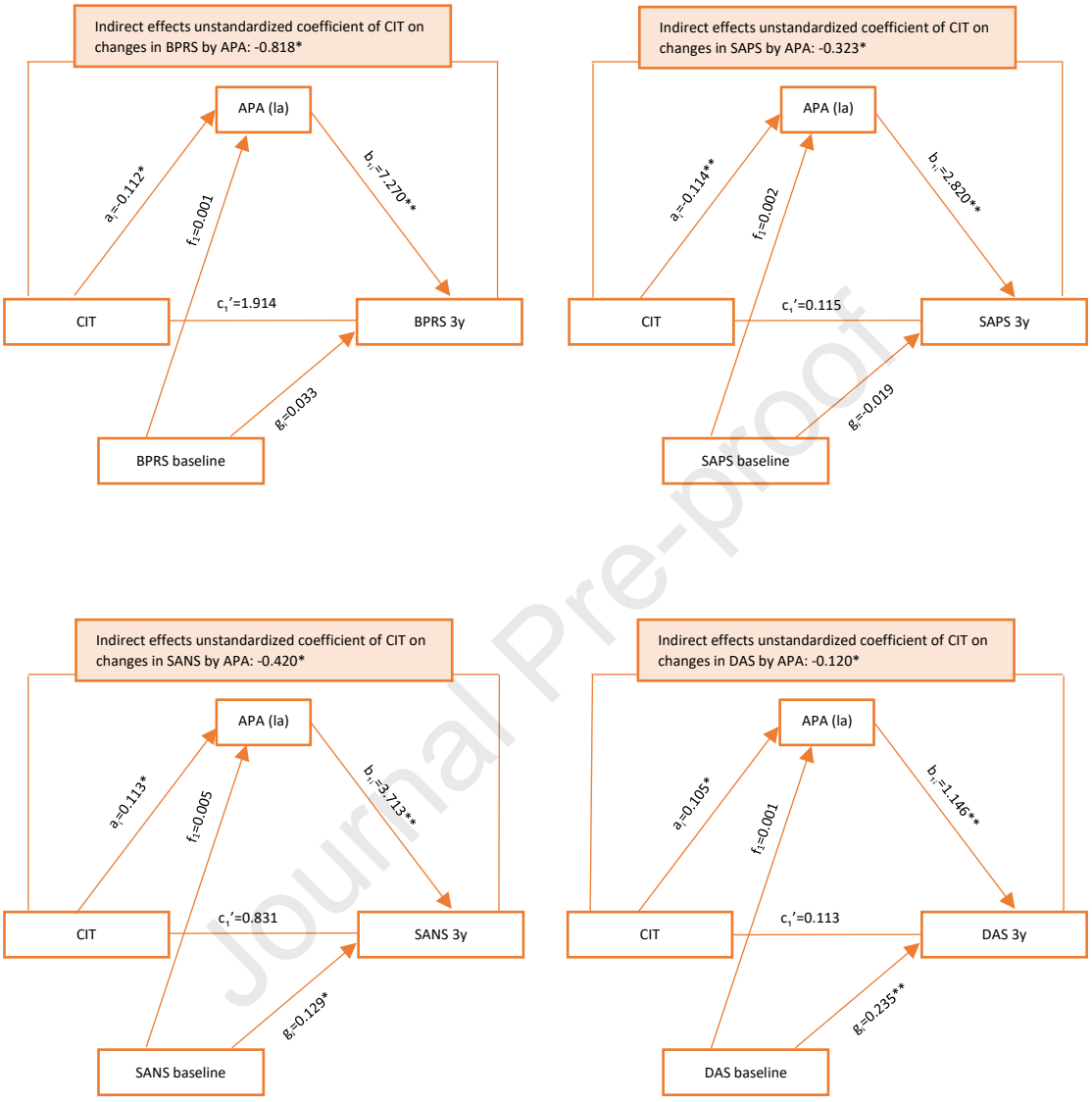


Figure 2. Mediation model diagrams with unstandardized coefficients of direct and indirect effects of CIT on BPRS-3y, SAPS-3y, SANS-3y and DAS-3y by APA (la). (Using baseline variables as covariates).



CIT: Childhood Interpersonal Trauma; APA (la): Academic Premorbid Adjustment (late adolescence); BPRS: Brief Psychiatric Rating Scale; SAPS: Scale for Assessment of Positive Symptoms; SANS: Scale for Assessment of Negative Symptoms; DAS: Disability Assessment Scale; *: p<0.05; **: p<0.01.

Conflict of interest

The authors have no conflict of interest to declare.

Author's contributions

All the authors have participated and have made substantial contributor for this paper.