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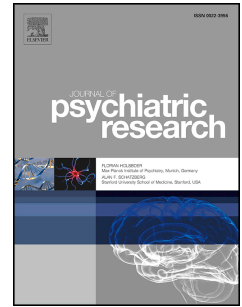
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# Accepted Manuscript

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**Revisiting the association between childhood trauma and psychosis in bipolar disorder: a quasi-dimensional path-analysis.**

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**Abstract**

**Background:** Childhood trauma has been associated with a more severe clinical expression of bipolar disorder (BD). However, the results that specifically associated traumatic events and psychotic features in BD have been inconsistent, possibly due to the low resolution of the phenotypes being used.

**Methods:** 270 normothymic patients with BD completed the Childhood Trauma Questionnaire (CTQ) and the Peters Delusion Inventory (PDI) that assessed 21 delusional beliefs. Patients were characterized for the lifetime presence of psychotic features during episodes and cannabis misuse in accordance with DSM-IV. We performed a series of path analyses to investigate the links from three types of childhood abuse (physical, sexual and emotional) directly to delusional beliefs and psychotic features, and indirectly through cannabis misuse.

**Results:** A first path analysis showed no link between any of the childhood abuse types and psychotic features when only a categorical definition of psychosis was used. When incorporating the quasi-dimensional measure of delusional beliefs in a second path analysis, we found that emotional and physical abuse and cannabis misuse were each directly associated with PDI score. PDI score and psychotic features were strongly correlated. Childhood abuse did not operate through cannabis misuse to increase delusional beliefs. Including type of BD in the model did not alter the results.

**Conclusion:** Emotional and physical abuse, but also cannabis misuse, increased delusional beliefs in patients with BD. Using a quasi-dimensional measure of psychotic symptoms in BD provided higher resolution of the psychosis phenotype and helped reconcile ambiguous findings from previous studies.

## Introduction

Among environmental risk factors that contribute to the pathophysiology of bipolar disorder (BD) (Lichtenstein et al., 2009), childhood traumatic events are considered to be one of the major determinants (Etain et al., 2008). Indeed, reviews of case-control studies have demonstrated that childhood trauma is reported as more frequent and severe in patients with BD as compared to unaffected individuals (Aas et al., 2016; Daruy-Filho et al., 2011; Etain et al., 2008; Etain et al., 2010; Fisher and Hosang, 2010; Maniglio, 2013). A study from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) also found an increased risk for BD in those individuals exposed to childhood physical abuse (Sugaya et al., 2012), BD thus being ranked fourth in the top associated psychiatric disorders (after PTSD, ADHD, and suicide attempt). Furthermore, childhood trauma is not only a risk factor for BD but also for a more severe clinical expression of the disorder (Aas et al., 2016; Agnew-Blais and Danese, 2016; Etain et al., 2013), including earlier age at onset, rapid cycling, high levels of psychiatric comorbidities and suicide attempt among other clinical characteristics.

Findings regarding associations between childhood trauma and psychotic features in BD have been relatively inconsistent due to heterogeneity in sample sizes, the type of assessment for childhood trauma employed, and the definitions used for psychotic features (mainly presence of lifetime delusions or hallucinations) (see online Supplementary Table S1). The majority of studies published before 2013 reported no associations between childhood trauma and psychotic features in BD, with the exception of two (Hammersley et al., 2003; Romero et al., 2009). All these studies have been included in a recently published meta-analysis (Agnew-Blais and Danese, 2016) that concluded in favour of an association between childhood trauma and greater psychosis severity in BD. However, this conclusion deserves some comment. First, removing the study that contributed the most to the effect size estimates (Romero et al., 2009) resulted in a non-significant estimate for the meta-analysis of the association between childhood maltreatment and psychosis severity. This study has some particularities compared to the other included studies, such as being performed in a large sample of youths (age range 7-17) and including a large proportion of BD-NOS (Bipolar Disorder Not Otherwise Specified) patients (Romero et al., 2009). Second, another positive study found an association between spontaneous self-report of trauma and auditory hallucinations and might be viewed as questionable because of the method used to assess childhood trauma and the extraction of this sample from a clinical trial of cognitive-behavioural therapy in BD (Hammersley et al., 2003). One previous study published in 2007 has not been included in the meta-analysis (Kauer-Sant'Anna et al., 2007) and showed no association between childhood trauma and psychotic features. More recently, Cakir et al. found an association between childhood trauma and psychotic features (Cakir et al., 2015), while the largest published sample to date found no association with delusions, but with hallucinations, in a sample of 2019 patients with BD (Upthegrove et al., 2015). Therefore, whether there is an association between early adversity and delusions and/or hallucinations in BD remains unclear.

Using a more dimensional approach (quantitative symptom measure) and combining it with the traditional categorical approach (presence/absence of psychotic features) might help reconcile these conflicting results. Indeed, Allardyce et al. (2007) found that incorporating continuous symptom measures and categorical diagnoses improved aetiological understanding of psychosis (Allardyce et al., 2007). It also seems

crucial to consider the impact of different subtypes of trauma (e.g., emotional, physical and sexual abuse, and neglect) as their associations with psychotic symptoms may not be uniform (Ajnakina et al., 2016; Fisher et al., 2010), as well as taking into account the correlation between them as different trauma types often co-occur (Finkelhor et al., 2007). Finally, incorporating other environmental factors (such as cannabis misuse) into the analyses may also be of potential interest since they could moderate or mediate the impact of childhood trauma on psychosis (Aas et al., 2016; Sideli et al., 2015). Therefore, we sought to explore the associations between several types of childhood trauma and psychotic symptoms in a sample of stabilized BD patients, taking into account the overlap between trauma types and including both a continuous measure of delusional experiences and a dichotomous measure of psychotic symptoms. We focussed on delusions because of their greater frequency (as compared to hallucinations) in patients with BD. Indeed, lifetime presence of psychotic features is high in patients with BD (more than two-thirds of patients with subtype I) (Etain et al., 2012), with delusions being around twice as frequent as hallucinations (Black and Nasrallah, 1989; Dunayevich and Keck, 2000; Keck et al., 2003).

## **Material and methods**

### ***Samples***

Patients fulfilled DSM-IV criteria (American Psychiatric Association, 1994) for bipolar disorder (BD) type I or II and were recruited during their follow-up appointments at three university-affiliated psychiatric departments in France (Paris/Créteil, Bordeaux, Nancy). Patients were interviewed by trained psychiatrists or psychologists, using the French version (Preisig et al., 1999) of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). The following inclusion criteria were used: older than 18 years and currently normothymic (i.e., to have a Montgomery-Asberg Depression Rating Scale score and a Mania Rating Scale score below 5) (Bech et al., 1978; Montgomery and Asberg, 1979). All included individuals were of Caucasian origin. This research protocol received appropriate Ethical Committee and Institutional Review Board approvals. We obtained written informed consent from all study participants before inclusion. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

### ***Clinical variables related to BD***

Patients were interviewed using the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), providing lifetime DSM-IV Axis I diagnoses (American Psychiatric Association, 1994). A set of variables was extracted from the DIGS to characterize the clinical expression of BD. The age at onset (AAO) of BD was determined retrospectively and was defined as the age at which a patient first met DSM-IV criteria for a major depressive or (hypo)manic episode according to information collected with the DIGS. Suicide attempt and rapid cycling were recorded as present if they occurred at any point during the course of BD (lifetime presence). Substance misuse (for alcohol or cannabis) was coded as present if the patient fulfilled the DSM-IV criteria for abuse or dependence to these substances at any point during the course of

their BD (lifetime presence). Lifetime psychosis was considered present if any episode (whatever polarity) could be considered as severe with psychotic features (delusions or hallucinations) according to DSM-IV criteria and the data collected using the DIGS.

### ***Assessment of childhood trauma and delusional beliefs***

Childhood traumatic events were recorded using the French validated version (Paquette et al., 2004) of the Childhood Trauma Questionnaire (CTQ), a 28-item self-report questionnaire (Bernstein and Fink, 1998). The CTQ yields a total score and five subscale scores with 5 items each for Emotional and Physical Neglect (EN and PN), as well as Emotional, Physical and Sexual Abuse (EA, PA and SA). The remaining three items can be used as an indicator of minimization of traumatic experiences and were not utilised in this paper. All variables (CTQ total score and scores for the 5 subtypes) were used as continuous variables measuring trauma severity.

The Peters Delusions Inventory (PDI) is composed of 21 items scored yes or no that assess a wide range of delusional beliefs across the lifetime (Peters et al., 2004; Peters et al., 1999). The total score is obtained by summing the number of positive answers (maximum score=21). The items are phrased to capture continuous traits rather than categorical states, and thus the PDI can be considered as a quasi-dimensional measure of delusions (Claridge, 1994; Peters et al., 2004). Indeed, the total score has been shown to be normally distributed with higher scores more indicative of clinically-relevant delusional ideation (Peters et al., 2004). We used a validated French version of the questionnaire (Verdoux et al., 1998) that was used in a previous study of pedigrees with schizophrenia or bipolar disorder (Schurhoff et al., 2003).

### ***Statistical analysis***

Descriptive statistics (Mean (SD) and N (%)) were used to examine the characteristics of the sample. Non-parametric tests were used to correlate continuous variables (Spearman rho test). Comparisons between groups were conducted using t-tests. Significance was evaluated based on a two-tailed test with a critical value set at 0.05. All statistical analyses were implemented with Mplus 6.1 (Muthén and Muthén, 2007).

Path analyses from each trauma type to the continuous delusional beliefs measure (PDI score) and the categorical BD with psychotic features diagnosis were performed using WLSMV estimator (Weighted Least Squares Mean and Variance) to deal with categorical variables. The model examined both direct and indirect associations between the CTQ subscales and the psychosis outcomes. The model also estimated correlations amongst (i) the trauma types, and (ii) the quasi-dimensional and categorical outcomes. A path diagram representation of the model was then drawn: straight single-headed arrows represented regression paths; the curved two-headed arrow represented correlations.

An iterative procedure allowed the selection of the best-fitting model. The path analysis started with a saturated model in which all variables were interrelated. Then non-significant path correlations/associations were gradually excluded until a good-fitting model was reached. Goodness of fit was reported using standard indices: the Chi-square statistic, Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA). Rules of thumb for determining acceptable model fit were as follows: a non-significant Chi-square test,



a CFI value of 0.90 or above, and RMSEA values close to 0.05 or below. All path coefficients and correlations are reported as standardized estimates.

## Results

The sample comprised 270 patients with BD, of which 60.7% were women, and 71.1% had BD type 1. The mean age at inclusion was 43 years ( $SD=12.5$ ). The mean total score on the CTQ was 41.8 ( $SD=11.67$ ; median=41; range 25-96). The mean score on the PDI was 6.51 ( $SD=4.06$ ; median=6; range 0-20). Fig. 1 presents the percentage of patients answering “yes” for each of the 21 items of the PDI. Three items were endorsed “yes” by more than half of the sample (hints/double meaning, people who are not what they seem to be, being a special or unusual person) and nine additional items were endorsed “yes” by more than a quarter of the sample. Qualitatively, most of these 12 items cannot be considered as mood congruent, with the exception of 4 (being a special or unusual person, persecution in some way, being someone very important, conspiracy against you), meaning that psychotic experiences were not restricted to those congruent with mood in our sample.

The PDI score was significantly correlated with the CTQ total score ( $\rho=0.21$ ,  $p=0.001$ ), and the emotional and physical abuse sub-scale scores ( $\rho=0.28$ ,  $p<0.001$ ; and  $\rho=0.24$ ,  $p<0.001$ , respectively), with a modest correlation with the sexual abuse sub-scale score ( $\rho=0.15$ ,  $p=0.015$ ). The PDI score was not significantly correlated with the emotional ( $\rho=0.10$ ,  $p=0.087$ ) or physical ( $\rho=0.08$ ,  $p=0.203$ ) neglect sub-scale scores. The patients scoring in the highest tertile of the CTQ total score distribution were more likely to be scoring in the highest tertile of the PDI score distribution ( $OR=3.43$ , 95% CI 1.59-7.35,  $p=0.001$ ).

As shown in Tables 1 and 2, a higher PDI score was associated with several clinical characteristics of the patients: BD type 1, lifetime presence of psychotic features and cannabis misuse, a lower age at interview and an earlier age at onset of BD. Correlations between CTQ total score and PDI score were also significant in the subsamples of patients without lifetime presence of psychosis ( $\rho=0.21$ ,  $p=0.03$ ) or without cannabis misuse ( $\rho=0.22$ ,  $p=0.001$ ) and to a lesser extent in those with BD type 2 ( $\rho=0.21$ ,  $p=0.08$ ). So the results observed in the whole population were not likely to be biased by the large proportion of patients with BD type 1 or with psychotic features during mood episodes.

We then performed three path-analyses. Due to some missing data, these analyses only included 255 patients. We also restricted these analyses to the three CTQ subscales that were significantly correlated with the PDI score. In the first path analysis (Fig. 2), we used three subtypes of childhood trauma (emotional, physical and sexual abuse - all continuous variables), lifetime presence of cannabis misuse (dichotomous variable), and lifetime presence of psychotic features (dichotomous variable). As expected, there were strong correlations between the three trauma subtypes, meaning that they were not independent of each other. In the first model, we found no direct pathway from trauma to cannabis misuse or to psychotic features (only at a trend level between physical abuse and psychotic features). In this model, psychotic features were only significantly associated with cannabis misuse. In the second path analysis (see Fig. 3), we incorporated the PDI score (continuous variable). This measure of delusional beliefs and the categorical measure of psychotic features were highly correlated. We did not find any direct paths from childhood abuse to either cannabis misuse or psychotic

features. PDI score was mainly driven by emotional abuse (and to a lesser extent by physical abuse) and by cannabis misuse. There was also a modest direct association between cannabis misuse and psychotic features (that was not fully mediated by PDI). Including type of BD in the model did not alter the results (see online Supplementary Fig. S2). This was confirmed statistically as the difference between the second and third models was not significant ( $\chi^2_{diff}=-2.08$ ,  $df_{diff}=2$ ,  $p>0.10$ ).

## Discussion

In this sample of patients with BD who have been assessed in the remission period, we found that frequency of reported exposure to childhood trauma was associated with higher levels of delusional beliefs. This was mainly observed in relation to emotional and physical abuse and even in those patients without psychotic features or lifetime cannabis misuse. No significant associations between different types of childhood abuse and lifetime presence of psychotic features were evident when only this categorical variable was included in the model. However, further analyses revealed a major contribution of emotional abuse (with a smaller contribution from physical abuse) to the measure of delusional beliefs, and also an independent contribution from cannabis misuse. Not surprisingly, delusional beliefs and lifetime psychotic features were highly correlated, but interestingly without any direct association between childhood abuse and the categorical measure of psychotic features. The high proportion of BD subtype 1 in our sample did not appear to bias the results.

This path analysis goes some way to reconciling the ambiguous findings from previous studies. Indeed, 6 out of 10 studies exploring this issue in samples of patients with BD tended to exclude links between childhood trauma and lifetime delusional experiences. This is thus consistent with our results, as we found no direct links between childhood abuse and psychotic features when relying only upon a categorical measure. Nevertheless, we did find that reported exposure to abusive experiences in childhood was associated with increased odds of delusional beliefs in BD patients when this was measured quasi-dimensionally. Therefore, our findings suggest that future studies focusing on the association between childhood trauma and psychotic symptoms in BD may benefit from using quasi or fully dimensional assessments of psychotic symptoms that go beyond a categorical diagnosis of “lifetime psychotic features” and provide a higher resolution of the psychosis phenotype.

This path analysis also took into account the respective contribution of each subtype of trauma (Aas et al., 2016), which is important as they are likely to co-occur or to be inter-related (Etain et al., 2010). Indeed we have previously demonstrated a preferential role of emotional trauma in the susceptibility to BD (Etain et al., 2010), in the influence on the clinical expression of the disorder (Etain et al., 2013), and also on dimensional measures of emotional reactivity (Aas et al., 2014a; Etain et al., 2008). This goes beyond the classical view that only “high grade” childhood traumas (i.e. physical and sexual abuse) are likely to increase the occurrence of psychopathology. Our findings indicate that exposure to other types of childhood traumas, such as emotional abuse, might be sufficient for the development of psychotic phenomena in vulnerable individuals.

Some authors have argued that early life stress subtypes in childhood and adolescence might predict the development of different types of psychopathology in adults (Carr et al., 2013). This might be underpinned by differential responses of biological pathways according to trauma subtypes. For example, it has been proposed that there is a heterogeneous relationship among different indices of HPA-axis functioning and trauma subtype:

physical abuse has been shown to be associated with faster reactivity to acute stress, while emotional abuse was associated with delayed recovery of cortisol following acute stress (Kuhlman et al., 2015). These potential mechanisms require further investigation. Unfortunately in our study we lacked information about the timing of exposure to the different trauma subtypes, which might also impact upon associations with psychosis (Fisher et al., 2010). Indeed, some subtypes of trauma might be particularly deleterious when they occurred during critical neurodevelopmental periods (Alameda et al., 2015; Khan et al., 2015; Pechtel et al., 2014; Schalinski and Teicher, 2015). Therefore, what remains to be explored is whether the age of occurrence of different childhood trauma subtypes impacts upon development of psychotic phenomena in the context of BD.

This study also adds further support to the existing literature in favour of the involvement of several environmental factors in the emergence of psychopathological traits. A review of 22 longitudinal studies has grouped risk factors for developing BD into 3 clusters: neurodevelopment, substances, and physical/psychological stress (Marangoni et al., 2016). Our path analysis demonstrated that emotional abuse and cannabis misuse independently contributed to increased delusional beliefs. These results are consistent with previous work that suggests both childhood trauma and cannabis misuse are involved in predicting the age at onset of BD (Aas et al., 2014b), the risk of developing schizophrenia (Sideli et al., 2015), faster transition to psychosis in at-risk individuals (van Nierop et al., 2013), or higher risk of psychotic symptoms in population-based studies (Konings et al., 2012), among other examples. Further complexity is added when effects of a combination of early adversity or cannabis exposure and susceptibility genes are explored in BD (Alemany et al., 2014; De Pradier et al., 2010; Vinkers et al., 2013).

Some limitations of the present study should be noted. The CTQ did not provide information about timing and chronicity of trauma exposure and the PDI did not provide an in-depth assessment of psychotic experiences other than delusions (such as hallucinations). Therefore, our results do not contradict those obtained by the 2 out of 4 positive studies in the literature that reported associations with hallucinations but not with delusions. Further studies are therefore required that specifically investigate hallucinations using dimensional measures. Moreover, the total PDI score is only a quasi-dimensional measure of delusions (Claridge, 1994; Peters et al., 2004) and thus it would be useful for future studies to utilise a fully dimensional measure that captures the severity of delusional experiences. Additionally, although childhood trauma was assessed using a validated questionnaire, the assessment was retrospective and thus over- or under-reporting events due to recall bias or cognitive reappraisal are not excluded. However, a previous study has shown that individuals with psychosis were able to reliably report in adulthood on experiences of abuse during childhood (Fisher et al., 2011), while another study demonstrated similar findings specifically in patients with BD (Shannon et al., 2016). Another limitation is that as this study was cross-sectional and there was no random assignment to exposure, no causal link between childhood abuse and delusional ideas could be confirmed. Finally, since this analysis was exploratory by nature, we did not apply any correction for multiple testing, though including variables together in a pathway model minimised the number of tests conducted.

## Conclusion

Childhood abuse (predominantly emotional abuse) and cannabis misuse were independently associated with increased delusional beliefs in this sample of patients with BD. Combined with previous work focused on associations between childhood trauma and dimensions of psychopathology in BD (Aas et al., 2014a; Etain et al., 2008), these results support the hypothesis that environmental factors such as early adversity and exposure to cannabis may drive the emergence of an admixture of psychosis, emotional reactivity or lability that cut across traditional diagnostic boundaries such as mood disorders and schizophrenia (van Nierop et al., 2015). Future studies should replicate these findings but also extend this research by incorporating dimensional measures of hallucinations and genetic risk factors into the models. Our results highlight that a quasi or fully dimensional approach might provide a better solution than relying on categorical measures alone when studying the association between childhood trauma and psychosis in BD (Henry and Etain, 2010).

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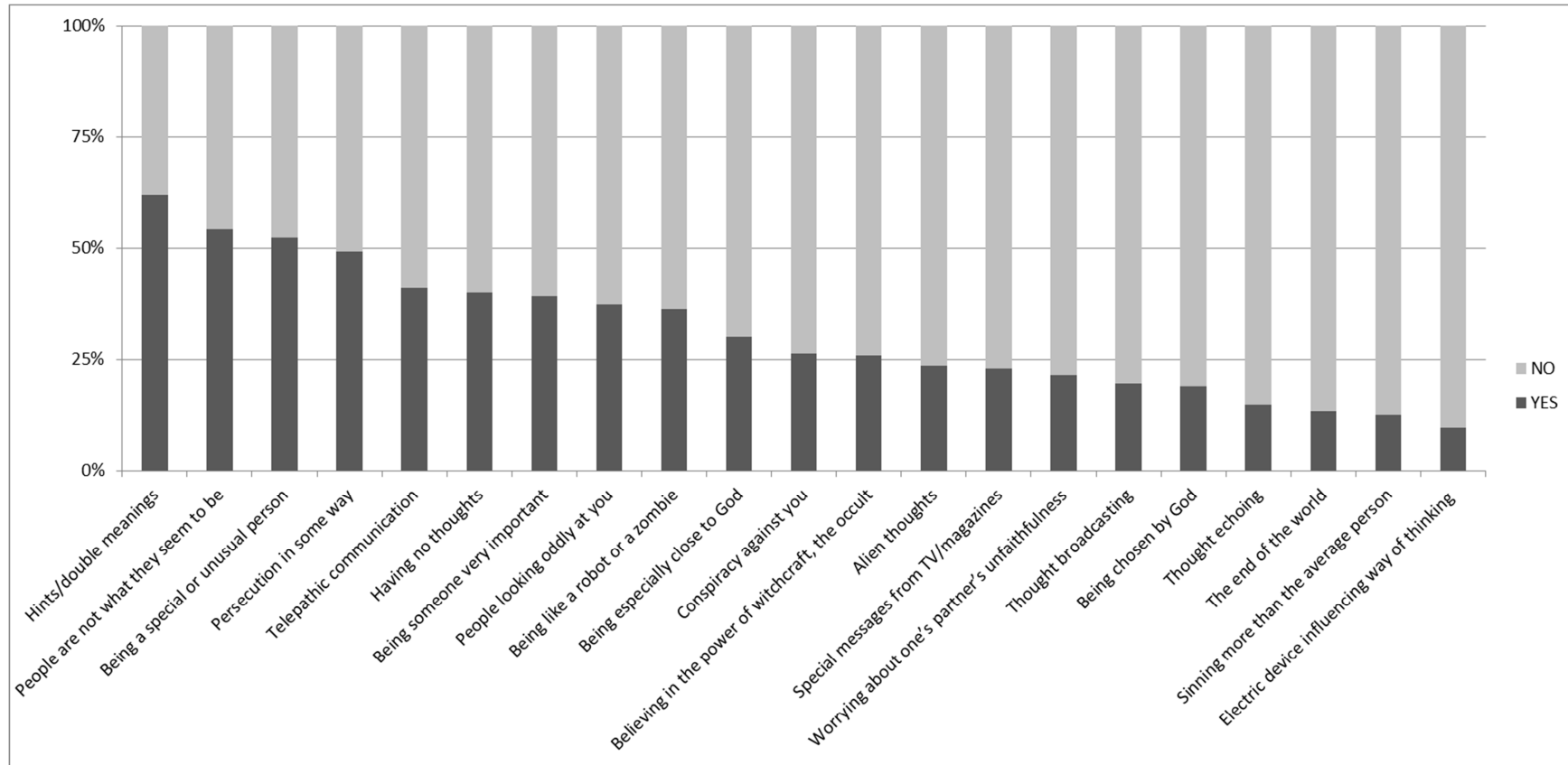
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**Figure 1: Percentage of patients with bipolar disorder endorsing each of the 21 items of the Peters Delusion Inventory**



**Table 1: Associations between delusional beliefs and categorical clinical characteristics of bipolar disorder patients**

Variables	PDI Mean (SD)		Statistical results	
	yes	no	t test	p value
Male gender	6.43 +/- 4.43	6.57 +/- 3.82	-0.27	0.79
BD Type 1	7.18+/-4.04	4.84 +/-3.69	-4.27	<b>0.0001</b>
Lifetime psychosis	7.72 +/-4.19	5.09 +/-3.44	-5.44	<b>0.0001</b>
Alcohol misuse	6.92 +/- 4.07	6.47 +/-4.08	-0.69	0.49
Cannabis misuse	8.65 +/- 3.97	6.26 +/- 4.02	-3.11	<b>0.002</b>
Rapid cycling	6.41 +/- 4.07	6.45 +/- 4.03	0.64	0.95
Suicide attempt	6.73 +/- 3.93	6.39 +/- 4.15	-0.67	0.51

BD: bipolar disorder; PDI: Peters Delusion Inventory; SD: Standard Deviation.

**Table 2: Correlations between delusional beliefs and continuous clinical characteristics of bipolar disorder patients**

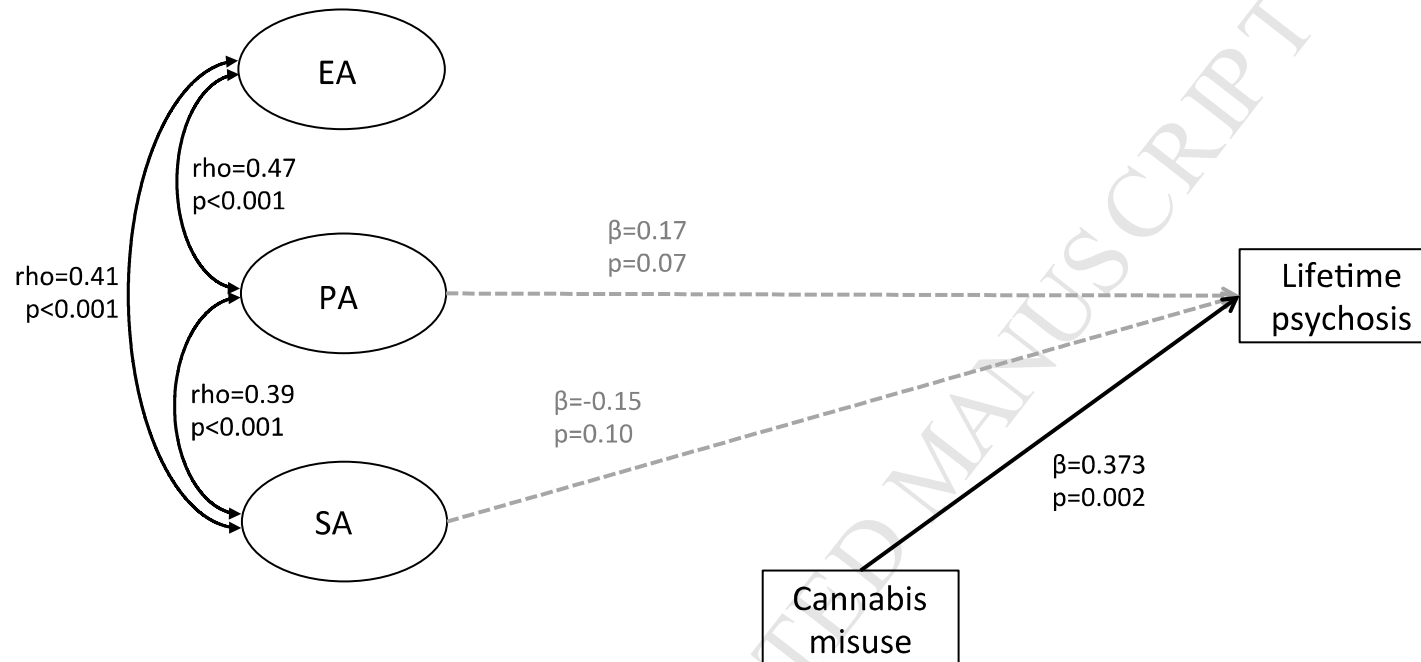
	Correlation with the PDI score	
	Rho *	p value
Age at interview	-0.165	<b>0.007</b>
Duration of illness	-0.008	0.89
Age at onset of BD	-0.159	<b>0.01</b>

BD: bipolar disorder; PDI: Peters Delusion Inventory

\* Spearman correlation coefficient

Figure 2: Path analysis diagram including three subtypes of childhood abuse, cannabis misuse and psychotic features

## MODEL 1



N=255

Chisquare Test of Model fit=148.26,  $p<0.001$ 

RMSEA (Root Mean square of Approximation):

Estimate =0.000,  $p<0.001$ 

CFI/TLI: CFI=1.000

TLI=1.000

All coefficients ( $\beta$ ) are standardized—  $<0.005$ 

— 0.005-0.05

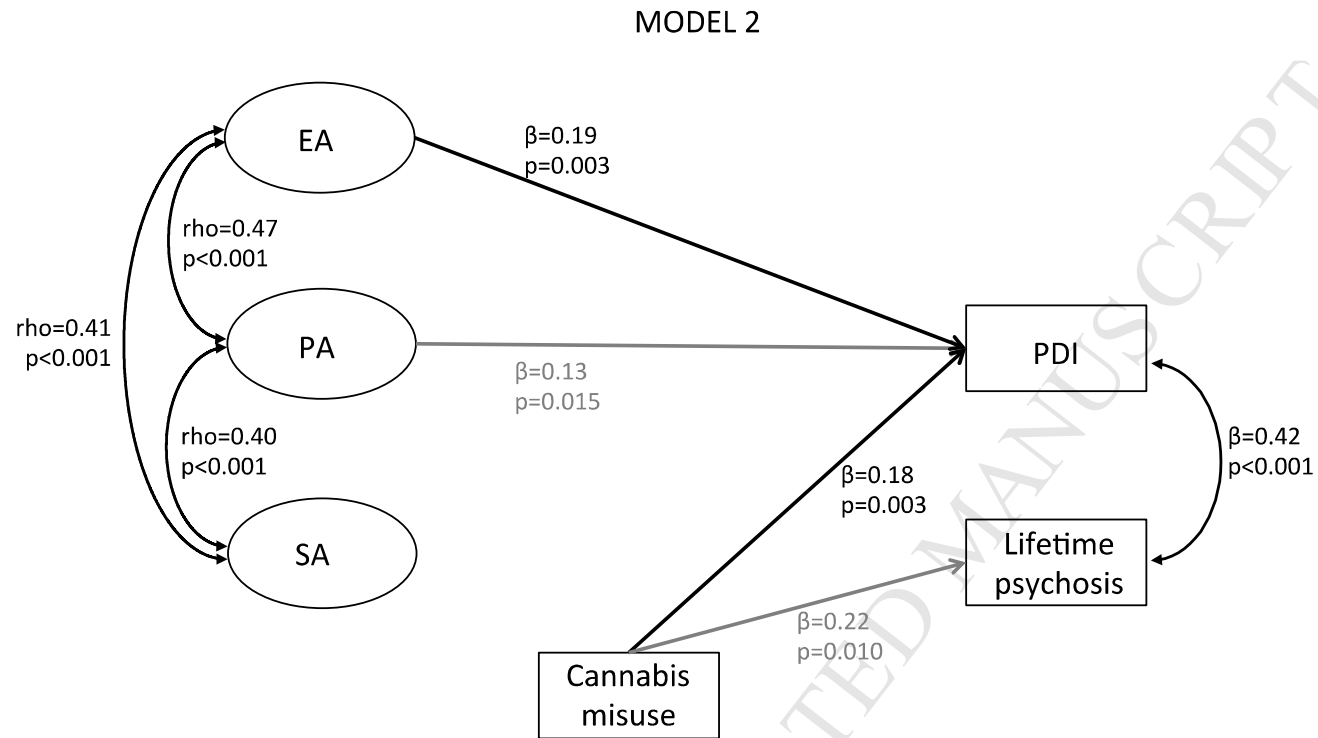
- - - 0.10-0.05

EA: Emotional Abuse, PA: Physical Abuse, SA: Sexual Abuse

Straight single-headed arrows represent regression paths and curved tow-headed arrows represent correlations.

For reasons of clarity, the paths corresponding to  $p$  values  $>0.10$  were not included in the path diagram.

**Figure 2: Path analysis diagram including three subtypes of childhood abuse, PDI scores, cannabis misuse and psychotic features**



N=255

Chisquare Test of Model fit=9.105,  $p=0.2452$

RMSEA (Root Mean square of Approximation):

Estimate =0.034,  $p=0.613$

CFI/TLI: CFI=0.987 TLI=0.971

All coefficients ( $\beta$ ) are standardized

—  $<0.005$       — 0.005-0.05

EA: Emotional Abuse, PA: Physical Abuse, SA: Sexual Abuse, PDI: Peters Delusion Inventory.

Straight single-headed arrows represent regression paths and curved tow-headed arrows represent a correlation.

For reasons of clarity, the paths corresponding to  $p$  values  $>0.05$  were not included in the path diagram.

**Highlights**

- We modelled the links between childhood trauma and psychosis in bipolar disorders.
- We used a categorical and a quasi-dimensional measure of psychotic symptoms.
- Childhood abuse was not associated with the categorical measure of psychosis.
- Emotional and physical abuses were associated with greater delusional beliefs.
- Cannabis use was associated with delusional beliefs independent of childhood abuse.

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**Conflict of interest**

None. The authors declare that they have no competing financial interests, or other interests that might be perceived to influence the results and discussion reported in this paper.

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**Contributors**

BE and MLa initiated the study and performed the statistical analyses.

BE, CH, KMB, JP Kahn included and assessed the participants.

BE and HLF interpreted the data and wrote the paper.

FB is the principal investigator of the study.

BE and MLe are scientific coordinators of the study.

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