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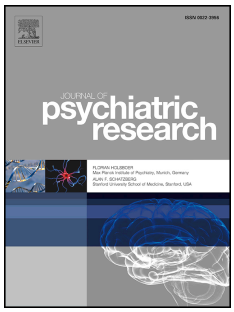

Childhood trauma, *BDNF* Val66Met and subclinical psychotic experiences. Attempt at replication in two independent samples

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PII: S0022-3956(16)30242-4

DOI: 10.1016/j.jpsychires.2016.08.014

Reference: PIAT 2937

To appear in: *Journal of Psychiatric Research*

Received Date: 21 April 2016

Revised Date: 19 August 2016

Accepted Date: 19 August 2016

Please cite this article as: de Castro-Catala M, van Nierop M, Barrantes-Vidal N, Cristóbal-Narváez P, Sheinbaum T, Kwapil TR, Peña E, Jacobs N, Derom C, Thiery E, van Os J, van Winkel R, Rosa A, Childhood trauma, *BDNF* Val66Met and subclinical psychotic experiences. Attempt at replication in two independent samples, *Journal of Psychiatric Research* (2016), doi: 10.1016/j.jpsychires.2016.08.014.

Childhood trauma, *BDNF* Val66Met and subclinical psychotic experiences. Attempt at replication in two independent samples.

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Running title: Childhood trauma, *BDNF* and psychotic experiences.

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ABSTRACT

Childhood trauma exposure is a robust environmental risk factor for psychosis. However, not all exposed individuals develop psychotic symptoms later in life. The Brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism (rs6265) has been suggested to moderate the psychosis-inducing effects of childhood trauma in clinical and nonclinical samples. Our study aimed to explore the interaction effect between childhood trauma and the *BDNF* Val66Met polymorphism on subclinical psychotic experiences (PEs). This was explored in two nonclinical independent samples: an undergraduate and technical-training school student sample (n=808, sample 1) and a female twin sample (n=621, sample 2). Results showed that childhood trauma was strongly associated with positive and negative PEs in nonclinical individuals. A *BDNF* Val66Met x childhood trauma effect on positive PEs was observed in both samples. These results were discordant in terms of risk allele: while in sample 1 Val allele carriers, especially males, were more vulnerable to the effects of childhood trauma regarding PEs, in sample 2 Met carriers presented higher PEs scores when exposed to childhood trauma, compared with Val carriers. Moreover, in sample 2, a significant interaction was also found in relation to negative PEs. Our study partially replicates previous findings and suggests that some individuals are more prone to develop PEs following childhood trauma because of a complex combination of multiple factors. Further studies including genetic, environmental and epigenetic factors may provide insights in this field.

Keywords: childhood trauma, *BDNF* Val66Met, psychosis, psychotic experiences, gene-environment interaction, psychosis proneness.

1. INTRODUCTION

The maturation of most brain areas starts early in the embryonic stages and continues into childhood and adolescence (Lenroot and Giedd, 2006), requiring a complex interplay of genetic and environmental factors. Disruption of these factors can alter normal development, causing modifications in neuronal structure, function or connectivity (Lewis and Levitt, 2002). Specifically, prenatal environmental exposures (e.g. maternal nutrition deficiency, stress or infections during pregnancy) and postnatal environmental factors (e.g. early life adversity, growing up in an urban environment, minority group position and drug abuse) have been associated with psychotic outcomes (van Os et al., 2010). In this regard, early psychological stress, such as childhood trauma, has been related to the expression of psychotic symptoms in clinical and non-clinical samples, as shown in a recent meta-analysis (Varese et al., 2012).

Childhood trauma encompasses a range of adverse experiences suffered early in life, such as sexual, physical and emotional abuse, physical and emotional neglect, and other early-life events, such as the death of a parent. In this regard, patients from psychiatric units with a child abuse history are particularly likely to experience positive symptoms and tend to have the worst course and outcome of psychosis (Holtzman et al., 2013; Read et al., 2005). In the general population, associations between childhood trauma and schizotypy and psychotic experiences (PEs) have also been reported (Sheinbaum et al., 2014; Velikonja et al., 2014), including an increased expression of these traits and experiences in daily life for those exposed to childhood trauma (Cristóbal-Narváez et al., 2016a). However, there are large individual differences in response to early stressful events (Holtzman et al., 2013), which suggest that genetic factors may be moderating this response (van Winkel et al., 2013). Some studies have reported several genes that may moderate the impact of childhood adversity on mental health, such as the Brain-derived neurotrophic factor gene (*BDNF*) (Alemany et al., 2011), the Serotonin transporter gene (*SERT*) (Karg et al., 2011) or the FK506 binding protein gene (*FKBP5*) (Alemany et al., 2016; Collip et al., 2013; Cristóbal-Narváez et al., 2016b).

BDNF is a neurotrophin that plays an important role in several neurodevelopmental processes (e.g.: neuronal differentiation), synaptic and cognitive plasticity and, in addition, seems to influence some neurotransmitter systems (Buckley et al., 2011; Carvalho et al., 2008). Also, as a neurotrophin, a role of BDNF has been established in cell survival in response to stress (Sofroniew et al., 2001). BDNF secretion is affected by the common functional polymorphism (rs6265, C > T) that results in valine (Val) to methionine (Met) substitution at codon 66 (Val66Met). The Val allele of this polymorphism has been associated with risk for psychosis (e.g. schizophrenia or bipolar disorder) in both case-control (Lohoff et al., 2005; Neves-Pereira et al., 2005) and family-based studies (Geller et al., 2004; Neves-Pereira et al., 2002; Rosa et al., 2006; Sklar et al., 2002).

Gene-environment interaction (GxE) studies have investigated the role of *BDNF* as a moderator of the association between childhood trauma and different psychiatric phenotypes. Only two previous studies have analysed the childhood trauma x *BDNF* Val66Met interaction in relation to subclinical PEs in general population samples. The first study explored the interactions between *BDNF* and abuse, and *BDNF* and neglect (Alemany et al., 2011). They found that individuals carrying the Met allele who had been exposed to childhood abuse reported more positive PEs than those with the Val/Val genotype. The second study by Ramsay and colleagues attempted to replicate those findings, but was unable to find any significant interaction (Ramsay et al., 2013). Despite these contradictory results, there is independent evidence indicating that this polymorphism moderates the effects of stress exposure on cognition, brain structure and anxiety (Aas et al., 2013; Chen et al., 2006), in line with Alemany et al.'s findings.

Given these previous results, the aim of our study was to explore the modulating role of *BDNF* Val66Met on the association between childhood trauma and PEs, using two independent samples of healthy individuals. Consistent with functional studies and previous GxE research with the Val66Met polymorphism (i.e.: Aas et al., 2013; Alemany et al., 2011; Chen et al., 2006), we hypothesised that individuals carrying the Met allele (Met/Met and Val/Met) who have been exposed to childhood trauma are at higher risk of presenting with PEs in adulthood as compared with Val/Val subjects.

2. MATERIAL AND METHODS

Sample 1 – General population undergraduate and technical school students

Sample 1 comprised 808 subjects, including 547 university students from the Universitat Autònoma de Barcelona (UAB) and 261 students from 7 technical training schools in Barcelona (77 % were women; n=622). The mean age was 20.79 years (SD = 4.06; range = 17 – 54). Ninety-three percent of the subjects were of European origin (subject and both parents born in Europe). Further details of this sample can be found elsewhere (Barrantes-Vidal et al., 2013a, 2013b; de Castro-Catala et al., 2016).

To assess childhood trauma, all subjects were administered the Spanish version of the short form of the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998; Hernandez et al., 2013). This questionnaire consists of 28 questions enquiring about five types of childhood trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The score for each item ranges from 1 (never true) to 5 (very often true) according to the frequency to which subjects have experienced the statement during their childhood and adolescence. Following the guidelines for classification of CTQ scores proposed by Berstein and Fink (1998), the prevalence of each type of childhood trauma was calculated. A total childhood trauma score was computed by summing all the CTQ items. Also, the five types of childhood trauma were grouped into childhood abuse (sum of emotional, physical and sexual abuse) and childhood neglect (sum of emotional and physical neglect), in order to explore the differences between these two types of trauma. Childhood trauma data was available for 807 subjects.

PEs were assessed using the Spanish version of the Community Assessment of Psychic Experiences (CAPE) (Ros-Morente et al., 2011; Stefanis et al., 2002), a validated instrument for assessing subclinical symptoms in general population samples (Konings et al., 2006). The CAPE is a self-report questionnaire that measures the lifetime prevalence of PEs on a frequency scale ranging from 0 (never) to 3 (nearly always). It consists of 42 items that evaluate three dimensions of symptoms:

positive, negative, and depressive. A total sum score per dimension (positive and negative) of the frequency items was used for analyses.

Sample 2 – General population twins

Participants from sample 2 came from the *East Flanders Prospective Twin Survey* (Derom et al., 2013, 2002), a population-based survey that has prospectively recorded all multiple births in the province of East Flanders. As part of the survey, subjects were interviewed five times (T0 - T4) at approximately 3- to 4-monthly intervals. The five measurement points included the baseline measurement (T0), carried out at individuals' home, and four follow-up measurements (T1 - T4), collected using questionnaires. At baseline, sample 2 comprised 621 female subjects, including 174 monozygotic twin pairs, 112 dizygotic twin pairs, 2 twin pairs of unknown zygosity, and 45 of their non-twin sisters. Zygosity of each multiple birth was determined through examination of the placental membranes and vascular anastomoses, blood groups and DNA fingerprints. The mean age was 27.8 years (SD = 7.9; range = 18 - 61). Participants were of white ethnic group and of Belgian origin; 62 % had a higher education, 36 % had followed higher secondary school and 2 % had finished primary school only.

Childhood trauma was assessed at baseline using a self-report questionnaire based on the Dutch version of the 70-item CTQ original questionnaire (Arntz and Wessel, 1996; Bernstein et al., 1994). A shorter CTQ version was used in which the most explicit items related to sexual and physical abuse were omitted, as requested by the Twin Registry. Thus, subjects completed a 21-item questionnaire measuring positive events such as a happy childhood or youth, interparental or marital harmony and love, feeling safe and respect of privacy as well as negative events such as physical abuse, emotional neglect, material problems in parental household and stressful life events. The frequency of each item was rated on a scale from 1 (never) to 5 (always). Positive events were recoded to reflect adverse experiences or trauma. Cronbach's alpha for this 21-item questionnaire was 0.93. As in sample 1, a total childhood trauma score was calculated by summing the 21 items of the

questionnaire. In this sample, childhood abuse and neglect could not be calculated. From the total sample, 612 subjects completed the childhood trauma assessment.

All subjects completed the Dutch version of the CAPE (http://cape42.homestead.com) to assess PEs. They completed this questionnaire three times, at T0, T2 and T4. The CAPE total scores per dimension at each interview time were calculated as in sample 1.

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Universitat Autònoma de Barcelona (UAB) (sample 1) and the Maastricht University Medical Centre (sample 2). All subjects volunteered to take part in the study after being informed of the objectives of our research and provided informed consent at assessments.

Genotyping

From sample 1, 805 participants agreed on providing buccal mucosa on cotton swabs, from which genomic DNA was extracted using the Real Extraction DNA kit (Durviz S.L.U., Valencia, Spain). In this sample, the *BDNF* Val66Met polymorphism was genotyped using the TaqMan assay (Applied Biosystems). The genotyping reaction was performed according to the manufacturer's protocol on ABI PRISM 7900HT. The final volume was 5ul, which contained 5ng of genomic DNA, 2.5ul of Taqman Master Mix and 0.125ul of 40x genotyping assay (C_11592758_10). The genotype analysis of data was done with SDS v2.3 software (Applied Biosystems). For accuracy of genotyping, 20% of the samples (chosen randomly) were genotyped twice. Genotyping failed for 6 individuals from this sample.

In sample 2, genomic DNA was extracted from placental tissue, blood samples or buccal cell samples on sterile swabs. According to the appropriate protocol for each sample type, genomic DNA was extracted using QUIAamp DNA Mini Kits (Qiagen, Venlo, the Netherlands). The *BDNF* Val66Met was determined by KBioscience (Hertz, UK) using their proprietary allelic discrimination assay. For every monozygotic twin in the sample with genotypic data, the same genotypic data were included for the

co-twin, assuming identical genotypes for both twins. All dizygotic twins were genotyped. From the whole sample, genetic data were obtained for 473 subjects.

No genotyping discrepancies were expected neither between DNA obtained from different sample types (de Vries et al., 1996), nor between different genotyping technologies. Hardy-Weinberg equilibrium (HWE) was verified for each sample using an on-line Chi-squared HWE test calculator for biallelic markers (Rodriguez et al., 2009).

Due to the low frequency of Met/Met genotype, *BDNF* genotype was converted into a binary variable for the analyses: Met carriers (genotypes Met/Met and Val/Met) and Val/Val genotype.

Statistical analyses

Linear regression analyses were used to study the childhood trauma - *BDNF* Val66Met interaction in sample 1. CAPE positive and CAPE negative symptoms were tested as dependent variables using separate models, controlling for age and sex. Abuse x *BDNF* Val66Met and neglect x *BDNF* Val66Met effects were also examined in this sample. In the female twin sample (sample 2), given the different structure of the data, multilevel regression analysis was used (XTMIXED command). Two additional levels were added: (i) adjusting for clustering within twin pairs (as scores in the analysed variables are likely to be more similar between twin pairs) and (ii) adjusting for clustering within subjects (as the CAPE was measured three times and CAPE scores are more likely to be similar within subjects). Age was added as covariate in the multilevel analyses. All data were analysed using Stata version 13.1 (Stata/MP 13.1 for Windows, StataCorp LP, College Station, USA).

3. RESULTS

Descriptive of the variables

CAPE positive and negative data were available for 807 and 804 subjects from sample 1, respectively. In sample 2, 620 participants had complete CAPE positive data and 619 had complete CAPE negative data at T0, 438 participants had available CAPE positive and negative data at T2, and 480 participants

had complete CAPE positive and negative data at T4. The prevalence of each type of childhood trauma (see in brackets the threshold considered as presence of each type of trauma, according to Berstein and Fink (1998)) in sample 1 was: i) emotional abuse [> 8] 23.17 %, ii) physical abuse [> 7] 7.93 %, iii) sexual abuse [> 5] 9.67 %, iv) emotional neglect [> 9] 36.18 % and v) physical neglect [> 7] 12.39 %. This was not calculated in sample 2, given the alternative questionnaire used to assess childhood trauma. Descriptives of the variables included in the analyses are shown in Table 1. Genotype frequencies (Val/Val and Met carriers) were similar in both samples ($p > 0.05$, Table 1). No differences were observed in genotypic frequencies between males and females in sample 1 (Val/Val: males 62% and females 63%, $p > 0.05$). Males and females from sample 1 showed similar positive and negative PEs scores ($p > 0.05$, data not shown). Positive and negative PEs scores were higher in sample 1 than in sample 2 ($p < 0.05$, Table 1). This was also observed when considering only females ($p < 0.0001$ for both positive and negative dimensions). Complete data (PEs, childhood trauma and *BDNF* Val66Met genotype) were available for 799 and 460 participants from sample 1 and 2, respectively.

Impact of childhood trauma and *BDNF* genotype on psychotic experiences

There was a significant main effect of total childhood trauma in the model of positive and negative PEs in both sample 1 (positive PEs: B = 0.11, s.e. = 0.02, 95% CI: 0.08 – 0.15, $p < 0.001$ and negative PEs: B = 0.15, s.e. = 0.02 , 95% CI: 0.11 – 0.19, $p < 0.001$) and sample 2 (positive PEs: B = 0.11, s.e. = 0.01, 95% CI: 0.09 – 0.14, $p < 0.001$ and negative PEs: B = 0.15, s.e. = 0.02, 95% CI: 0.116 – 0.182, $p < 0.001$). In sample 1 both abuse and neglect were found to predict positive and negative PEs (see Table 2). No significant main effect of *BDNF* Val66Met genotype was found for positive or negative PEs in either sample (Table 2).

Impact of childhood trauma x *BDNF* Val66Met in predicting psychotic experiences

In sample 1, a significant interaction was found between total childhood trauma and *BDNF* Val66Met on positive PEs (B = -0.08, s.e. = 0.04, 95% CI: - 0.16 – -0.01, $p = 0.036$). Specifically, Val/Val subjects

reported more positive PEs than Met carriers when exposed to childhood trauma. When we divided the childhood trauma scores into abuse and neglect, this interaction effect on positive PEs was also found with neglect (B = -0.15, s.e. = 0.07, 95% CI: -0.28 – -0.01, p = 0.033), but not abuse, although a trend in the same direction was observed (B = -0.13, s.e. = 0.07, 95% CI: -0.26 – -0.003, p = 0.056). Regarding negative PEs, no significant interaction was found with any of the childhood trauma variables studied (data not shown).

In Sample 2, in which only total childhood trauma was estimated, there was a significant interaction effect on positive PEs (B = 0.05, s.e. = 0.03, 95% CI: 0.001 – 0.1, p = 0.045); carriers of the Met allele with childhood trauma exposure showed more positive PEs than Val/Val carriers (Figure 1G). This interaction was also significant for negative PEs (B = 0.13, s.e. = 0.04, 95% CI: 0.06 – 0.21, p = 0.001). Similarly, Met carriers exposed to childhood trauma reported more negative PEs than those Val/Val (Figure 1H).

When we observed that the results across both samples were in the opposite direction, we explored whether the GxE found in sample 1 was influenced by sex. This was considered relevant given that this sample was composed of both male and female participants (whereas sample 2 was all female). Sex-stratified analyses on positive PEs revealed that the interaction effects observed in sample 1 with total childhood trauma, abuse and neglect were significant only for males (Table 3, Figure 1A, 1B, 1C), but not females (see Table 3). Regarding negative PEs, sex-stratified analyses revealed significant interactions between the *BDNF* Val66Met and total childhood trauma, as well as abuse and neglect, on negative PEs in males (Table 3, Figure 1D, 1E, 1F) but not females (see Table 3).

4. DISCUSSION

The present study investigated the possible interplay between *BDNF* Val66Met genotype and childhood trauma on subclinical PEs using two independent samples of nonclinical young adults.

Firstly, our results show a consistent association between childhood trauma and PEs in healthy individuals. Secondly, a *BDNF* Val66Met x childhood trauma effect on PEs was observed in both samples, although discordant in terms of risk allele. Moreover, the GxE effect found in sample 1 seems to be sexually dimorphic.

Childhood trauma and subclinical psychotic experiences

In the present study, we observed an increased risk for PEs related to childhood traumatic experiences. This was detected in both samples, despite the differences in PEs' scores between samples, which probably is a consequence of the mean age of each sample (i.e.: sample 1 is approximately 7 years younger than sample 2). A pattern of diminished PEs prevalence over the life course after a peak during adolescence has been observed in other studies (Kelleher et al., 2012; Verdoux et al., 1998), suggesting that these symptoms may be part of normal development during childhood and adulthood development, but become abnormal (indicating pathology) with age. This was considered in the present study, correcting all analyses by age.

Our results relate traumatic experiences to a greater risk for PEs in two independent nonclinical samples are consistent with other studies analysing this in healthy individuals (van Nierop et al., 2014). Similar results have been found in a meta-analysis including nonclinical and clinical studies analysing childhood adversities in relation to psychotic symptoms and psychosis. The odds ratios (ORs) associated were situated around 3 for both phenotypes (Varese et al., 2012). Evidence in the same line has been provided in a review by Velikonja et al. (2014) focusing on schizotypy, the underlying vulnerability for psychosis-spectrum psychopathology that is expressed across a wide range of personality traits, PE, subclinical and clinical psychosis phenomenology, presumably reflecting the expression of common causal factors (Barrantes-Vidal et al., 2015; van Os et al., 2009). In the Velikonja et al. review, they found an association between all types of trauma and schizotypy, with ORs ranging between 2.01 and 4.15.

Exposure to stress causes the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which activates several pathways that regulate gene expression for metabolism, immune function, cognition, and brain development, preparing the body to respond to stress. Exposure to severe stress (e.g. childhood trauma) can alter this normal stress response (De Bellis and Zisk, 2014) and may precipitate a cascade of events that leads to aberrant neural circuit changes, including an abnormal increase in dopamine signalling or neurotrophic factors (e.g. BDNF) (Carbone and Handa, 2013; van Winkel et al., 2008). Alterations in HPA axis reactivity and related molecule levels have been found in patients with psychosis, as well as in subjects with schizotypal personality disorder, and ultra-high risk subjects (Myin-Germeys and van Os, 2007), suggesting that HPA axis function alteration may increase psychological vulnerability, predisposing persons to develop psychotic symptoms.

Childhood trauma x *BDNF* Val66Met and subclinical psychotic experiences

In the present study, we examined whether *BDNF* Val66Met moderated the association between childhood trauma and PEs in two independent samples of healthy subjects. According to our results, in sample 1, Val/Val subjects who had been exposed to childhood trauma or childhood neglect reported more positive PEs. This association was specific to males, as this was not observed in females. In sample 2, Met carriers with exposure to childhood trauma were observed to have more positive and negative PEs. It is challenging to interpret this results because, to our knowledge, there are only two previous studies analysing this specific GxE in healthy subjects, but none of them have examined sex differences. The first study showed a significant effect of Met allele x childhood abuse on positive PEs (Alemany et al., 2011), which seems to converge with the results of this study in sample 2, although this sample was composed only by female participants. The second study, by Ramsay et al. (2013), did not find any significant interaction. Overall, the results of our sample 1 support the importance of examining sex differences when analysing the *BDNF* x trauma effect on PE dimensions. There are also studies exploring this GxE interaction in clinical samples. Aas and colleagues, for example, explored the *BDNF* x childhood abuse effect on cognition and brain abnormalities in a sample of schizophrenic and bipolar patients. In this study, Met carriers with

childhood trauma exposure showed poorer cognitive functioning, reduced hippocampal volumes and larger ventricles (Aas et al., 2013). However, these findings have not been replicated in other samples (Hernaus et al., 2014).

The BDNF is a neurotrophin required for proper neurodevelopment and is also involved in essential functions in the mature brain (e.g.: synaptic plasticity) (see Autry and Monteggia (2012) for an extensive review on BDNF). The *BDNF* Val66Met polymorphism is reported to affect intracellular processing and secretion of the mature protein influencing neurogenesis and plasticity. In this sense, the BDNF-Met protein shows a defective secretion and is associated with lower distribution of BDNF protein in neurons (Chen et al., 2006, 2004; Egan et al., 2003). Despite these findings, the underlying neurobiology mediating the effect of this particular polymorphism on brain functioning and its interaction with other genetic factors are still not well understood. However, it seems evident that inappropriate or inadequate neurotrophic support during brain development could underlie structural and functional disorganization of neural and synaptic networks (Lu and Martinowich, 2008), leading to an impaired brain with, probably, a decreased ability to make the normal and necessary adaptive changes according to the inputs received.

Along these lines, the *BDNF* Met allele has been related to reduced hippocampal and prefrontal cortex volumes (Pezawas et al., 2004), two brain areas highly involved in cognition, consolidation of information, memory, and behaviour. Consistent with this, *BDNF* Met carriers have shown memory dysfunctions (Chen et al., 2004), impairment in learning and memory (Chen et al., 2006; Soliman et al., 2010), and cognition (Altmann et al., 2016; Lu et al., 2012). Such impairments are a core feature of schizophrenia (Heinrichs and Zakzanis, 1998; Medalia and Thysen, 2008) and can also be observed in an attenuated form in non-clinical and at-risk populations (Piskulic et al., 2016). Case-control and family studies have shown contradictory results in relation to the allele of risk of this polymorphism. Although a recent meta-analysis pointed towards Met as the risk allele for schizophrenia (Kheirollahi et al., 2016), some studies have found associations with the Val allele (Neves-Pereira et al., 2005; Rosa et al., 2006). These apparently contradictory findings regarding the allele of risk are also

observable across studies conducted in relation to other psychiatric phenotypes, such as bipolar disorder and depression (Lohoff et al., 2005; Oswald et al., 2004). The reason for these inconsistencies is unclear. The different pattern of results may suggest that cumulative and/or interactive effects of other genes of minor effect with the variability on *BDNF* (e.g. the genes Catechol-O-methyltransferase (*COMT*) or *SERT*; Gutiérrez et al., 2015; Han et al., 2008) or epigenetic factors (Boulle et al., 2012) are operating in the expression of psychopathology.

Another factor to consider may be the subject's sex. There is evidence of sex differences in healthy brain structure, function, and neurotransmission (Cosgrove et al., 2007). These differences can also be observed in relation to risk for psychopathology (Aleman et al., 2003; Cahill, 2006), showing males to have a higher susceptibility for schizophrenia, with earlier age of onset and an overall poorer clinical prognosis (Godar and Bortolato, 2014). Moreover, several studies have shown a different genetic effect on psychosis risk depending on the subject's sex, for example with the *COMT* gene (e.g.: de Castro-Catala et al., 2015; Harrison and Tunbridge, 2008; Tunbridge and Harrison, 2011) or the Zinc finger protein 804A gene (Zhang et al., 2011). In line with this, we found a *BDNF* x childhood trauma effect on psychosis proneness in males, but not in females (sample 1). All these studies point out the existence of a gender-specific mechanism underlying brain development and functioning, that may be led by sexual hormones (i.e.: estrogens and androgens) (see review by Godar and Bortolato, 2014). In addition, these biological differences may interact with gender-dimorphic sociocultural factors influencing the impact of childhood trauma on the brain-mind development and gene expression patterns. Actually, there is some evidence suggesting that sex differences might be relevant not only in terms of differential rates of childhood adversities (e.g., Tolin and Foa, 2006) and PEs (e.g., Maric et al., 2003), but also in the association between childhood trauma and psychosis phenotypes (Fisher et al., 2009; Garcia et al., 2016). Since sample 2 was composed of females only, this sex-specific effect could not be explored.

The findings of the present study, although partially replicate previous findings, do not provide conclusive results. They should be considered in light of some limitations, such as the two different

questionnaires used to assess childhood trauma in each sample. In sample 2 some explicit questions on physical and sexual abuse were omitted, which could have resulted in an underestimation of experienced trauma. It is possible that some individuals scored zero for trauma, although they had experienced abuse. However, since the correlation between different types of trauma tends to be high (Bellis et al., 2014), the effect of the omission of these items is likely limited. Furthermore, the present study may be underpowered for the sex-stratified interaction analyses. The retrospective assessment of childhood trauma which may bias incidence rates, the proportion of males and females studied, and the sample size are also limitations of the present study. In this regard, future studies should be done in this field considering larger samples with comparable sex groups and genetic, environmental and/or epigenetic factors to better understand the modulating effect of this gene on psychosis and psychosis proneness.

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Acknowledgments:

This work was supported by research projects funded by the Spanish Ministry of Economy and Competitiveness (PSI2011-30321-C02-02, PSI2014-54009-R, Red de Excelencia PSI2014-56303-REDT (PROMOSAM: Investigación en Procesos, Mecanismos y Tratamientos Psicológicos para la Promoción de la Salud Mental), Fundació La Marató de TV3 (091110), Comissionat per a Universitats i Recerca of the Generalitat de Catalunya (2014SGR1070 and 2014SGR1636). N. Barrantes-Vidal is funded by the Academia Research Award (Institució Catalana de Recerca i Estudis Avançats; ICREA) from the Catalan Government.

Table 1 Descriptives of the two samples included in the study: *BDNF* Val66Met genotype frequencies (Val/Val and Met carriers, including Met/Met and Val/Met genotypes) and mean scores (SD, range) for total childhood trauma, abuse and neglect, and for the positive and negative dimensions of subclinical psychotic experiences.

	Sample 1 n=808	**Sample 2** n=621	**Comparison**
Genotype frequencies (n (%))			
BDNF Val/Val	501 (63%)	302 (64%)	χ^2=0.167 p=0.683
BDNF Met carriers	298 (37%)	171 (36%)	
Subclinical psychotic experiences[1] (mean (SD, range))			
Positive	8.04 (4.88, 0-29)	3.60 (3.54, 0-28)	**t=19.13 p<0.001**
Negative	9.15 (5.26, 0-35)	7.08 (5.07, 0-27)	**t=7.49 p<0.001**
Childhood trauma[2] (mean (SD, range))			
Total childhood trauma	32.95 (8.76, 25-84)	34.89 (11.98, 19-95)	–
Abuse	18.15 (5.03, 15-50)	–	–
Neglect	14.79 (4.92, 10-41)	–	–

[1] Subclinical psychotic experiences were assessed using the Community Assessment of Psychic Experiences (CAPE).

[2] Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ) (sample 1) and a CTQ-based questionnaire (sample 2). Note that no comparisons have been done between the total childhood trauma scores, given the two different questionnaires used.

Table 2 Main effects of total childhood trauma, abuse and neglect, and the *BDNF* Val66Met polymorphism (Val/Val *vs.* Met carriers) on positive and negative subclinical psychotic experiences in the two samples included in the present study.

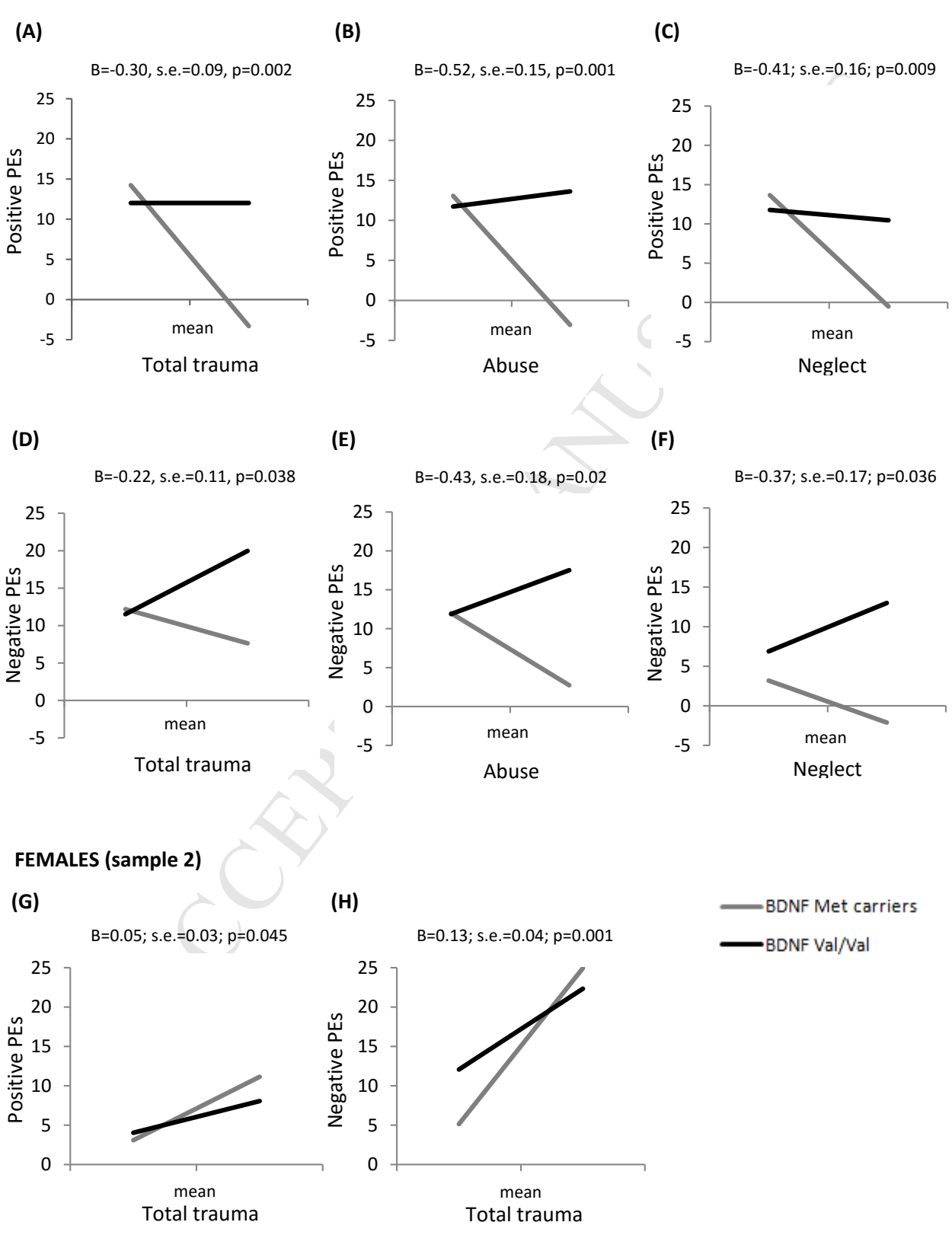
	Positive subclinical psychotic experiences		**Negative subclinical psychotic experiences**	
	Sample 1	Sample 2	Sample 1	Sample 2
Total childhood trauma	**B=0.11 s.e.=0.02 p<0.001 95% IC 0.08 – 0.15**	**B=0.11 s.e.= 0.01 p<0.001 95% IC 0.09 – 0.14**	**B=0.15 s.e.=0.02 p=<0.001 95% IC 0.11 – 0.19**	**B=0.15 s.e.= 0.02 p<0.001 95% IC 0.12 – 0.18**
Abuse	**B=0.20 s.e.=0.03 p<0.001 95% IC 0.13 – 0.26**	–	**B=0.18 s.e.=0.04 p<0.001 95% IC 0.11 – 0.25**	–
Neglect	**B=0.15 s.e.=0.03 p<0.001 95% IC 0.08 – 0.21**	–	**B=0.28 s.e.=0.04 p<0.001 95% IC 0.24 – 0.35**	–
BDNF Val66Met	B=0.12 s.e.=0.35 p=0.726 95% IC -0.55 – 0.80	B=0.04 s.e.= 0.34 p=0.911 95% IC -0.62 – 0.70	B=-0.56 s.e.=0.38 p=0.145 95% IC -1.31 – 0.19	B=0.15 s.e.= 0.48 p=0.755 95% IC -0.80 – 1.1

Table 3 Interaction effects by sex (males and females) between childhood trauma (total, abuse and neglect) and the *BDNF* Val66Met polymorphism (Val/Val *vs.* Met carriers) on positive and negative subclinical psychotic experiences in the two samples studied (sample 1 and sample 2).

	Sex	**Positive psychotic experiences**		**Negative psychotic experiences**	
		Sample 1	Sample 2	Sample 1	Sample 2
Childhood abuse x BDNF	Males	**B=-0.52 s.e.=0.15 p=0.001 95% CI: -0.82 – -0.21**	---	**B=-0.43 s.e.= 0.18 p=0.02 95% CI: -0.78 – -0.07**	---
	Females	B=-0.03 s.e.=0.07 p=0.728 95% CI: -0.17 – 0.12	---	B=0.05 s.e.= 0.08 p=0.576 95% CI: -0.11 – 0.2	---
Childhood neglect x BDNF	Males	**B=-0.41 s.e.=0.16 p=0.009 95% CI: -0.72 – -0.11**	---	**B=-0.37 s.e.= 0.17 p=0.036 95% CI: -0.71 – -0.03**	---
	Females	B=-0.08 s.e.=0.08 p=0.267 95% CI: -0.23 – 0.07	---	B=-0.0001 s.e.= 0.08 p=0.999 95% CI: -0.16 – 0.16	---
Total childhood trauma x BDNF	Males	**B=-0.30 s.e.=0.09 p=0.002 95% CI: -0.48 – -0.11**	No males in this sample	**B=-0.22 s.e.= 0.11 p=0.038 95% CI: -0.43 – -0.01**	No males in this sample
	Females	B=-0.23 s.e.=0.04 p=0.469 95% CI: -0.11 – 0.05	**B=0.05 s.e.= 0.03 p=0.045 95% CI: 0.001 – 0.11**	B=0.02 s.e.= 0.05 p= 0.710 95% CI: -0.07 – 0.11	**B=0.13 s.e.= 0.04 p=0.001 95% CI: 0.06 – 0.21**

Note that childhood trauma was assessed with the CTQ in sample 1 and an adapted version of the CTQ in sample 2.

Figure 1 Graphic representation of the significant interaction effects by sex (males and females) between childhood trauma (total, abuse and neglect) and the *BDNF* Val66Met polymorphism (Val/Val *vs.* Met carriers) on positive and negative subclinical psychotic experiences (PEs) in the two samples studied (i.e.: sample 1 and sample 2).



Highlights:

Association between childhood trauma and subclinical psychotic experiences.

BDNF Val66Met polymorphism moderate this association (GXE).

Possible involvement of sex in the GXE interaction on psychotic experiences

Role of funding source:

Funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report nor in the decision to submit the paper for publication.

Contributors:

N. Barrantes-Vidal, T. Kwapil, R. van Winkel and A. Rosa managed the design, analysis and interpretation of the data. T. Sheinbaum, P. Cristóbal-Narváez, M. de Castro-Catala and E. Peña participated in the collection and design of databases of sample 1. N. Jacobs, C. Derom, E. Thiery and J. van Os participated in the collection and design of the sample 2 study. M. de Castro-Catala and E. Peña conducted the lab work of sample 1. M.de Castro-Catala and M. van Nierop undertook statistical analysis with input from T. Kwapil, R. van Winkel and A. Rosa. M de Castro-Catala and M. van Nierop wrote the initial manuscript, which was further edited by all the authors. All authors contributed to and approved the final manuscript.