# The Interaction of the Oxytocin Receptor Gene and Subtypes of Child Abuse on Social Cognition in Euthymic Patients With Bipolar Disorder Type I

**Ulises Rios** ( uarios@uc.cl )
Universidad de Valparaiso https://orcid.org/0000-0001-6227-4451
**Javier Moran**
universidad de valparaiso
**Jimena Hermosilla**
Hospital del Salvador de Valparaíso
**Rene Gonzalez**
Universidad de Valparaíso
**Paulina Muñoz**
Hospital Dr Gustavo Fricke
**Luisa Herrera**
Universidad de Chile
**Pablo R Moya**
Universidad de Valparaíso Facultad de Ciencias: Universidad de Valparaiso Facultad de Ciencias
**Juan Pablo Jimenez**
universidad de chile

**Research**

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# Abstract

**Background**: Most studies on cognitive impairment in Bipolar Disorder (BD) have neglected the role of early stress, despite the high frequency of childhood maltreatment in this clinical group. The aim of this study was to establish a connection between a history of emotional, physical, and sexual abuse in childhood and social cognition (SC) functioning in patients with BD type I in euthymia, and to test a possible moderating effect of the polymorphism rs53576 in the oxytocin receptor (OXTR) gene.

**Results:** We found a high frequency of child abuse, indicating that BD patients who had been victims of physical and emotional abuse as children, and were carriers of the GG genotype at OXTR rs53576, displayed higher social cognition alterations, specifically in an emotion recognition test.

**Conclusions:** The gene-environment interaction study presented here proposes a Differential Susceptibility model of a genetic polymorphism that can be plausibly associated with SC functioning. This evidence might help to identify at-risk clinical subgroups within a diagnostic category with well-established intra-group heterogeneity such as BD. Future research aimed at testing the inter-level impact of early stress constitutes an ethical-clinical duty in light of the high rates of childhood abuse reported in bipolar patients.


# 1. Background

Bipolar Disorder (BD) has been linked to social cognition (SC) impairments even during periods of euthymia (Samame, 2013). The importance of these studies derives from evidence connecting these deficits with psychosocial functioning in bipolar patients (Van Rheenen et al., 2014; Martino et al., 2011). Despite the vast literature regarding cognition alterations in BD, very few studies have analyzed the early stress variable (Aas et al., 2016). This omission may be relevant given the evidence for the impact of early stress on subsequent neural development and cognitive functioning (Pechtel et al., 2011) as well as the clear data about the high frequency of child abuse in patients with BD (Daruy-Filho et al., 2011; Agnew-Blais et al., 2016; Ríos et al., 2020).

The few studies comparing bipolar patients with and without a background of child abuse have reported significant differences between these groups in both SC and neurocognitive tests (Jiménez et al., 2017; Russo et al., 2015). Interestingly, the evidence for greater cognitive deficits in bipolar patients with a history of childhood trauma may be grounded in hypotheses with a reasonable degree of biological plausibility (Teicher et al., 2003; Danese et al., 2017).

# Oxytocin, oxytocin receptor gene, and intermediate phenotypes

The oxytocin (OXT) system participates in the regulation of several processes involved in SC functioning (Meyer-Lindenberg et al., 2011), both in the cognitive route of SC –theory of mind (Schneider-Hassloff et al., 2016; Domes et al., 2007) and emotion recognition (Shahrestani et al., 2013; Schulze et al., 2011)– and the affective route of SC –empathy (Rodrigues et al., 2009; Gong et al., 2017)–. Some of these studies

have examined genetic variations of the single nucleotide polymorphism rs53576 (G/A), located in the third intron of the OXT receptor (*OXTR*) gene, which has been linked to phenotypes of social behavior in humans (Epstein et al., 2012).

Hypotheses linking OXT with mood disorders (Cochran et al., 2013) have been scarcely studied in patients with BD. In this regard, authors have reported a higher serum level of OXT in bipolar patients compared to healthy controls in both symptomatic periods and euthymia (Turan et al., 2013). Determining the association between the serum level of a neuropeptide and BD may be complex, given the high phenotypic variability within this diagnostic category. In this sense, other studies have focused on measuring intermediate functioning dimensions, such as SC (Tas et al., 2015).

*OXTR* gene variants have been associated with outcomes at several levels, including the diagnosis of schizophrenia (Montag et al., 2013), suicidal behavior (Parris et al., 2018) and depressive symptomatology (McQuaid et al., 2013; Thompson et al., 2014). Only a handful of studies on *OXTR* have focused on the association with *intermediate phenotypes* (Meyer-Lindenberg et al., 2006) as a strategy for identifying groups of patients with a common neurobiological substrate that can be targeted with more specific interventions. Studies that have adopted this approach have reported an association between *OXTR* and SC functioning (Uzefovsky et al., 2015; Davis et al., 2014).

The relevance of genetic studies focused on intermediate phenotypes may be strengthened by designs that analyze gene-environment interaction. Most studies on *OXTR* gene variants have shown that the G allele of rs53576 is associated with protective social traits, such as pro-social behavior (Kogan et al., 2011) and better empathic ability (Gong et al., 2017); however, authors who have evaluated its interaction with a background of early trauma have reported a pattern of greater vulnerability for this allelic variant. Studies on the interaction between *OXTR* gene, history of child abuse and emotional regulation in adult life have shown that carriers of the rs53576 GG genotype display less emotional regulation if they had been victims of early trauma (Bradley et al., 2011; Hiraoka et al., 2019). This pattern of differential vulnerability of the *OXTR* rs53576 G allele has also been observed in functional imaging studies, which report strong gray matter reduction in the bilateral ventral striatum, along with increased amygdala responsiveness to emotional facial expressions (Dannlowski et al., 2016).

Gene-environment interaction studies in patients with BD are scarce and generally focused on neurocognitive measures, evaluating the moderating effect of genetic polymorphisms other than *OXTR* gene variants (Savitz et al., 2007; Aas et al., 2013). To the best of our knowledge, this is the first study to measure gene-environment interaction in patients with BD focusing on SC and *OXTR*. Based on the available evidence, we hypothesized that carriers of the *OXTR* rs53576 G allele will have a poorer performance on SC as they have experienced greater trauma. In addition, considering the possible differential effects on brain development linked to subtypes of child abuse (Teicher et al., 2016) and the evidence indicating that subtypes of child abuse are connected with SC alterations (Pope et al.2014; Russo et al.,2015), we sought to identify specific trauma subtypes whose association with poorer performance on SC could be moderated by *OXTR* rs53576.

# 2. Methods

# Patients

101 euthymic bipolar outpatients were recruited from the Mood Disorders Unit of Hospital Psiquiátrico del Salvador (Valparaíso, Chile) and the Outpatient Psychiatry Unit of Hospital Gustavo Fricke (Viña del Mar, Chile).

Inclusion criteria were as follows: (a) bipolar I DSM-IV-TR diagnosis, (b) age 18–65 years, (c) fulfilling euthymia criteria for at least 3 months, defined as a score of ≤ 6 on the Young Mania Rating Scale (YMRS) and of ≤ 8 on the Hamilton Depression Rating Scale (HDRS) and (d) the capacity to provide written informed consent. We excluded patients who were active drug users and who had received electroconvulsive therapy over the last 3 months. Patients who did not fully completed the instruments used in this study were also excluded, resulting in a final sample of 82 individiduals.

The participants were 46.5 years old on average (SD = 14,9 years); 65.7% of them were women. The age at onset of BD was 23.3 years (SD = 9.66), the number of hospitalization was 3,4 (SD = 4,3) and the number of suicide attempts was 1,2 (SD = 2.0)

40.2% of the patients reported being victims of at least one type of abuse as a child. The average of abuses was 0.8 ± 1.3. The frequencies per subtype of abuse were: 40,2% for sexual abuse, 26,8% for physical abuse, 32,9% for emotional abuse, 18.3% for emotional neglect and 18.3% for physical neglect. Our analysis by sex showed that 71% of the women and 51% of the men had suffered at least one type of abuse as children ($p < 0.02$).

We genotyped the rs53576 polymorphism located in the *OXTR* gene. This polymorphism was not in Hardy Weinberg equilibrium ($\chi^2 = 19.8$, p-value = 0.000009), which is probably explained by the bias in the sample selection, i.e., patients with BD. Since this polymorphism has been linked to several behavioral traits, the selected group does not represent the general population. As for the distribution of the genotype frequencies of *OXTR* rs53576, 20% of the were GG, while 80% were GA + AA; we did not find differences by sex or age. Likewise, there were no differences in the age of onset of BD or number of hospitalizations.

# Procedure and instruments

The subjects' history of child abuse was evaluated using the Spanish language version of the Childhood Trauma Questionnaire - Short Form (Berstein et al., 1994; Behn et al., 2020). Briefly, this self-report instrument comprises 28 items that refer to five subtypes of child abuse: sexual abuse (SA), emotional abuse (EA), physical abuse (PA), physical neglect, and emotional neglect. For ethical-clinical reasons, the self-report instrument was completed by each patient in a clinical setting, confidentially and in the presence of their treating physician. In this study, as recommended by Aas et al. (2013), we only considered the abuse scales.

Cognitive functioning was evaluated with social and non-social cognition. For the former dimension, we used the Spanish language version of TASIT (The Awareness of Social Inference Test) (McDonald, 2003), specifically the emotion evaluation task. This test evaluates respondents' ability to recognize emotions by showing them 20 micro-videos in which actors simulate situations that represent the basic emotions of fear, disgust, surprise, sadness, and anger.

This study was approved by the ethics committee of the Valparaíso-San Antonio Health Service, Chile. All examinations were performed according to the tenets of the Declaration of Helsinki. All patients were informed about the study and gave their signed consent.

# Genotyping

After the interview, blood samples (6 mL) were taken from the patients and placed in EDTA-coated tubes. The DNA extraction was performed using the NucleoSpin Blood kit (Macherey-Nagel, Germany) following manufacturer´s protocol. The *OXTR* rs53576 allelic variants were genotyped using a TaqMan® probe (SNP ID C___3290335_20, Applied Biosystems, USA) in a AriaMX thermocycler (Agilent, USA) following manufacturer´s protocol. Hardy-Weinberg equilibrium was tested by comparing the observed and expected genotypes using $\chi 2$.

# Analysis

Simple moderation analysis was performed using Hayes' Process Macro v 3.0 (2018) for SPSS; this macro is widely used in research to perform moderation and mediation analysis. It has several benefits over SEM models such as the need for less coding to generate same results o la capacidad de estimar cada ecuación del modelo de regression de forma independiente (see Hayes, Montoya & Rockwood, 2017). The analysis considered a bootstrapping sample of 5000, which allowed solving the lack of normal distribution of the sample (Currant-Everett, 2017), generating bootstrping confidence intervals for the interpretation of results.

First, the association between trauma scores of each of the five subscales of the CTQ and performance in social cognition, moderated by OXTR rs53576, was evaluated as a way to identify specific interactions according to types of trauma. For all analyses the moderating variable was coded as AA/AG (0) and GG (1).

Next, as a way of evaluating whether the cumulative effect of trauma is moderated by the genetic variable, a new independent variable was generated from the sum of CTQ scales that were on the cut-off score for "moderate" trauma. Because there are five scales, the values range from 0 to 5.

For all analyses all continuous variables were mean centered.

# 3. Results

### GxE and social cognition functioning by specific types of trauma

TASIT total score was regressed onto each of the five subscales of the CTQ and its interaction with the genetic variable.

A moderating effect was observed for the models that incorporated the physical abuse scales as an independent variable ($F(3,78) = 2.84$, $p = .043$, $R^2 = 0.10$) and emotional abuse ($F(3,78) = 3.21$, $p = 0.028$, $R^2 = 0.11$). In the case of physical abuse, the genetic variable showed an interaction effect (b=-0.46, 95% CI [-0.80, -0.12], t= -2.76, p = < 0.01) for GG (b = 0.80, 95% CI [-0.68, -0.04], p = 0.03), but not for AA/AG (b = -0.20, 95% CI [-0.007, 0.20], p = 0.07). In the case of emotional abuse, the moderating variable showed an interaction effect (b=-0.43, 95% CI [-0.72, -0.14], t= -2.93, p < 0.01), for GG (b = 0.80, 95% CI [-0.61, -0.06], p = 0.02), but not for AA/AG (b= -0.29, 95% CI [-0.003, 0.19], p = 0.06). Both results are shown graphically below:

### GxE and social cognition by sum of traumas

The model based on the sum of traumas as an independent variable was not significant (interaction coefficient=-0.80, 95% CI [-1.72, 0.11], t= -1.74, p = < 0.09). Based on this result, we sought to assess whether the cumulative effect of trauma would be more associated with the presence of abuses that showed moderation of the rs53576 genotype in the previous step. For this purpose, a new variable was generated from the sum of PA and AD with values between 0 and 2.

The model was significant ($F(3,78) = 3.021$, $p = 0.04$, $R^2 = 0.10$), showing an interaction effect of rs53576 (b=-2.11, 95% CI [-3.55, -0.67], t= -2.91, p = < 0.01) for GG (b = 0.80, 95% CI [-2.75, -0.17], p = 0.03), but not for AG/AA (b=-0.20, 95% CI [-0.003, -1.30], p = 0.05). The results are shown in Fig. 2.

## 4. Discussion

Our study revealed that euthymic patients with BD type I that were victims of physical and emotional abuse as children and have the GG genotype at OXTR rs53576 displayed greater social cognition alterations, especially in an emotion recognition test.

Our findings support the hypotheses of previous studies (Bradley et al., 2011; Hiraoka et al., 2019) suggesting that the OXTR rs53576 GG genotype constitutes a Differential Susceptibility genotype (Belsky et al., 2009) when dealing with early stress conditions. The gene-environment interaction model has been confirmed in studies focused on outcomes belonging to various levels, including increased depressive symptomatology (McQuaid et al., 2013), alterations in emotional regulation tests (Bradley et al., 2011; Hiraoka et al., 2019), and morpho-functional modifications in the limbic system (Dannlowski et al., 2015). The present study adds evidence for gene-environment interaction, now focusing on an intermediate phenotype such as SC functioning, and thus it provides data that may improve our comprehension of previous hypotheses centered on more complex variables. In other words, alterations in emotional recognition tasks may well be related to greater demands on emotional regulation processes and their morpho-functional correlates in the limbic system. Such a clinical context may also shed light on why

depressive symptomatology indexes are greater in carriers of the *OXTR* rs53576 GG genotype who have been affected by child abuse.

Our findings also highlight differences on the role of the child abuse subtypes. Most studies have employed general measures of child abuse, leaving out the more specific characteristics of the traumatic experience and their possible differential effects on the brain (Teicher et al., 2016). Our results revealed an interaction only in the presence of PA and EA, with no interaction with other types of abuse, despite the evidence indicating its undeniable impact on the life cycle of bipolar patients (Maniglio,2013). These results are consistent with studies that have reported an association between the PA and EA subtypes and SC performance, specifically in emotional recognition tests (Russo et al 2015; Pope et al., 2014). In light of these results, the hypothesis that sexual abuse experiences have a course over a person's development that differs from that of other types of abuse (Gibb, Chelminski, & Zimmerman, 2007) should be considered in future research. Nevertheless, due to limitations such as the limited sample size and methodological aspects of the genotype grouping (GG vs GA/AA), these hypotheses should be cautiously weighed. Similarly, the interpretation of the results should be prudent given the limited information about the more specific characteristics of each person's traumatic experience in childhood. In this regard, future studies should explore the processes of therapeutic reparation that may have taken place in the life cycle of patients after the child abuse episode. As suggested in studies on the effect of early interventions (Sheridan et al., 2012), this variable may attenuate or revert the long-term impact on brain function. Similarly, future research should also consider data about the age when the abuse occurred as there is evidence for a differential vulnerability in specific brain regions depending on the neural development period when the stressor occurs (Andersen et al., 2008). Lastly, the association between child abuse and insecure attachment patterns (Ford et al., 2009; Kefeli et al., 2017) suggests the importance of measuring childhood trauma from a relational perspective.

The relevance of generating evidence, specifically regarding BD, lies in the fact that cognitive alterations in this group have resulted in the design of therapeutic interventions and preventive strategies (Solé et al., 2017; Lahera et al., 2013) that have overlooked the role of early stress. Most recommended therapeutic interventions are informed by the assumption that this diagnostic category entails an inherent cognitive deficit, presuming that the neuroprogression occurs as a consequence of the allostatic load of the disease (Kapczinski et al., 2016; Lopez-Jaramillo et al., 2010). This perspective reflects a possible biomedical bias, which has omitted the analysis of early psychosocial variables in studies on cognitive dysfunction in BD.

Our findings highlight the need to rethink the design of new therapeutic approaches from a preventive perspective, with strategies aimed at reducing the incidence of child abuse (Mc Millan et al., 2009) in populations known to be at greater risk (Agnew-Blais et al., 2016; Ríos et al., 2020) as well as through interventions intended to encourage specific emotional regulation and mentalization skills (Fonagy et al., 2002) from a relational perspective. Conducting research aimed at testing interventions that manage to reduce the inter-level impact of early stress (Danese et al., 2012) represents an ethical-clinical duty in light of the high rates of child abuse in patients with BD.

This study has pioneered the exploration of SC in patients with BD using a gene-environment interaction model. Our aim was to provide data about SC deficits employing a hypothesis that presumes that adverse relational events in early life have an impact and that they interact with genetic variants of a plausibly related polymorphism such as OXTR rs53576. The description of a Differential Susceptibility genotype associated with the functioning of intermediate phenotypes may contribute to the identification of at-risk clinical subgroups within a diagnostic category with well-established intra-group heterogeneity such as BD.

# Declarations


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Mood Disorders Program. Hospital Psiquiátrico del Salvador de Valparaíso. Chile


### Authors' contributions

All individuals included as authors of the paper have contributed substantially to the scientifc process leading up to the writing of the paper. Such contribution includes the conception and design of the project, the performance of experiments and the analysis and interpretation of data. All authors read and approved the fnal manuscript.

### Consent for publication

The work described has not been submitted for publication in whole or in part elsewhere and all the authors listed have approved the manuscript that is enclosed.

### Competing interests

All authors disclose any actual or potential competing interest including any fnancial, personal or other relationships with other people or organizations within 3 years of beginning the submitted work that could inappropriately infuence, or be perceived to infuence, this work.


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### Ethical approval

This study was approved by the ethics committee of the Valparaíso-San Antonio Health Service , Chile. All examinations were performed according to the tenets of the Declaration of Helsinki. All patients were informed about the study and gave their signed consent

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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# Figures

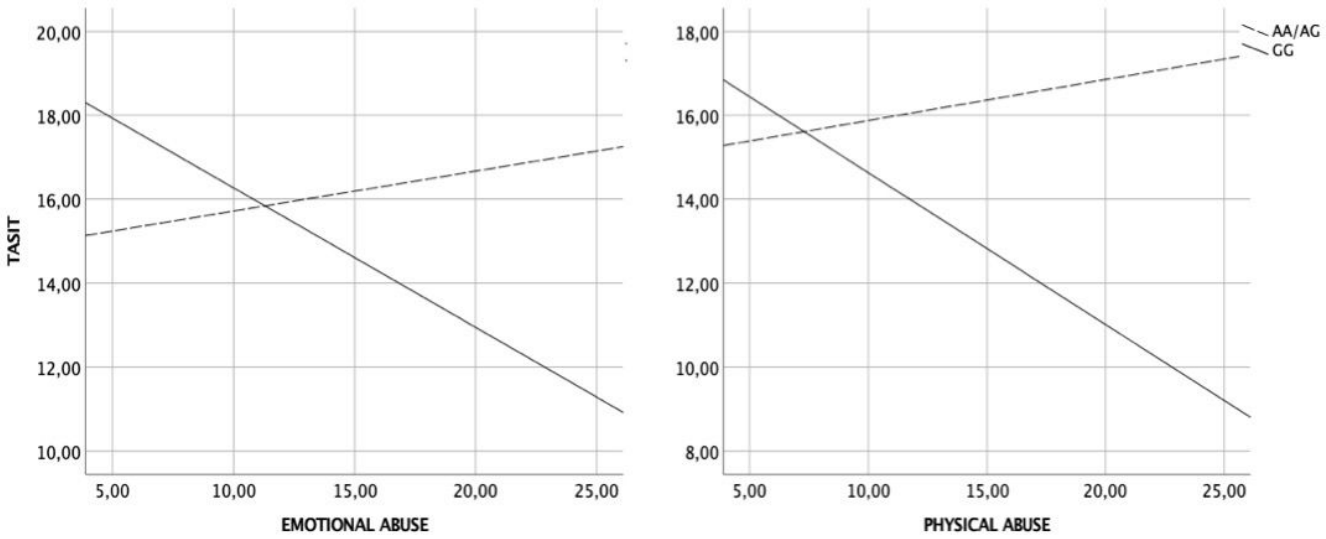


**Figure 1**

GxE and social cognition functioning by specific types of trauma

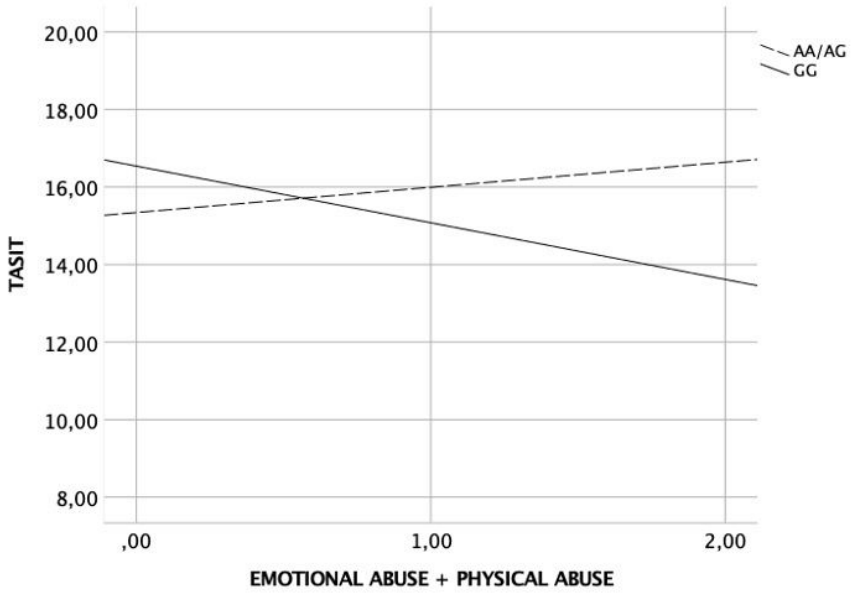


**Figure 2**

GxE and social cognition by sum of traumas

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- DATAARTICLEGXE.xlsx