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The Associations Between Endogenous Oxytocin Levels and Emotion Recognition in Bipolar Disorder

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ABSTRACT:

The associations between endogenous oxytocin levels and emotion recognition in bipolar disorder

Objective: Recent studies in patients with Bipolar Disorder (BD) have revealed problems in emotion recognition, specifically for negative emotions, which have been subsequently related to amygdala activity. Previously, the prosocial neuropeptide oxytocin has been shown to be one hormone that alters emotion perception capacities and modulates amygdala response. Accordingly, the aim of this study was to see if plasma oxytocin levels have specific effects on predicting emotion recognition patterns in BD.

Methods: Twenty-eight remitted BD patients were recruited for this study and the Vienna Emotion Recognition Task was given. In addition, blood samples were collected for plasma oxytocin analysis.

Results: Strong associations were found between fearful emotions and basal oxytocin levels, which were supported by a stepwise regression analysis. Patients with higher levels of basal oxytocin also exhibited greater recognition of fearful emotions.

Conclusions: The relationship between recognition of fearful faces and individual endogenous oxytocin levels may contribute to explaining individual differences in social functioning and amygdala dysfunction in BD.

Keywords: bipolar disorder, oxytocin, face recognition, emotion perception

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INTRODUCTION

Bipolar Disorder (BD) is a disabling chronic mental health disorder defined by manic and depressive episodes and high rates of suicide attempts as a result of emotional dysregulation[1]. A large body of literature has shown that people with bipolar disorder exhibit deficits in emotion recognition (ER)[2] and such deficits may even precede the onset of BD[3]. By and large, most

studies on emotion recognition in BD have revealed a more selective deficit for the recognition of negative emotions, independent of mood episodes. For instance, Lembke et al.[4] found that manic BD patients had deficits in recognizing fearful and angry faces, but not other emotions. They found that patients tended to label fear as surprise, which the authors explained as one possible explanation for aggressive approach behavior throughout the mania. In addition, Getz et al.[5] demonstrated that these deficits in recognizing negative emotions were not related to medication in BD. In 2004, Venn et al.[6] compared euthymic bipolar patients with healthy controls and found less accurate recognition of fearful faces. In another study, Hoertnagl et al.[7] reported that BD patients had deficits in recognizing disgust, anger and happiness in facial expressions. They further demonstrated that patients tend to misidentify emotions as being fearful or angry.

Regarding the cognitive and biological predictors of such deficits, the ER problems in BD have been attributed to the biases of emotional congruency in the past[8]. In other words, studies have argued that the perception of the emotion changes according to the mood stage of the BD patient, due to altered behavioral approach tendencies in these mood swings[9]. However, this proposal is partially flawed due to the demonstrated deficits in emotion recognition at the euthymic stage, and even in people at-risk of developing BD. Following this, several studies have defined BD as the prototypical disorder characterized by the dysregulation of approach behavior (reviewed in[10]). Taken together, our knowledge on the potential mechanism underlying ER deficits in BD is still far from being clear[11]. Today, accumulating evidence has proposed the neuropeptide oxytocin as one possible modulator of emotion recognition in humans, and hence it may play a role in explaining ER deficits of BD patients[12-17].

Recent evidence has revealed a potential neurobiological correlate of impaired emotion recognition in BD, namely the dysfunction of the amygdala[12]. One example identified the amygdala response to emotional faces as a neuronal marker of patients who are vulnerable to develop BD[13]. Studies investigating the modulators of emotion-related amygdala responses in healthy participants have also highlighted the importance of the neuropeptide oxytocin[14], due to its involvement in emotion recognition, and the regulation of stress[15]. In healthy populations, Kirsch et al.[16] demonstrated that intranasal administration of a single dose of oxytocin reduced activation of the amygdala in response to fear-inducing emotions such as anger and fear. With regards to psychiatric populations, it has been reported that oxytocin administration attenuates the amygdala response to fearful and angry faces in patients with social anxiety disorder, but not healthy controls[17].

In regards to the relationship between oxytocin and emotion recognition capabilities, a study by Fischer-Shofty et al.[18] showed an increased recognition of fearful faces after oxytocin administration, and therefore argued that oxytocin administration may initially exert an excitatory effect on the amygdala, which results in an improved recognition of fearful faces. In another study, oxytocin administration decreased the reaction time for correctly identifying fearful facial expressions, and also reduced the misclassification of positive emotions as negative ones[19,20]. It is crucial to note that most of the studies exploring the effects of oxytocin on emotion recognition have been performed with external administration[21], which appears to have similar effects when compared to the effects of endogenous oxytocin[22]. For instance, Goldman et al.[23] found decreased discrimination rates of facial emotions in schizophrenia patients with lower plasma oxytocin levels. Taken together, it is most likely that oxytocin plays some role in the recognition of emotions, which is also tightly linked to the modulation of amygdala activity. These findings may be particularly important for BD patients when the well-replicated findings of amygdala dysfunction and ER deficits are taken into consideration.

Some previous studies also investigated the specific role of the oxytocinergic system in mood

disorders. For example, low serum levels of oxytocin have been demonstrated in patients with BD in comparison to healthy people[24]. Interestingly, another study demonstrated that low oxytocinergic and vasopressinergic activity induced a counter-increase in concentrations of the hypothalamo-pituitary carriers of vasopressin and oxytocin (neurophysins I-II) in the cerebrospinal fluid of BD patients, but not healthy controls[25]. Moreover, postmortem studies underlined an increased number of oxytocin-expressing neurons in the periventricular nucleus in bipolar depression, which was argued to be associated with the chronic activation of the hypothalamic-pituitary-adrenal axis and emotional dysregulation[26].

Accordingly, the aim of this research was to study the role of plasma oxytocin levels in emotion recognition capacities in patients with BD. Our first hypothesis was that the recognition of negative emotions is predicted by endogenous oxytocin levels in BD, and second that individual differences in basal oxytocin levels have differential effects on the recognition of different emotions in BD.

METHODS

Twenty-eight medicated euthymic bipolar-I disorder patients (13 males; mean age: 40.75±11.25; mean duration of illness: 13.39±9.74 years) at symptomatic remission for the last 3 months (Hamilton: 1.18±1.74; Young: 0.61±1.03) were recruited from the Psychiatry Department of Celal Bayar University Hospital. The diagnoses were confirmed by SCID interview. Two of the patients were diagnosed with schizoaffective disorder and were therefore excluded from the study. All patients were medicated and receiving mood stabilizers (35% received lithium; 40% valproate; 20% lamotrigine; 5% second generation antipsychotics with mood stabilizing features i.e. quetiapine). Notably, none of the female patients were receiving oral contraception. All participants gave written consent and the study was approved by the local ethics committee.

Emotion Recognition Test

The Vienna Emotion Recognition Task (VERT-K:[19]) was conducted to evaluate emotion recognition capacities. The VERT-K consists of 36 colored photographs of facial expressions containing an equal proportion of five basic emotions as well as neutral expressions. The test was not validated in the Turkish, but the transcultural relevance of using emotion recognition scales to evaluate emotion perception is well documented in the literature[39]. Patients were instructed to identify the emotion depicted in each photograph from a multiple choice of 6 emotion labels: anger, disgust, fear, happiness, sadness, and neutral, and the final score reflected the accuracy of emotion identification skills.

Plasma Oxytocin Assessment

All blood samples were collected between 11:00 a.m. and 3:00 p.m., because of the peak pulsatile release of oxytocin[38]. Patients were asked to refrain from eating or doing physical exercise 60 minutes before the beginning of the protocol and during the experiment.

To measure basal oxytocin levels, a 5 cm^3 sample of blood was collected at the start of the experiment in an EDTA tube containing aprotinin hormone (EDTA-Aprotinin Tubes, Greiner Bio-One GmbH, Germany), and then centrifuged at 4°C at 4000g for 20 min, after which the plasma was separated into two tubes. Plasma was stored in a freezer at -80°C until the assessment day and assayed in duplicate. For the analyses, considering the debate on the plasma extraction procedure[28], we preferred to use a novel commercially available extraction-free Elisa kit (Bachem S-1355 Oxytocin - EIA Kit, Extraction-free CE-marked) with an incubation period of 24 hours according to the protocol. For human serum or plasma samples, typical sensitivity (Av. IC50) was 0.15 ng/ml with a range of 0-10 ng/ml. The mean plasma oxytocin level of our samples was 327.43±191.62 pg/ml.

Data Analyses

In the preliminary step, we checked the data for assumptions of normality. Due to high variability in plasma oxytocin levels, logarithmic transformation was employed for all analyses. To test our first hypothesis we first performed Pearson correlational analyses and a stepwise regression analysis using the plasma oxytocin levels and the emotion recognition accuracy scores. For evaluating our second hypothesis, we dichotomized the plasma oxytocin levels using the group median, resulting in two groups: a low oxytocin group and a high oxytocin group (summarized in Table 1). A multivariate GLM (MANCOVA) analysis was conducted for controlling the subject-wise errors. We included the oxytocin groups as the fixed factor and the accuracy scores for the emotion recognition task as the dependent variable. Demographic and clinical variables were checked at first to see if there were group differences. The variables with significant group differences were planned to be included as covariates, prior to data analyses. All analyses were done with SPSS (Version 20) data analysis software, and p values ≤0.05 were accepted as significant.

RESULTS

According to the results, we found a significant correlation between emotion recognition accuracy scores and basal oxytocin levels only for fearful faces (r=0.498, p=0.007), but not with other emotions (Neutral: r=-0.111, p=0.57; Disgust: r=-0.236, p=0.23; Anger: r=0.147, p=0.46; Happy: r=-0.145, p=0.46; Sad: r=0.086, p=0.67). Notably, oxytocin levels were not correlated with sociodemographic and clinical variables. The stepwise regression with emotion recognition accuracy scores taken as independent predictors and plasma oxytocin as dependent variable revealed that plasma oxytocin levels were significantly predicted (R^2 adjusted=0.248) by the recognition of fearful faces (Beta=0.022; t=2.92; p=0.007). The scatter plot of the association between plasma oxytocin levels and fearful faces is presented in Figure 1.

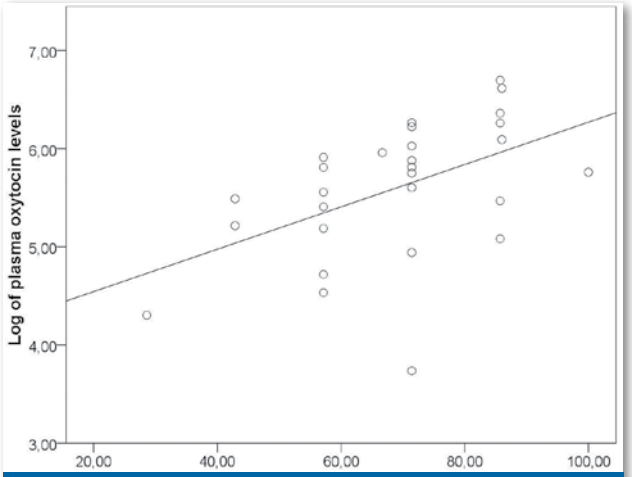

Figure 1: Scatter plot of individual correlations between the plasma oxytocin levels and accuracy of fearful faces
R^2 linear= 0.248

In regards to our second hypothesis, none of the demographic (gender, age) or clinical variables were significantly different between low and high oxytocin groups. In addition, we did not observe significant group differences between the oxytocin levels of male and female patients in both groups. Nevertheless, the group difference on duration of illness was approaching significance (F(1,27)=3.07, p=0.09), showing a longer duration of illness for the high oxytocin group (16.5±11.1 years) when compared to the low oxytocin group (10.29±7.28 years). Therefore, duration of illness was treated as a covariate for the multivariate GLM analyses. Accordingly, there was a statistically significant difference between the low and high oxytocin group on the combined dependent variables (F(6,20)=2.64, p=0.047; Wilks' Lambda=0.55; n_p^2=0.44). When the results for the dependent variables were considered separately, the only group difference to reach statistical significance, using a Bonferroni adjusted alpha level of 0.01, was for the recognition of fearful faces (F(1,25)=6.57, p=0.017, n_p^2=0.20). An inspection of the mean scores (see Table 2) indicated that patients in the high oxytocin group reported higher levels of accuracy on the recognition of fearful faces (M=76.23, SD=12.28) as compared to patients in the low-oxytocin group (M=61.22, SD=16.27).

Table 1: Between-group differences of socio-demographic, clinical and oxytocin data

	Low Oxytocin (n:14)			High Oxytocin (n:14)			
	n	Mean	S.D.	n	Mean	S.D	Sig
Age (Years)		38.14	10.87		11.41	0.23	0.28
Gender							
Male	6			7			0.70
Female	8			7			
Duration of Illness (years)		10.29	7.28		16.50	11.10	0.092
Number of Hospitalization		2.00	1.62		1.85	2.12	0.88
Plasma oxytocin levels (pg/ml.)		180.79	81.27		474.07	152.77	<0.001.

Table 2: Between-group differences of independent variables

	Low Oxytocin (n:14)		High Oxytocin (n:14)			
	Mean	S.D.	Mean	S.D.	F Value (df)	Sig.
VERT-K Neutral	82.14	26.53	58.33	37.41	3.15 (1,25)	0.09
VERT-K Disgust	38.10	23.96	32.56	21.54	0.912 (1,25)	0.35
VERT-K Fear	61.22	16.27	76.23	12.28	6.57 (1,25)	0.02
VERT-K Angry	85.71	22.77	84.29	29.54	<0.001 (1,25)	0.99
VERT-K Sad	75.00	20.41	72.13	17.65	0.003 (1,25)	0.96
VERT-K Happy	93.54	11.61	77.62	31.77	3.04 (1,25)	0.09

VERT-K; The Vienna Emotion Recognition Task

DISCUSSION

The results of the present study demonstrate that endogenous oxytocin levels in BD patients have a selective effect on the recognition of emotional facial expressions, specifically for fear, as opposed to other emotions. Furthermore, there appears to be a subgroup of patients with higher oxytocin levels, who thus have better recognition capacities of fearful faces. Additionally, although not correlated with oxytocin and not significant between groups, the slightly lower accuracy scores in the recognition of neutral pictures in the high oxytocin group may be a suggestion of an increased sensitivity towards emotional cues because this group demonstrated a greater tendency to attribute some emotional valance to the neutral expressions.

Many chronic psychiatric disorders manifest deficits in emotion recognition in which the neurocognitive deficits have been suggested to be one potential cause[29]. However, previous efforts in attempting to explain emotion recognition deficits through neurocognitive impairments in BD have shown mixed results. For example, Addington et al.[30] found that neurocognitive deficits in schizophrenia have successfully predicted emotion recognition deficits, whereas this was not the case for the euthymic bipolar patients in their study. Bozikas et al.[31] found significantly worse recognition of emotions when compared to healthy controls in a group of remitted BD patients, and they also demonstrated that these deficits were not attributed to problems with facial emotion perception per se, but rather to the perception of the relative valence of facial expressions indicating emotions. In another study Getz et al.[5], demonstrated that emotion recognition deficits are mainly based on impairments in perceiving the social cues on the face. They also demonstrated that these deficits are independent from medication and duration of illness.

Findings from previous neuroimaging studies on emotional processing skills and the associated amygdala structure and function in BD may help to explain our findings. It has been consistently reported that BD patients have an increased amygdala response to fear inducing emotional stimuli, when compared to healthy participants[32,33].

However, Yurgelun-Todd et al.[34] found that this higher amygdala activity in BD led to significantly worse recognition of fearful faces in a group of euthymic BD patients. Further to this, oxytocin has been found to have an initial excitatory role and a later regulatory role on amygdala activity, which is selective for fear inducing situations such as recognition of fearful faces in healthy participants[18,21]. Taken together, although speculatively, in light of our findings, and considering the modulating effects of oxytocin on the amygdala, our data suggests that the underlying endocrinological mechanism for amygdala hyperactivity in BD for fearful emotions may be related to individual differences in endogenous oxytocin levels. Furthermore, the BD subgroup with higher oxytocin levels in our sample may have had better recognition for fearful faces because of an intact modulation of the amygdala response through the oxytocinergic system.

The main drawback of this work is the lack of a healthy control group, and therefore we do not have comparable normative data for the oxytocin levels. However, considering the well-replicated amygdala dysfunction in BD and the poorer recognition of fearful faces, our findings on oxytocin may be particularly relevant for patients with BD. In addition, according to previous data on plasma oxytocin levels, it seems likely that the BD subgroup with oxytocin levels above the group average exhibited levels that are were similar to a healthy population[24], therefore indirectly supporting a normative activity of oxytocin for the emotion recognition accuracy. Some studies statistically controlled for the effects of medication on oxytocin by calculating standardized doses; however, there is no such calculation method in BD patients and hence this issue is a general obstacle in controlling the effects of medication in studies with medicated BD patients. Nevertheless, previous studies conducted in other clinical populations did not find such confounding effects of medication over oxytocin levels. Regarding the median-split, it is legitimate to use this approach in cases where the categorized variables represent two different hypothetical in-group differences like our case (i.e. high oxytocin sub-group, low oxytocin sub-group;[35]). Regarding oxytocin measurement, we did not control for the body mass index of the participants, which may be another limitation, as it has been shown to have some influence on oxytocinergic activity[36,37]. In addition, although our time window for collecting blood samples is appropriate for the suggested peak pulsatile rhythm of oxytocin[38], future studies may consider narrowing this time window to improve standardization. Regarding emotions, surprised expressions may often be misidentified as fearful and the VERT-K does not include surprised expressions[39]. It might be interesting for future studies to explore the effects of oxytocin on the recognition of fearful vs. surprised expressions.

To the best of our knowledge, this is the first work to provide preliminary evidence for the potential role of oxytocin in predicting emotion recognition in BD. As a note, our relatively small sample size may not permit us to draw firm conclusions. However, by investigating individual differences in the neuroendocrinology within a population with mood disorders, and specifically the concurrent effects of endogenous oxytocin on emotion recognition, we can gain more insight into subject-wise differences on emotion regulation and social behavior (i.e. 7). Future studies could focus on the therapeutic effects of oxytocin administration on amygdala activity in BD, and whether this may differentially benefit BD patients with lower endogenous oxytocin levels.

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