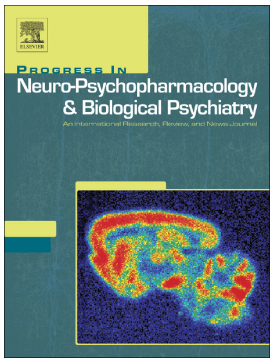

Adverse childhood experiences mediate the negative association between borderline personality disorder symptoms and plasma oxytocin

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Adverse childhood experiences mediate the negative association between borderline personality disorder symptoms and plasma oxytocin

Emilia L. Mielke[a, $], Julian Koenig[b, c, d, $], Sabine C. Herpertz[a], Sylvia Steinmann[e], Corinne Neukel[a], Pelin Kilavuz[c], Patrice Van der Venne[c, g], Katja Bertsch[a, f, $], Michael Kaess[c, d, $]

[a] Department of General Psychiatry, Center for Psychosocial Medicine, Medical Faculty, University of Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany

[b] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Robert-Koch-Straße 10, 50931 Cologne, Germany

[c] Department of Child and Adolescent Psychiatry, Centre of Psychosocial Medicine, Medical Faculty, University of Heidelberg, Blumenstr. 8, 69115 Heidelberg, Germany

[d] University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland

[e] Department of Psychosomatics and Psychotherapeutic Medicine, Central Institute of Mental Health Mannheim, University of Heidelberg, J 5, 68159 Mannheim, Germany

[f] Department of Psychology, Ludwig-Maximilians-University Munich, Leopoldstr. 13, 80802 Munich, Germany

[g] Institute of Psychology, University of Heidelberg, Hauptstr. 47- 51, 69117 Heidelberg, Germany

[$] shared first/last authorship

Corresponding author:

Emilia L. Mielke, M.S.
Department of General Psychiatry, Center for Psychosocial Medicine
Medical Faculty
University of Heidelberg
Voßstraße 4
69115 Heidelberg, Germany
Tel.: +49 6221 - 56 32476
Fax: +49 6221 - 56 5998
Email: Emilia.Mielke@med.uni-heidelberg.de

Abstract

Background: Interpersonal dysfunction is a core symptom of borderline personality disorder (BPD) and may be closely linked to adverse childhood experiences. According to a recent model on the pathology of BPD, the neuropeptide oxytocin might play an important role in the development and maintenance of the disorder. However, so far, only few studies with small adult samples have reported reduced baseline oxytocin levels in BPD that may be linked to adverse childhood experiences.

Methods: We examined baseline plasma oxytocin levels in 131 female patients with BPD and 124 non-BPD female controls across a large age span (12–50 years). Additionally, 113 female patients with less than five DSM-IV BPD features were included to examine the association between plasma oxytocin levels and the number of fulfilled BPD criteria. We also explored associations between plasma oxytocin and adverse childhood experiences as well as depressive symptoms in BPD.

Results: Patients with BPD had reduced plasma oxytocin levels compared to non-BPD controls and this was independent of age. Plasma oxytocin was negatively associated with the number of fulfilled BPD criteria. The exploratory regression model revealed no association between plasma oxytocin and depressive symptoms but an association between plasma oxytocin and adverse childhood experiences, which in fact mediated the relationship between BPD criteria und plasma oxytocin.

Conclusion: In a large sample of individuals with BPD across a large age span, our results replicate and extend previous reports of reduced plasma oxytocin levels that might be related to adverse childhood experiences thus providing further evidence for a prominent role of oxytocin in BPD.

Keywords: trauma, maltreatment, adversity, depression, social cognition

1. Introduction

Borderline personality disorder (BPD) has a prevalence of approximately 2% in the general population and 20% among psychiatric inpatients (American Psychiatric Association, 2013). Due to incremental costs for the health care system, it is considered as one of the most expensive mental disorders (Bode, Vogel, Walker, & Kröger, 2017; Soeteman, Hakkaart-van Roijen, Verheul, & Busschbach, 2008). One of the core symptoms of BPD is interpersonal dysfunction (American Psychiatric Association, 2013). Individuals with BPD are hypersensitive towards interpersonal threats and often respond with either social avoidance or impulsive, aggressive behaviors to feeling threatened, provoked, or rejected (Herpertz & Bertsch, 2014; Salgado, Pedrosa, & Bastos-Leite, 2020). Such behaviors are not only harmful to the individual, but also cause severe problems in the interaction with other people, such as relatives and friends as well as therapists.

In 2015, we have presented a model on the pathology of BPD according to which the neuropeptide oxytocin might play an important role in the development and maintenance of BPD and particularly associated interpersonal dysfunction (Herpertz & Bertsch, 2015). In line with previous models and empirical data, we assume adverse childhood experiences, such as constant invalidation, abuse and neglect, or insecure attachment as important environmental factors potentially shaping the oxytocin system. Across species, interactions between the oxytocin system and early experiences are well documented. Offspring of less sensitive or abusive parents have been found to show lower oxytocin levels in plasma (humans; Opacka-Juffry & Mohiyeddini, 2012) and cerebrospinal fluid (humans; Heim et al., 2009) and a reduced oxytocin receptor density (animals; Baker et al., 2017). Furthermore, oxytocin receptors have been found throughout the rat (Ermisch, Landgraf, & Möbius, 1986; Veinante & Freund-Mercier, 1997) and human (Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013) brain with highest density in brain regions involved in the processing of fear and danger (amygdala) as well as social reward (striatum, cingulate cortex). Together these results have increased the hopes for new treatment options targeting interpersonal dysfunctions.

In fact, a series of studies has reported promising effects of intranasal oxytocin administration to healthy (primarily) male participants who showed reduced amygdala and stress reactivity to threat

and fear cues (Kanat, Heinrichs, Schwarzwald, & Domes, 2015; Kirsch et al., 2005) or enhanced cooperative behavior after receiving oxytocin vs. placebo (Alvares, Hickie, & Guastella, 2010; Berends et al., 2019). Despite a growing inconsistency in study results, there are now also some reports available in individuals with BPD (Jawad, Ahmad, & Hashmi, 2021). Intranasal oxytocin administration was found to reduce threat sensitivity by normalizing fast fixation changes to the eyes of angry faces and amygdala activation in response to angry faces in individuals with BPD (Bertsch, Gamer, et al., 2013). Other studies have shown that intranasal oxytocin administration decreased amygdala and insula reactivity to negative interpersonal stimuli (Lischke, Herpertz, Berger, Domes, & Gamer, 2017), normalized social approach-avoidance behavior (Schneider et al., 2020) and improved affective empathy and approach motivation in patients with BPD (Domes et al., 2019).

Furthermore, there are first reports of reduced baseline oxytocin levels in small samples of adult patients with BPD compared to healthy volunteers (Bertsch, Schmidinger, Neumann, & Herpertz, 2013; Carrasco et al., 2020; Ebert, Edel, Gilbert, & Brüne, 2018; Jobst et al., 2016). Interestingly, these data suggest an association between baseline oxytocin and early adversity, insecure attachment, as well as interpersonal dysfunctions. However, the impact of these studies is limited due to their small sample sizes, their focus on adults with a long duration of illness, and a strict categorical comparison of patients with BPD and healthy controls.

Another factor that might contribute to differences in oxytocin in patients with BPD compared to healthy controls besides adverse childhood experiences are depressive symptoms. Up to 80% of patients with BPD experience at least one episode of major depressive disorder in their life (Rao & Broadbear, 2019; Zanarini et al., 1998). In addition, depression has been associated with lower oxytocin levels (Scantamburlo et al., 2007; Thomas & Larkin, 2019; Thul, Corwin, Carlson, Brennan, & Young, 2020). However, studies on alterations of oxytocin in relation to depressive symptoms in patients with BPD are missing.

To overcome these shortcomings, we investigated baseline plasma oxytocin levels in a large sample of female individuals with BPD (i.e., defined by fulfilling five or more DSM-IV criteria) and non-BPD control women not meeting any BPD DSM-IV criteria aged between 12 and 50 years. We

additionally collected data from individuals with some, but less than five DSM-IV BPD features in order to provide a perspective on the association between oxytocin and the number of fulfilled BPD criteria. Furthermore, adverse childhood experiences and depressive symptoms were assessed using self-reports. To achieve this, unpublished oxytocin data from two independent samples that were all analyzed at the same laboratory were pooled.

Based on previous studies, we expected reduced baseline plasma oxytocin levels in individuals with BPD compared to non-BPD controls. We also expected a negative association between plasma oxytocin and the number of fulfilled BPD criteria. In addition, we wanted to explore the effects of adverse childhood experiences and depressive symptoms beyond BPD symptomatology on plasma oxytocin levels and hypothesized negative associations between oxytocin levels and adverse childhood experiences as well as depressive symptoms.

2. Methods and Materials

2.1. Participants

The sample comprised *N*=131 female patients with a DSM-IV defined diagnosis of BPD (BPD; M_{age}=24.2, *SD*=9.3, range: 13–49 years), *N*=124 non-BPD female control participants without any DSM-IV defined BPD features, (CON; M_{age}=23.1.9, *SD*=9.0, range: 12–50 years), and *N*=113 female control participants with some BPD features who, however, did not fulfill the full diagnosis, i.e. five or more DSM-IV criteria (BPD-FEA; M_{age}=14.7, *SD*=1.5, range: 12–19 years).

Note that *DSM-IV* was used for diagnostic criteria, since the study started before the existence of *DSM-5* which however includes diagnostic criteria for BPD in line with *DSM-IV* (American Psychiatric Association, 2000, 2013). Patients with BPD had to currently fulfill at least five of the nine *DSM-IV* borderline criteria to be allocated to the BPD group. Female patients endorsing between one and four *DSM-IV* borderline criteria were allocated to the BPD-FEA group (BPD features). Patients in the BPD group and the BPD-FEA group had a number of comorbid diagnoses (for a detailed

description see Table 1). Non-BPD female control participants (CON) did not fulfill any DSM-IV borderline criteria and were mostly healthy without any lifetime or current mental disorder diagnoses or psychiatric treatment according to interviews (see 2.2 for details on measures). In *N*=9 adolescents, a current mental disorder other than BPD was found in the interview (MINI-KID; see Table 1). To ensure that this did not affect the current results, analyses were performed with and without non-BPD control participants with a current mental disorder.

Table 1 Mental disorders according to MINI-KID, IPDE and SCID-I interviews in patients with BPD (BPD), non-BPD control participants (CON), and control participants with some BPD features (BPD-FEA)

	BPD *N* = 131				BPD-FEA *N* = 113		CON *N* = 124	
	Current		Lifetime		Current		Current	
	N	%	*N*	%	*N*	%	N	%
Antisocial personality disorder	1	0.8	2	1.5	0	0.0	0	0.0
Avoidant personality disorder	34	26.0	18	13.7	12	10.6	0	0.0
Brief psychotic disorder	0	0.0	1	0.8	0	0.0	0	0.0
Bipolar disorder II	0	0.0	2	1.5	0	0.0	0	0.0
Major depressive episode	24	18.3	62	47.3	0	0.0	0	0.0
Minor depressive episode	20	15.3	0	0.0	56	49.6	4	3.2
Dysthymia	17	13.0	0	0.0	9	8.0	1	0.8
Posttraumatic stress disorder	23	17.6	32	24.4	4	3.5	0	0.0
Body dysmorphic disorder	1	0.8	0	0.0	0	0.0	0	0.0
Somatic symptom disorder	1	0.8	0	0.0	2	1.8	0	0.0
Panic disorder	11	8.4	15	11.5	4	3.5	1	0.8
Agoraphobia with/without panic	11	8.4	2	1.5	9	8.0	1	0.8
Anxiety disorder	1	0.8	0	0.0	4	3.5	0	0.0
Social phobia	37	28.2	31	23.7	20	17.7	0	0.0
Specific phobia	12	9.2	11	8.4	5	4.4	1	0.8
Obsessive-compulsive disorder	7	5.3	7	5.3	2	1.8	0	0.0
Alcohol dependence/abuse	14	10.7	10	7.6	13		0	0.0
Sedative dependence/abuse	0	0.0	3	2.3	0	0.0	0	0.0
Cannabis dependence/abuse	4	3.1	1	0.8	7		0	0.0
Stimulants dependence/abuse	2	1.5	1	0.8	0	0.0	0	0.0
Hallucinogen dependence/abuse	1	0.8	0	0.0	0	0.0	0	0.0
Opioid dependence/abuse	0	0.0	2	1.5	0	0.0	0	0.0
Polysubstance dependence/abuse	1	0.8	4	3.1	2	1.8	0	0.0
Nicotine dependence/abuse	8	6.1	12	9.2	0	0.0	0	0.0
Bulimia nervosa	16	12.2	20	15.3	5	4.4	0	0.0

Anorexia nervosa	4	3.1	15	11.5	8	7.1	0	0.0
Attention deficit and/or hyperactivity disorder	3	2.3	0	0.0	8	7.1	1	0.8
Conduct disorder	16	12.2	0	0.0	17	15.0	1	0.8
Pervasive developmental disorder	0	0.0	0	0.0	0	0.0	1	0.8

There were no lifetime mental disorders in the CON group. Lifetime mental disorders were not formally assessed in the adolescent BPD and BPD-FEA group (AtR!Sk).

Data for the present analyses were pooled from two different studies. In these studies, participants were recruited via advertisements in newspapers and internet, clinical referral from in- and outpatient units, as well as letters sent to randomly selected samples of local inhabitants (healthy volunteers). The first study was a subproject of the Clinical Research Unit 256 (kfo 256; Schmahl et al., 2014) that aims at investigating mechanisms of disturbed emotion processing in BPD (http://www.kfo256.de). Participants, whose data included oxytocin data, were included in the current study. The second study consisted of adolescents (age 12- 17 years) recruited from the specialized outpatient clinic for risk-taking and self-harm behaviour "Ambulanz für Risikoverhalten und Selbstschädigung (AtR!Sk)" (Kaess, Ghinea, Fischer-Waldschmidt, & Resch, 2017) at the Department of Child and Adolescent Psychiatry, University of Heidelberg, as well as adolescent controls. Only participants whose data comprised oxytocin data were included in the current study. Please note, that only the second study with adolescent participants included control participants with some BPD features who, however, did not fulfill the full diagnosis. Therefore, the BPD-FEA group only consisted of adolescent participants. To ensure that this did not affect the current results, analyses were performed with age as a covariate.

Exclusion criteria in the adult sample (kfo-256): Current alcohol or drug abuse (urine toxicology screening), alcohol or drug abuse in the last two months prior to the study or reported alcohol or drug dependence in the last 12 months, use of psychotropic medication in the last two weeks prior to the study, any neurological disorders, severe medical illness, and lifetime diagnosis of schizophrenia or schizoaffective disorder, any endocrine disorder or medical disorder with endocrine implications. Exclusion criteria in the adolescent sample (AtR!Sk): acute psychotic symptoms or lacking German speech comprehension.

The studies were performed in accordance to the ethical standards laid out by the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty of the University of Heidelberg. All participants as well as all caregivers of the adolescent participants gave written consent before their participation after the study procedures were fully explained to them and received a monetary compensation.

2.2 Measures

All participants took part at face-to-face interviews with qualified and trained diagnosticians for the assessment of BPD criteria and axis I diagnoses. Intelligence quotients (IQ), adverse childhood experiences and depressive symptoms were assessed with standardized questionnaires. Please note that different instruments were used in the adult (kfo-256) and the adolescent (AtR!Sk) sample. Reliability and validity have been previously shown for all instruments. Also note that German versions of all instruments were used since the study took part in Germany.

BPD criteria and psychopathology. kfo-256: BPD criteria were assessed with the *International Personality Disorder Examination* (IPDE; Bronisch & Mombour, 1994) for DSM-IV and current and lifetime axis 1 disorders with the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I; First, Spitzer, Gibbon, & Williams, 2002). AtR!Sk: BPD criteria were assessed with the *Structured Clinical Interview for DSM-IV Axis II Personality Disorders* (SCID-II; Wittchen, Zaudig, & Fydrich, 1997) and current and lifetime axis I disorders with the *Mini International Neuropsychiatric Interview for Children and Adolescents* (MINI-KID; Sheehan et al., 1999).

Intelligence Quotient (IQ). kfo-256: the IQ was assessed with *Raven's Standard Progressive Matrices* (SPM; Heller, Kratzmeier, & Lengfelder, 1998). AtR!Sk: the IQ was assessed with the Hamburg Wechsler Intelligence Scale for Children-IV (HAWIK-IV; Petermann & Petermann, 2010).

Adverse childhood experiences. kfo 256: adverse childhood experiences were measured with the *Childhood Trauma Questionnaire* (CTQ; Bernstein et al., 1994), a self-rating questionnaire with

the five subscales emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (Cronbach's α=0.79-0.94 for the different subscales suggesting good to excellent internal consistency). The total CTQ score reflects the sum of all items and thus all subscales. AtR!Sk: adverse childhood experiences were assessed with the *Childhood Experiences of Care and Abuse questionnaire* (CECA.Q; Kaess et al., 2011). The CECA.Q is an adaptation of the CECA interview covering modules for parental care (antipathy and neglect), physical and sexual abuse. For the purpose of this study, we created dimensional scores for each subscale as well as a total score by summarizing all four CECA.Q subscales (Cronbach's α=0.60-0.92 for the different subscales suggesting acceptable to excellent internal consistency).

Depressive symptoms. kfo 256: Current depressive symptoms were assessed with the *Beck Depression Inventory* (BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), a self-report questionnaire asking for depressive symptoms within the past two weeks (Cronbach's α=0.90-0.93 indicating excellent internal consistency). AtR!Sk: Current depressive symptoms were measured with the *Depression Inventory for Children and Adolescents* (DIKJ; Stiensmeier-Pelster, Schürmann, & Duda, 2000), a self-report questionnaire for depressive symptoms (Cronbach's α=0.87-0.92 indicating good to excellent internal consistency).

2.3. Baseline plasma cortisol

In all studies, 5ml blood samples were drawn via venipuncture from the crook of the arm under sterile conditions by trained medical personal. Blood sampling took place at baseline, i.e., before any further tests or interviews were applied. Kfo-256: Blood samples were collected between 12 p.m. and 5 p.m. Participants were instructed to not consume any caffeine or alcohol 24h prior to blood draw and to not eat, smoke, or drink anything but water 2h before blood was taken. AtR!Sk: Fasting blood samples were collected between 8:30 and 9:00 a.m. All blood samples were subsequently sent to the central laboratories of the Heidelberg University Hospital for further analyses.

Oxytocin. Blood was drawn into EDTA vacutainer tubes, which were immediately cooled in ice-chilled water at 4 °C. The samples were then centrifuged at 4 °C at 4000 rpm for 5 min, aliquoted and stored at −20 °C. Plasma samples were sent on dry ice to the central laboratories of the Heidelberg University Hospital, where they were analyzed using an enzyme-linked immunosorbent assay (ELISA) by Cloud Clone (Houston, TX, US) according to the protocol of the manufacturer. The assay detection limit was 12.35 pg/ml with a minimum detectable dose of less than 4.99 pg/ml. There was no significant cross-reactivity with other related neuropeptides. The intra-assay coefficient of variation was <10% and the inter-assay coefficient of variation was <12%.

Estradiol. To control for potential effects of the menstrual cycle, blood was collected in heparin-plasma vacutainer tubes and analyzed for plasma estradiol levels using chemiluminescence immunoassays (ACS:180® Estradiol-6 II-test from Bayer Diagnostics, Germany). The assay detection limit was 10.0 pg/ml. The cross-reactivity with other related compounds was minimal. The intra-assay coefficient of variation was <6% and the inter-assay coefficient of variation was <7%.

2.4. Statistical analyses

Data processing and preliminary analyses. Less than 5% of values were missing across all variables. Data was first checked for violations of the assumption of normality and statistical outliers, which were defined as any values three times the interquartile range (3xIQR) above the third quartile (Q3) or below the first quartile (Q1). This revealed *N*=1 (0.27%) outlier in oxytocin data and *N*=6 (1.63%) outliers in estradiol data. However, estradiol levels were all within the normal range provided by the analyzing laboratory. The assumption of normality was only violated for estradiol data. After the exclusion of outliers, there were no violations of the assumption of normality. To ensure that these violations did not affect the current results, analyses were performed with and without outliers.

Demographic and questionnaire data of the BPD group, the BPD-FEA group, and the non-BPD control group were compared with analyses of variance (ANOVAs; IBM SPSS version 22.0). In cases of significant effects in the ANOVA, we used the Tukey's HSD test in case of variance

homogeneity and the Games-Howell test in case of variance inhomogeneity as post-hoc tests. Since adverse childhood experiences and depressive symptoms were assessed with different instruments in kfo-256 and AtR!Sk, data was first standardized within the samples (see above) using z-transformation and then pooled for group comparison and regression analyses.

Main analyses. Group differences in plasma oxytocin levels were analyzed with an analysis of covariance (ANCOVA) with the between subject-factor "group" (BPD, BPD-FEA, CON) and the covariates of no interest, "estradiol" (to control for possible effects of menstrual cycle) and "age". For the ANCOVA, we used Bonferroni-corrected post-hoc analysis in case of significant effects.

Next, a multiple linear regression was calculated to first assess the association between plasma oxytocin and BPD criteria controlled for estradiol and age. In a second block, multiple regression analysis was used to assess the effects of adverse childhood experiences and depressive symptoms beyond BPD symptomatology on plasma oxytocin levels. More specifically, a forced entry regression approach was used including two blocks. First, BPD criteria, age and plasma estradiol were used as independent variables. In the second block, BPD criteria, age, plasma estradiol levels, adverse childhood experiences as well as depressive symptoms were used as independent variables to assess additional effects of the latter two variables.

Finally, we performed exploratory mediation analyses to ascertain whether differences in adverse childhood experiences (mediator, M) accounted for the link between BPD criteria (independent variable, IV) and plasma oxytocin levels (dependent variable DV). Estradiol and age were used as covariates of no interest. We used the PROCESS macro by Hayes, which uses ordinary least squares regression, yielding unstandardized path coefficients for total, direct, and indirect effects (Hayes, 2018). To calculate the 95% confidence intervals (CI) for the indirect effect and inferential statistics, bootstrapping with 20000 samples was used (Davidson & MacKinnon, 1993).

We employed a two-tailed $p<.05$ for all statistical analyses. As a measure of effect size, partial eta squared (η_p^2) is reported. For a more accurate graphical presentation of the results, we calculated unstandardized residuals of plasma oxytocin without the influence of the covariates estradiol and age

by computing a linear regression model with plasma oxytocin as the dependent variable and the covariates as independent variables, and saving the unstandardized residuals as a new variable.

3. Results

Preliminary analyses. Details on demographic data can be found in Table 1. There was a significant group difference in age ($F(2,360)=54.35$, $p<.001$, $\eta_p^2=.23$, variance homogeneity could not be assumed; see Table 2). On average, the BPD-FEA group was significantly younger than the BPD group ($p<.001$) and the CON group ($p<.001$), while the BPD and CON group did not differ in age ($p=.589$). There was a significant group difference in the Intelligence Quotient (IQ) ($F(2,357)=15.74$, $p<.001$, $\eta_p^2=.08$; see Table 2). On average, the CON group had a significantly higher IQ than the BPD group ($p=.002$) and the BPD-FEA group ($p<.001$), while the BPD and BPD-FEA group did only differ on a trend level ($p=.055$). Significant group differences were also found with regard to the number of BPD criteria ($F(2,363)=1605.38$, $p<.001$, $\eta_p^2=.90$, variance homogeneity could not be assumed; see Table 2), self-reported adverse childhood experiences ($F(2,322)=71.18$, $p<.001$, $\eta_p^2=.31$, variance homogeneity could not be assumed; see Table 2), and depressive symptoms ($F(2,332)=175.90$, $p<.001$, $\eta_p^2=.51$, variance homogeneity could not be assumed; see Table 2). In all three measures, the BPD group had significantly higher scores than the BPD-FEA group ($p<.001$) and the CON group ($p<.001$) and the latter had lower scores than the BPD-FEA group ($p<.001$). Importantly, plasma estradiol levels did not differ between groups ($F(2,356)=1.20$, $p=.303$, $\eta_p^2=.007$). Results remained the same, when non-BPD control participants (CON) with a current mental disorder and outliers (see 2.1. & 2.4.) were excluded from the analyses (see supplemental material for details).

Table 2 Demographic, psychometric and endocrine data

	Group			Group comparison		
	BPD (N = 131)	BPD-FEA (N =	CON (N = 124)			η_p^2
	$M \pm SD$		$M \pm SD$	F	p	

		113) *M* ± *SD*				
Age	24.21 ± 9.29	14.67 ± 1.53	23.07 ± 9.02	54.35	<.001	.232
IQ	106.30 ± 12.46	102.67 ± 12.37	111.50 ± 11.42	15.74	<.001	.081
DSM-IV Borderline criteria	6.22 ± 1.11	2.29 ± 1.07	0.00 ± 0.00	1605.38	<.001	.898
Adverse childhood experiences	0.65 ± 0.97	0.01 ± 0.90	-0.63 ± 0.28	71.18	<.001	.307
Depressive symptoms	0.71 ± 0.76	0.26 ± 0.76	-0.95 ± 0.56	175.90	<.001	.514
Plasma oxytocin (pg/ml)	201.94 ± 148.05	144.78 ± 144.74	255.26 ± 143.12	16.46	<.001	.033
Plasma estradiol (pg/ml)	73.70 ± 63.69	85.88 ± 86.38	72.35 ± 66.96	1,20	.303	.007

Main analyses.

Is BPD associated with reduced plasma oxytocin levels? The ANCOVA revealed a significant group effect in plasma oxytocin levels controlled for both plasma estradiol and age ($F(2,349)=10.75$, $p<.001$, $\eta_p^2=.06$; see Figure 1). According to post-hoc tests, the CON group had significantly higher plasma oxytocin levels than both the BPD group ($p=.003$) and the BPD-FEA group ($p<.001$), while the BPD group and the BPD-FEA group did not differ significantly in their plasma oxytocin levels ($p=.466$).

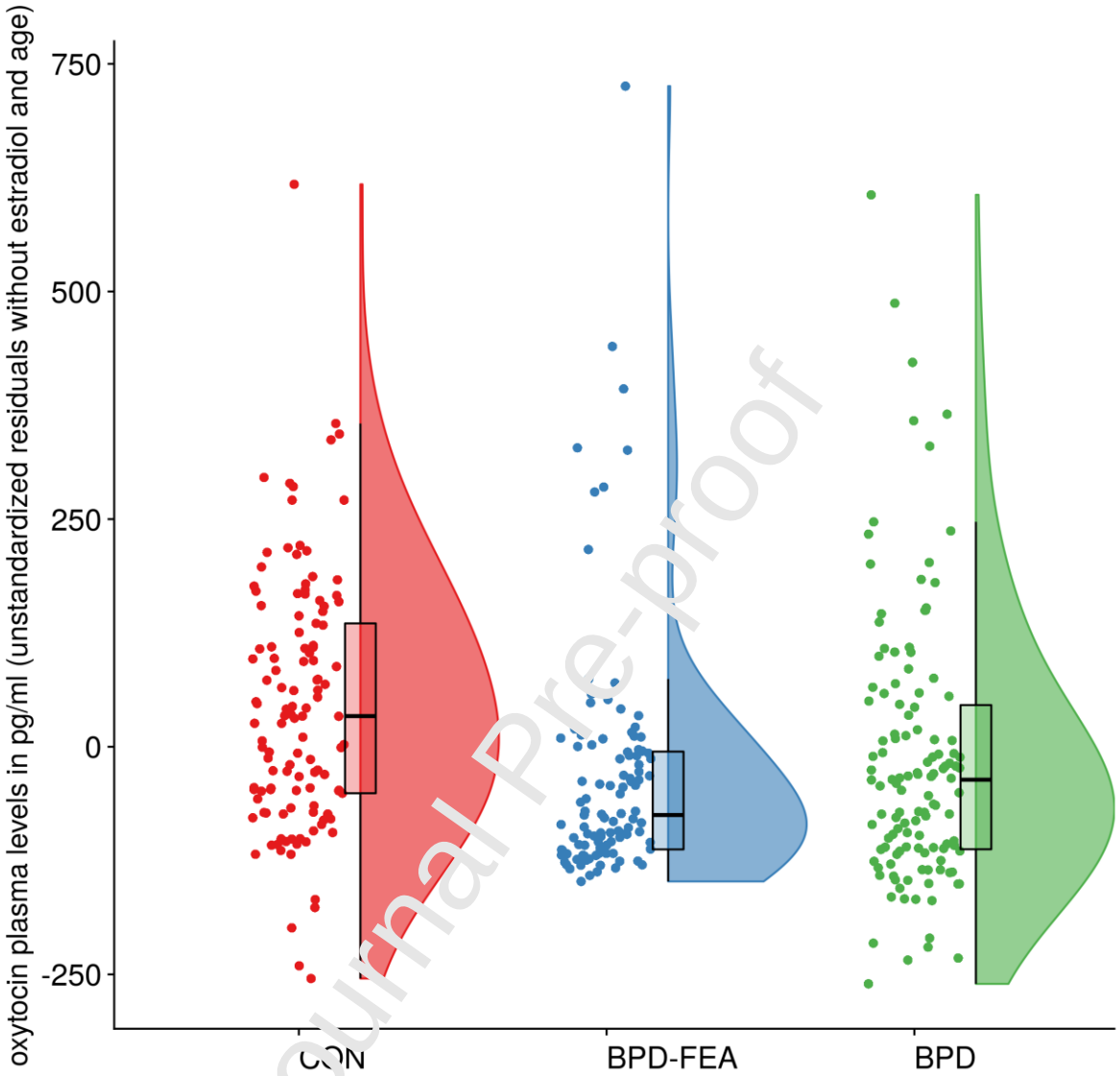

Figure 1: Significant group effect in plasma oxytocin levels independent of plasma estradiol and age ($F(2,349)=10.75$, $p<.001$, $\eta_p^2=.06$) with lower plasma oxytocin levels in female patients with Borderline personality disorder (BPD, $N=131$) and female control participants with some BPD features (BPD-FEA, $N=113$) compared to female non-BPD controls (CON, $N=124$).

A multiple linear regression was calculated to predict plasma oxytocin levels based on BPD criteria, age and estradiol. A significant regression equation was found ($F(3,309)=13.37$, $p<.001$, $R^2=.12$, $R^2_{Adjusted}=.11$). Participants' predicted plasma oxytocin level was equal to 128.18 – 9.26 (BPD-

criteria) + 5.74 (age) – 0.18 (estradiol). BPD criteria (β=-.17, p=.002) and age (β=.32, p<.001) were significant predictors of oxytocin plasma levels, whereas estradiol was not significant as a predictor of oxytocin plasma levels (β=-.09, p=.100; see Table 3). Participants' plasma oxytocin levels decreased 9.26 pg/ml for each additional fulfilled BPD criterium and increased 5.74 pg/ml for every year of life.

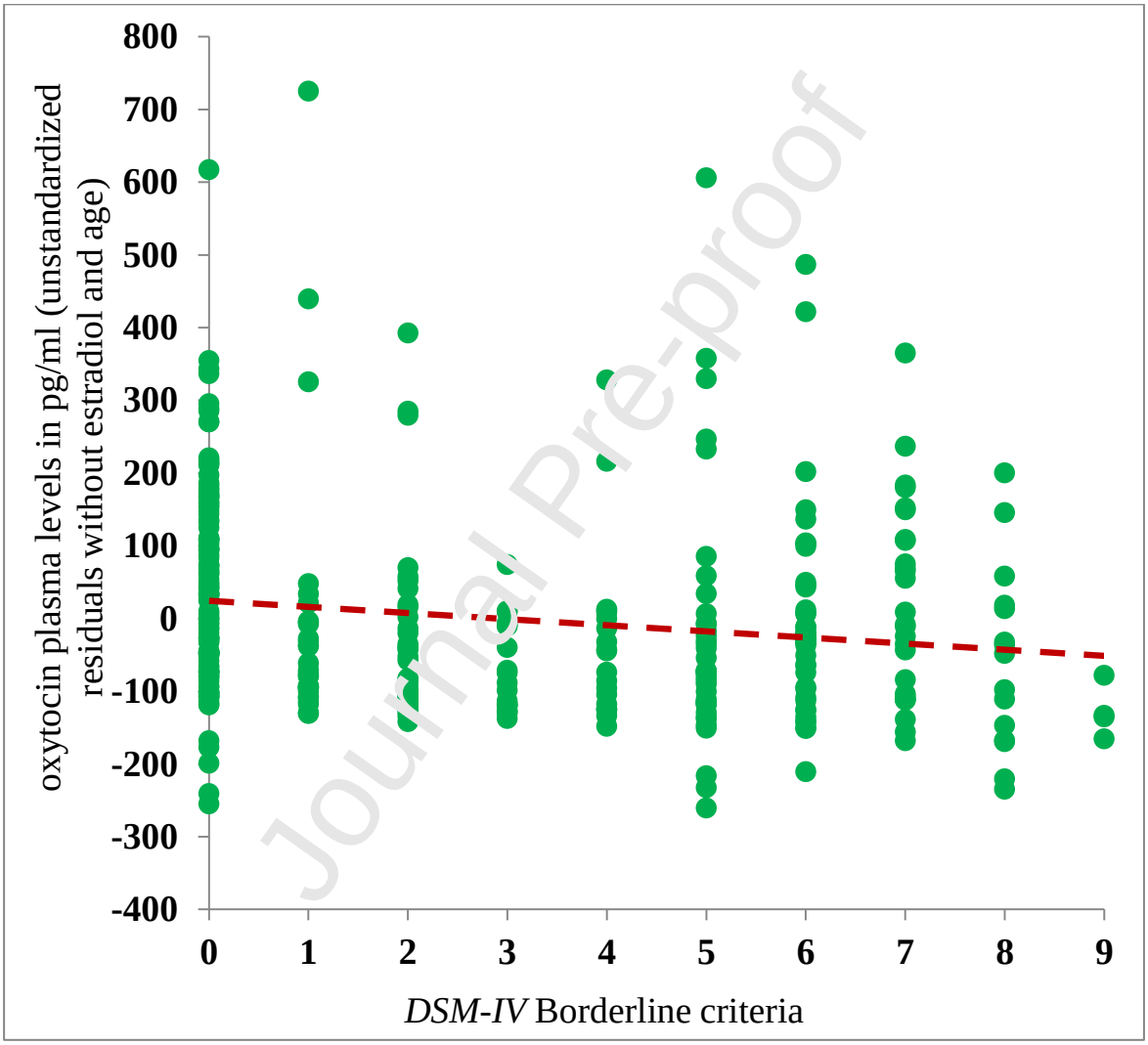

Figure 2: Negative association between plasma oxytocin levels and the numbers of Borderline personality disorder criteria controlled for estradiol and age (β=-.17, p=.002) across all three groups (N=368).

Do adverse childhood experiences and depressive symptoms explain variance in oxytocin plasma levels beyond BPD? In the second block of the multiple linear regression model adverse childhood experiences and depressive symptoms were added as independent variables to predict plasma oxytocin levels in addition to BPD criteria, age and estradiol. A significant regression equation was found ($F(5,307)=9.74$, $p<.001$, $R^2=.14$, $R^2_{Adjusted}=.12$). Participants' predicted oxytocin plasma level was equal to 104.93 – 1.47 (BPD-criteria) + 5.59 (age) – 0.14 (estradiol) – 21.94 (adverse childhood experiences) – 14.32 (depressive symptoms). Adverse childhood experiences ($\beta=-.14$, $p=.032$) and age ($\beta=.31$, $p<.001$) were significant predictors of plasma oxytocin levels, whereas depressive symptoms ($\beta=-.09$, $p=.206$) and estradiol ($\beta=-.07$, $p=.220$; see Table 3) were not significant as predictors of plasma oxytocin levels. Interestingly, after adding adverse childhood experiences and depressive symptoms to the model, BPD criteria was no longer a significant predictor of plasma oxytocin levels ($\beta=-.03$, $p=.730$; see Table 3). Participants' oxytocin plasma levels decreased 21.94 pg/ml for each score on the standardized scale of adverse childhood experiences (see 2.4. for details) and increased 5.59 pg/ml for every year of life. When non-BPD control participants (CON) with a current mental disorder and outliers were excluded from the analysis (see 2.1. & 2.4.), adverse childhood experiences turned into a non-significant trend predictor for oxytocin plasma levels ($\beta=-.13$, $p=.060$) (see supplemental material for details).

Table 3 Exploratory multiple regression analysis

		B	SE B	β	*p*	VIF
Step 1						
	Constant	128.18	23.15		<.001	
	BPD	-9.26	3.03	-.168	.002	1.05
	Age	5.74	0.98	.322	<.001	1.05
	Estradiol	-0.18	0.11	-.088	.100	1.00
Step 2						
	Constant	104.93	24.40		<.001	
	BPD	-1.47	4.26	-.027	.730	2.12
	Age	5.59	0.98	.314	<.001	1.07

Estradiol	-0.14	0.11	-.066	.220	1.03
Adverse childhood experiences	-21.94	10.21	-.142	.032	1.56
Depressive symptoms	-14.32	11.31	-.093	.206	1.91

Note: R^2=.12 for Step 1, ΔR^2=.02 for Step 2 (p=.021).

A simple exploratory mediation was performed to analyze whether the association between BPD criteria and plasma oxytocin levels seen in the multiple regression analysis (direct path) would be mediated by adverse childhood experiences. An effect of BPD criteria on plasma oxytocin levels was observed (B=-9.40, p=.002). After entering the mediator "adverse childhood experiences" into the model, BPD criteria predicted the mediator significantly (B=0.20, p<.001), which in turn predicted plasma oxytocin levels significantly (B=-24.70, p=.013). We found that the relationship between BPD criteria and plasma oxytocin levels was fully mediated by adverse childhood experiences (indirect effect ab=-4.85, 95%-CI[-8.31, -1.80]). Results remained the same, when non-BPD control participants (CON) with a current mental disorder and outliers (see 2.1. & 2.4.) were excluded from the analyses (see supplemental material for details).

4. Discussion

Replicating and extending previous findings, the current study revealed reduced plasma oxytocin levels in a large sample of female individuals with BPD (features) compared to non-BPD female controls across a large age span. Since we not only included a large sample of individuals with a DSM-IV BPD diagnosis, but also a sample of individuals with BPD features below the categorical threshold, we were able to show a negative association between plasma oxytocin levels and the number of fulfilled BPD symptoms for the first time. Furthermore, plasma oxytocin was related to adverse childhood experiences which in fact fully mediated the association between BPD criteria and plasma oxytocin thus providing support for a possible role of oxytocin in the interplay between childhood adversity and BPD.

First and most importantly, the findings of reduced plasma oxytocin levels in individuals with BPD compared to non-BPD controls confirm our a priori hypothesis. In addition, the findings replicate

and extend our previous results in an albeit smaller and adults-only sample (Bertsch, Schmidinger, et al., 2013). The results further support a recent model on the pathology of BPD according to which alterations in the oxytocin system play an important role in the development and maintenance of the disorder. In addition, oxytonergic dysregulation in BPD might explain interpersonal dysfunctions, such as threat hypersensitivity, social avoidance or aggressive outbursts according to this model (Herpertz & Bertsch, 2015). Two further important aspects should be considered: first, a different detection method for oxytocin was used in another laboratory in the current compared to our previous study (Bertsch, Schmidinger, et al., 2013), demonstrating the robustness of the effect independent of analytical procedures. More specific, while a sensitive radioimmunoassay (Landgraf, Neumann, Holsboer, & Pittman, 1995) was used in our previous study (Bertsch, Schmidinger, et al., 2013), we used an enzyme-linked immunosorbent assay (ELISA, see 2.3.) in the current study. Second, our sample consisted of female participants with a wide and heterogeneous age range (12 to 50 years). While our analyses suggested an association between plasma oxytocin levels and age, the association between BPD criteria and oxytocin levels was independent of age. To our knowledge, this is the first study investigating plasma oxytocin levels in individuals with BPD including adolescent participants and therefore a wide age range. Results suggest early oxytonergic dysregulation – not only in adult patients with BPD, but also in adolescent individuals with BPD. This raises the question of cause and effect: Does BPD lead to oxytonergic dysregulation or does oxytonergic dysregulation lead to the development of BPD?

Oxytocin is known for its crucial role in social cognition and behavior, including attachment, trust, emotion recognition, theory of mind, and affiliation (Ishak, Kahloon, & Fakhry, 2011; Lee, Macbeth, Pagani, & Young, 2009). Oxytocin release reduces stress, anxiety, and amygdala activity and might therefore also reduce defensive behavior and at the same time enable prosocial behavior (Campbell, 2010; Carter, 1998; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Individuals with BPD show hyperactivity of the amygdala and heightened stress responses in social interactions, which can lead to interpersonal dysfunction (Bertsch, Hillmann, & Herpertz, 2018; Drews, Fertuck, Koenig, Kaess, & Arntz, 2019). Dysregulation in the oxytonergic system might be one factor contributing to these interpersonal deficits of individuals with BPD. In fact, oxytocin has been

proposed as a novel target for pharmacotherapy (Ripoll, Triebwasser, & Siever, 2011). There are first reports of beneficial effects of intranasal oxytocin administration on social information processing and social behavior in patients with BPD (Brüne et al., 2013; Domes et al., 2019; Schneider et al., 2020). However, other studies could not find such effects (Bartz et al., 2011; Brüne, Kolb, Ebert, Roser, & Edel, 2015; Ebert et al., 2013), which might be at least partly due to small sample sizes or varying oxytocin dosages. Mixed results could however also suggest that more factors might be involved in reduced plasma oxytocin levels and beneficial effects of intranasal oxytocin in patients with BPD. Identifying specific factors associated with BPD and reduced oxytocin plasma levels in patients with BPD could help to identify patients, for whom oxytocin might be a beneficial treatment option.

One such factor could be adverse childhood experiences. Previous reports already suggested lower plasma oxytocin levels in individuals reporting high levels of adverse childhood experiences (Bertsch, Schmidinger, et al., 2013) or insecure attachment (Jobst et al., 2016). In line with these results and our a priori hypothesis, we found a negative association between plasma oxytocin and adverse childhood experiences in the current study. It has been previously suggested that dysregulation in the oxytonergic system following traumatization might be connected to psychopathology (Herpertz & Bertsch, 2015). Moreover, resilience might be considered as a protective factor against oxytonergic dysregulation (Li, Hassett, & Seng, 2019; Mielke et al., 2018). In the current study, the exploratory mediation analysis showed that adverse childhood experiences fully mediated the association between BPD criteria and plasma oxytocin. Therefore, childhood adversity might be one major factor contributing to oxytonergic dysregulation in individuals with BPD. This is an important result, since adverse childhood experiences are known as the most important environmental risk factor for BPD (Solmi et al., 2021). Patients with BPD often report constant invalidation, neglect, or abuse by primary caregivers (Porter et al., 2020). Together with a biological vulnerability, this has been regarded as an important developmental factor for BPD (Fatimah et al., 2020; Mainali, Rai, & Rutkofsky, 2020). The current results suggest that alterations in the oxytocin system in patients with BPD might be a consequence of adverse childhood experiences, although longitudinal studies are needed to fully unravel these temporal associations. In any way, the current

results provide further support for an important role of the oxytocin system in patients with BPD (Herpertz & Bertsch, 2015).

Contrary to our hypothesis, oxytocin levels were not related to depressive symptoms in BPD. This is not in line with previous reports of lower plasma oxytocin plasma levels in depressed patients (Scantamburlo et al., 2007; Thomas & Larkin, 2019). However, it has been previously discussed that dysregulations in the oxytonergic system might not be associated to depression per se, but rather to specific symptoms of depression. In fact, Thomas and Larkin (2019) showed, that plasma oxytocin levels were negatively associated with negative thinking in depressed patients. With regard to the current findings, the insignificant association between oxytocin plasma and depressive symptoms underlines the notion that reduced oxytocin levels in BPD may not be explained by depressive symptoms which are oftentimes found in these individuals.

Beside these main results, a positive association between plasma oxytocin levels and age should be mentioned. This association also explained why the control group with BPD features had the lowest oxytocin plasma levels. This group only consisted of adolescent participants, who had significantly lower oxytocin levels due to the association between plasma oxytocin levels and age. Future studies should also include adult participants with BPD features. Although age-related changes in the oxytonergic system have been proposed (Ebner, Maura, Macdonald, Westberg, & Fischer, 2013), the literature remains scarce, inconclusive, and is dominated by animal studies. While some studies have found no differences in plasma oxytocin levels between younger and older rats (Melis, Stancampiano, Fratta, & Argiolas, 1992; Zbuzek, Fuchs, Zbuzek, & Wu, 1988), other studies have found a decrease (Elabd et al., 2014) or an increase in oxytocin plasma levels from puberty to older age in rats and mice (Fliers & Swaab, 1983; Keck et al., 2000). For humans, there are even less studies. One study in humans found no age-related changes in plasma oxytocin in both males and females (Plasencia, Luedicke, Nazarloo, Carter, & Ebner, 2019). However, the older subjects were aged 63–81 and therefore likely postmenopausal with menopause known as an independent negative predictor of plasma oxytocin (Maestrini et al., 2018). Participants in the current study were female and aged between 12 and 50 years. We did not measure Tanner stages in the adolescents as a measure of

puberty or menopause in older adults. However, we added estradiol as a covariate of no interest in all analyses to control for potential effects of the concentration of sex hormones. To our knowledge this is the first study showing an association between plasma oxytocin levels and age in humans in a dimensional approach. Still, results need to be replicated in large non-clinical human samples with a more detailed history and assessment of puberty and (peri-)menopause.

Several advantages of the current study have already been mentioned including the large sample size and wide age range as well as inclusion of a group of individuals with BPD features below the diagnostic cutoff. Nevertheless, some limitations should be noted. First, only female participants were included in the current study and results cannot be generalized to men. Sex differences in BPD symptom expression (Hoertel, Peyre, Wall, Limosin, & Blanco, 2014) and plasma oxytocin levels (Marazziti et al., 2019) have been reported. Therefore, future studies will have to extend the current findings to male participants. Second, for reasons of ethics and practicability, we measured oxytocin in the blood and not in the cerebrospinal fluid (CSF). The link between plasma oxytocin levels, central nervous system neuropeptide function and behavior is complex and remains unclear (Meyer-Lindenberg et al., 2011; Valstad et al., 2017). Future studies will have to examine oxytocin levels in CSF as well as plasma in patients with BPD. Third, the current results are based on data from different studies. Therefore, adverse childhood experiences and depressive symptoms were assessed with different age-appropriate instruments. We used standardization to increase comparability. In addition, the BPD-FEA group only consisted of adolescent participants. To ensure that this did not affect the results, analyses were performed with age as a covariate. However, results should be replicated in a coherent study. Fourth, as the reported results are based on cross-sectional data reduced basal concentrations of oxytocin might represent evidence for oxytonergic dysregulation, but could also reflect altered behavior or experience in patients with BPD, such as reduced social interaction. Future studies should investigate dynamic changes of evoked oxytocin release in response to stress or social interaction. Fifth, we relied on participants to follow certain instructions (fasting etc. – see. 2.3. for details) before blood was taken, as oxytocin levels are known to be influenced by factors such as food intake (Onaka & Takayanagi, 2019). As the study sample included participants with BPD and BPD

features, we cannot be certain instructions were followed by all of the participants. However, due to the large sample size and our outlier analysis analyses should be robust.

4.1 Conclusion

Taken together, the current study revealed reduced plasma oxytocin levels in female individuals with BPD compared to non-BPD controls and a negative relationship between plasma oxytocin levels and BPD criteria as well as adverse childhood experiences, which in fact mediated the relationship between BPD criteria und plasma oxytocin levels. The results thus replicate and extend previous findings in a large, independent, and age heterogeneous sample using a different method for oxytocin detection. In addition, the current study revealed that plasma oxytocin reductions in BPD were independent of age and strengthen the notion that oxytonergic dysregulation might be an important factor in the interplay between early adversity and the development of BPD and could thus be a potential target for therapeutic interventions.

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Conflict of interest: none.

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AuthorStatement

Emilia L. Mielke: Formal analysis, Writing - Original Draft, Visualization **Julian Koenig:** Conceptualization, Methodology, Validation, Writing - Review & Editing **Sabine C. Herpertz:** Conceptualization, Methodology, Validation, Writing - Review & Editing, Funding acquisition **Sylvia Steinmann:** Investigation, Data Curation **Corinne Neukel:** Investigation, Data Curation, Writing - Review & Editing **Pelin Kilavuz:** Investigation, Data Curation **Patrice Van der Venne:** Investigation, Data Curation **Katja Bertsch:** Conceptualization, Methodology, Validation, Writing - Review & Editing, Funding acquisition **Michael Kaess:** Conceptualization, Methodology, Validation, Writing - Review & Editing, Funding acquisition

Conflict of interest: none.

Ethical Statement

The studies were performed in accordance to the ethical standards laid out by the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty of the University of Heidelberg. All participants as well as all caregivers of the adolescent participants gave written consent before their participation after the study procedures were fully explained to them and received a monetary compensation.

Highlights

- patients with BPD show reduced plasma oxytocin levels compared to non-BPD controls
- oxytocin is negatively associated with BPD criteria and adverse childhood experiences
- adverse childhood experiences mediated the association between oxytocin and BPD criteria
- oxytocin levels are not related to depressive symptoms in BPD
- plasma oxytocin levels are positively associated with age