Psychoneuroendocrinology 113 (2020) 104541

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Serum oxytocin levels are elevated in body dysmorphic disorder and related to severity of psychopathology

Angela Fang[a,*], Ryan J. Jacoby[a], Clare Beatty[a], Laura Germine[b], Franziska Plessow[c], Sabine Wilhelm[a], Elizabeth A. Lawson[c]

[a] OCD and Related Disorders Program, Massachusetts General Hospital and Harvard Medical School, United States
[b] Institute for Technology in Psychiatry, McLean Hospital and Harvard Medical School, United States
[c] Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, United States

ARTICLE INFO

Keywords:
Oxytocin
Serum
Secretion
Body dysmorphic disorder
Psychopathology
Social cognition

ABSTRACT

The neurobiological mechanisms underlying the pathophysiology of body dysmorphic disorder (BDD) are not well-understood. Oxytocin is a central nervous system peptide which regulates socioemotional functioning and may mediate physiologic processes in a range of psychiatric disorders, particularly those characterized by interpersonal dysfunction. Examining the role of oxytocin in the development and maintenance of BDD may elucidate new targets for intervention. The present study examined endogenous serum oxytocin levels in BDD. Given the prominent deficits in social functioning in BDD, we expected that BDD would be characterized by low basal serum oxytocin concentrations, relative to healthy controls, and that low oxytocin levels would be associated with BDD symptom severity as well as poor performance on measures of social cognition. Twenty individuals with BDD and 28 healthy controls completed a fasting blood draw consisting of frequent sampling every five minutes for one hour to measure pooled levels of oxytocin. Contrary to our hypotheses, people with BDD displayed higher concentrations of oxytocin, compared to their healthy control counterparts, and their oxytocin levels were positively correlated with BDD symptom severity. There were no associations between oxytocin levels and measures of social cognition. These findings suggest increased production of endogenous oxytocin in BDD. Prospective research is needed to determine whether this contributes to or is a consequence of BDD symptomatology.

1. Introduction

Body dysmorphic disorder (BDD) is an obsessive-compulsive related disorder affecting approximately 1.7–2.4 % of the general population (Buhlmann et al., 2010; Koran et al., 2008; Rief et al., 2006). BDD often causes severe disability, such that many patients stop working, drop out of school, and even become housebound due to appearance-related concerns (Didie et al., 2008; Phillips et al., 2005b, c). Estimates suggest that between 24–28 % of patients with BDD attempt suicide in their lifetime (Phillips et al., 2005a; Phillips, 2007). Despite its prevalence and impairment, little is known about neuroendocrine contributions to BDD. This is a major unexamined gap in the literature, as it has important implications for advancing the discovery of markers of BDD illness and illness progression, as well as the identification of new targets for intervention.

Accumulating evidence suggests that the neurohormone oxytocin mediates physiologic processes in a range of psychiatric illnesses, particularly those characterized by social impairment (Bakermans-Kranenburg and van Ijzendoorn, 2013; Neumann and Slattery, 2016). Oxytocin is a nine amino acid peptide that is produced in specialized cells of the hypothalamus and has diverse effects throughout the brain via paracrine and synaptic release mechanisms, and throughout the body via release from the posterior pituitary gland into the peripheral circulation (Dölen, 2015). Central release and peripheral secretion may occur simultaneously or independently depending on the behavioral context and stimuli that trigger release (Neumann and Landgraf, 2012). As a neuromodulator, oxytocin plays a role in the regulation of socioemotional functioning (Leppanen et al., 2017) and has antidepressant and anxiolytic effects in animal models and human studies (Labuschagne et al., 2010; Neumann and Slattery, 2016; Scantamburlo et al., 2007). In people with BDD, experimental studies have demonstrated that intranasal administration of oxytocin may alter certain

* Corresponding author at: Massachusetts General Hospital, Harvard Medical School, Department of Psychiatry, OCD and Related Disorders Program, 185 Cambridge Street, Suite 2000, Boston, MA 02114, United States.
E-mail address: afang@mgh.harvard.edu (A. Fang).

https://doi.org/10.1016/j.psyneuen.2019.104541
Received 20 September 2019; Received in revised form 2 December 2019; Accepted 3 December 2019
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higher-order attributional biases (Fang et al., 2019) and resting state functional connectivity between brain regions involved in visual processing (Grace et al., 2019), which suggests that oxytocin may play a role in the pathophysiology of BDD. Oxytocin has also been implicated as a candidate biomarker of certain psychiatric disorders associated with BDD, such as psychosis, depression, anxiety disorders, and eating disorders, although the evidence has been mixed (Rutigliano et al., 2016). For example, in social anxiety disorder (which shares significant overlap with BDD in terms of social avoidance; Fang and Hofmann, 2010), plasma oxytocin levels were lower than controls when measured after the "Trust Game," a neuroeconomic test examining trust behavior (Hoge et al., 2012), but were found to not differ from healthy controls when measured at rest (Hoge et al., 2008). Among individuals with obsessive-compulsive disorder (OCD), one study found elevated levels of oxytocin in cerebrospinal fluid (CSF) via lumbar puncture, relative to healthy controls (Leckman et al., 1994), but another study found no between-group differences (Altemus et al., 1999). As body image disorders, BDD and anorexia nervosa (AN) have similar clinical features, and studies in AN have shown lower basal levels of oxytocin in serum (Lawson et al., 2011) and plasma (Monteleone et al., 2016), but peripheral oxytocin secretion in AN may be increased after meals, compared to controls (Lawson et al., 2012). Some evidence also suggests that serum and CSF oxytocin levels in AN may depend on weight-recovered status (Lawson et al., 2012; Frank et al., 2000). In addition, low fasting oxytocin levels were associated with alexithymia when analyzed across women with acute and partially recovered AN and female healthy controls (Schmelkin et al., 2017), as well as greater eating disorder psychopathology and anxiety in partially-recovered patients with AN (Afinogenova et al., 2016). Overall, the role of oxytocin in the pathophysiology of BDD and related disorders remains to be fully understood.

Within the domain of socioemotional processing, previous research examining the role of oxytocin suggests more consistent evidence in favor of oxytocin enhancing the recognition of basic emotions and expression of positive emotions in healthy humans rather than in clinical populations (Leppanen et al., 2017). However, one study in a BDD-related population (patients with eating disorders) found that exogenous administration of oxytocin led to an enhancement of emotion recognition in patients with bulimia nervosa, but not AN (Kim et al., 2015). Inconsistent findings in clinical samples may possibly be due to high between-disorder and within-disorder heterogeneity (Leppanen et al., 2017). Given that BDD is characterized by pervasive social avoidance and deficits in socioemotional processing, such as selective attentional biases to imagined flaws in one's own and corresponding areas in unfamiliar others' faces (Greenberg et al., 2014; Grocholewski et al., 2012), emotion recognition biases for contempt and anger (Buhlmann et al., 2006), and biases in perspective taking (Buhlmann et al., 2015), oxytocin may be a plausible biomarker of social cognitive deficits in individuals with BDD.

To date, no studies have assessed oxytocin levels in BDD. Our primary goal was to assess basal endogenous concentrations of oxytocin in individuals with BDD compared to healthy controls and determine their associations with markers of BDD pathology (e.g., BDD symptom severity) and impairments in various domains of social cognition. Based on previous reports of lower oxytocin levels associated with increased pathology and impaired social cognition in a related disorder, namely current or past AN (Afinogenova et al., 2016; Schmelkin et al., 2017), we hypothesized that BDD would be characterized by low basal serum oxytocin concentrations, relative to healthy controls, and that low oxytocin levels would be associated with increased BDD pathology and poor performance on measures of social cognition. To determine whether the association between oxytocin and BDD pathology occurs independent of related symptoms, we assessed subjective mood, anxiety, and attachment symptoms. Given the role of oxytocin in stress regulation (Neumann and Slattery, 2016), we also measured cortisol levels to explore whether oxytocin levels would be associated with a heightened stress response in BDD. We expected that low oxytocin levels would correlate with higher cortisol levels as well as greater subjective stress and anxiety levels.

2. Material and methods

2.1. Participants

We studied 50 male and female participants between ages 18–51. Individuals with BDD (n = 20, 11 females) were recruited from a specialty outpatient program and age-matched healthy controls (n = 30, 14 females) were recruited from the community. Participants in the BDD group met criteria for a principal diagnosis of BDD according to DSM-IV-TR[1] and demonstrated no current comorbid schizophrenia, bipolar disorder, psychotic disorder, or substance use disorder (as these were more likely to be primary conditions than BDD). Individuals in the healthy control (HC) group demonstrated no current psychiatric illness as indicated by the *Structured Clinical Interview for DSM-IV-TR* (SCID; First et al., 2002). Exclusion criteria for all participants were as follows: serious medical or endocrine illness (diabetes, untreated thyroid disease), active suicidal or homicidal ideation, steroid or hormone use, taking any form of hormonal contraception or not having regular menstrual cycles (females only), and positive pregnancy test (females only). The study protocol was approved by the Partners Healthcare human subjects research committee, and all participants provided written informed consent prior to study procedures.

2.2. Procedure

Participants attended two study visits at the Translational Clinical Research Center (TCRC): (1) screening assessment involving a clinical interview, history, and physical exam, and (2) experimental visit involving fasting blood draws and computerized social cognition tasks. Clinician-rated and self-report measures were administered after the screening assessment once participants were deemed eligible. Female participants attended main study visits during day 1–10 (early to mid-follicular phase) of their menstrual cycle to minimize differences in sex hormones that occur during the menstrual cycle, and all participants were reminded to avoid nicotine, alcohol, and caffeine for 24 h prior to the blood draw. All blood draws began between approximately 7:00-10:00AM following an 8 -h fast to account for natural fluctuations and anorexigenic properties of oxytocin. An intravenous catheter was placed, and frequent blood sampling for hormones (i.e., oxytocin, cortisol, estradiol [females only], and free testosterone [males only]) was performed every 5 min for one hour for an integrated assessment of pooled hormone levels. Oxytocin has a short half-life and is secreted in pulses allowing for tight control of its physiologic actions (Baskaran et al., 2017). Therefore, frequent sampling is a more sensitive approach to detect oxytocin deficiency because it enables an integrated measure of oxytocin to account for its pulsatile secretory dynamics (Aulinas et al., 2019). Serum was obtained in red top vaccutainers, spun at 2,800 rpm in a centrifuge for 10 min, separated into equal aliquots, and stored in a -80 °C freezer. Blood draws were performed by experienced research nurses at the TCRC, and interactions were kept to a minimum (e.g., no cell phone, reading, or television) to minimize the effects of social stimulation on oxytocin levels. After blood draws, study staff obtained participants' weight and height to calculate body mass index and administered computerized social cognition tasks.

[1] Although DSM-IV criteria were used in the SCID, all BDD participants endorsed multiple past-week repetitive behaviors during the clinician-administered BDD-YBOCS interview (M = 7.20, SD = 1.64, minimum = 4, maximum = 10). Thus, all BDD participants would have met current DSM-5 diagnostic criteria for BDD.

2.3. Clinician-rated and self-report measures

2.3.1. Clinician-rated measures

The screening assessment consisted of a diagnostic interview, using the SCID, and BDD-specific assessment using the *Yale-Brown Obsessive-Compulsive Scale Modified for BDD* (BDD-YBOCS; Phillips et al., 1997) and *Brown Assessment of Beliefs Scale* (BABS; Eisen et al., 1998) to evaluate BDD symptom severity and insight/delusionality, respectively. The BDD-YBOCS and BABS are complementary measures, as the BABS yields an insight score that goes toward the calculation of the BDD-YBOCS total score. The BDD-YBOCS is the primary outcome measure of symptom severity used in BDD treatment studies and conceptualizes BDD as an obsessive-compulsive related disorder. Therefore, similar to the YBOCS symptom severity instrument for OCD, the BDD-YBOCS total score reflects the sum of items assessing appearance-related obsessions, compulsions, insight, and avoidance. These measures were administered by experienced study staff (A.F. and R.J.J.) to determine diagnostic eligibility.

2.3.2. Self-report measures

All participants completed a battery of self-report measures assessing related mood, anxiety, and attachment symptoms to determine unique and shared associations between oxytocin levels and BDD pathology. These include: (1) *Body Dysmorphic Disorder Symptom Scale* (BDD-SS; Wilhelm et al., 2016)- severity of specific BDD symptom clusters (e.g., checking, grooming, cognitive symptoms, etc.), which are not accounted for in the BDD-YBOCS clinician-administered severity instrument, (2) *Depression Anxiety Stress Scale-21* (DASS; Lovibond and Lovibond, 1995)- subjective, dimensional symptoms of depression, anxiety, and stress, which may have independent relationships with oxytocin levels, (3) *Beck Depression Inventory-II* (BDI-II; Beck et al., 1996)- depressive symptoms congruent with DSM-IV diagnostic criteria of major depressive disorder, which overlaps significantly with BDD, (4) *Positive and Negative Affect Scales* (PANAS; Watson et al., 1988)- subjective state positive and negative affect, which allowed us to assess state versus trait aspects of psychopathology, (5) *Experience in Close Relationships Inventory* (ECR; Brennan et al., 1998)- attachment anxiety and avoidance, as BDD is characterized by insecure attachment styles.

2.4. Social cognition tasks

All participants completed the following tasks assessing various domains of social cognition, including emotion identification/recognition, emotion discrimination, and memory for faces:

2.4.1. Emotion Identification/Recognition Domain

2.4.1.1. Morphed emotion identification test (MEI; Bediou et al., 2007). Participants were asked to decide whether a morphed face looked angry, fearful, happy, or disgusted. Faces were morphed to be intermediate between a neutral face and an emotional face. Scores were based on number correct out of 60.

2.4.1.2. Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001). In contrast to the Morphed Emotion Identification Test, which assesses basic emotions and includes morphed images, this task is a measure of complex emotion recognition and includes static images. Participants saw the eye region of a set of faces and were asked to choose from four options of mental state words (unique to each item) that best described the emotion expressed. Scores were based on number correct out of 36.

2.4.2. Emotion discrimination domain

2.4.2.1. Queen square face discrimination test: emotion (QSFED; Garrido et al., 2009; Germine et al., 2011; Germine and Hooker, 2011; pitcher et al., 2008). This test is a measure of facial emotion discrimination. Participants were asked to judge if two sequentially presented faces with different identities were expressing the same or different emotion. Emotional stimuli included happy, angry, fearful, sad, disgusted, and surprised faces. Scores were based on number correct out of 75.

2.4.2.2. Queen square face discrimination test: identity (QSFID; Garrido et al., 2009; Germine et al., 2011; Germine and Hooker, 2011; pitcher et al., 2008). This counterpart to the "Emotion" test is a measure of facial identity discrimination. Participants were asked to judge if two sequentially presented faces with different emotional expression were the same or different person. Scores were based on number correct out of 75.

2.4.3. Face memory domain

2.4.3.1. Cambridge face memory test (CFMT; Duchaine and Nakayama, 2006). The Cambridge Face Memory Test is a measure of facial recognition and face learning ability. Participants were asked to learn and then recognize six male faces from different angles and under different lighting conditions. Scores were based on number correct out of 72.

2.5. Analytic approach

2.5.1. Biochemical analysis

Blood specimens were stored in a −80 °C freezer until data collection was completed. Serum samples were thawed and equal aliquots were pooled together from each of the 13 time points (including baseline) for an integrated measure of hormones for each participant. Samples were delivered to the lab on ice for batch processing at the Brigham Research Assay Core Laboratory. Oxytocin concentration was measured in unextracted serum by ELISA using reagents purchased from Enzo Life Sciences, Farmingdale, NY. The assay had a detection limit of 15 pg/mL. In-house quality control samples had a mean of 81 and 120 pg/mL, and a low- and high-quality control pools between-assay coefficient of variation (CV) of 18 % and 20 %, respectively. The cross-reactivity of Lys8-vasopressin, Arg8-vasopressin, met-enkephalin, vasoactive intestinal polypeptide, somatostatin, Ser4, Ile8-oxytocin, and a-atrial natriuretic polypeptide in the oxytocin assay is 0.02 %. We have previously reported a robust association between extracted and unextracted levels of serum oxytocin (Lawson et al., 2013). Primary gonadal hormones (estradiol and free testosterone) were assessed in females and males, respectively, using liquid chromatography mass spectrometry (LCMS) (estradiol: intra-assay CV < 5 %; inter-assay CV < 12 %; lower limit of detection 1 pg/mL; free testosterone: intra-assay CV < 2 %; inter-assay CV < 7 %; lower limit of detection 10 pg/mL). Cortisol was assessed in all participants using chemiluminescent immunoassay (Beckman Coulter; Fullerton, CA; intra-assay CV 4.4–6.7 %; inter-assay CV 6.4–7.9 %; lower limit of detection 0.4 ug/dL).

2.5.2. Statistical analysis

Statistical analyses were performed in SPSS 24. Continuous data are expressed as mean and standard error of the mean (SEM), and categorical data are expressed as percentages. Primary hypothesis-relevant outcomes included hormone levels (oxytocin), BDD pathology (BDD-YBOCS), and social cognition measures (MEI, RMET, QSFED, QSFID, CFMT). Although the BDD-SS also assesses BDD pathology, it only captures severity associated with certain symptom clusters in BDD and therefore was not included as a primary outcome measure. BABS scores contributed to BDD-YBOCS total scores and were not tested separately as dependent variables. Distributions of data were examined using the Shapiro Wilk test to ensure assumptions of normality were upheld. Logarithmic transformations were conducted when necessary to normalize the distribution of a particular variable (e.g., scores from the QSFID, RMET, MEI). All hormones were normally distributed (except estradiol, which was successfully log transformed). Transformations of self-report data were not performed, as many outcomes had zero values; rather, non-parametric tests were used. Linear regression models were

used to examine group differences, as well as main effects of sex and group by sex interactions, given reported effects of sex in oxytocin (Dumais and Veenema, 2016). We used Spearman rho correlation analyses to examine associations for non-normal variables and Pearson r correlation analyses to examine associations for normally distributed variables. Our main question of group differences in oxytocin levels was first tested in the total sample across sexes, and then examined for main effects of sex and group by sex interactions. Partial correlation analyses were conducted to examine the relationship between oxytocin levels and BDD pathology while controlling for related mood, anxiety, and attachment symptoms in BDD. Covariates were assessed for collinearity and only those which independently and significantly contributed to the outcome were included (e.g., BDI-II, ECR Avoidant and Anxious subscales). A priori hypotheses regarding group differences in oxytocin and association with BDD pathology and social cognition tasks were tested at $p < 0.05$. Exploratory associations between oxytocin and measures of stress, mood, anxiety, and attachment symptoms (cortisol levels, BDD-SS, DASS Depression/Anxiety/Stress subscales, BDI-II, PANAS Positive and Negative subscales, ECR Avoidant and Anxious subscales) were tested at a more stringent, Bonferroni-corrected threshold of $p < 0.005$ ($p = 0.05/10$). Two participants were excluded from all analyses: one HC male participant exhibited oxytocin levels > 5 *SD* above the mean for the entire sample and another HC female participant was not within day 1–10 of her cycle during her blood draw visit. Multiple imputation was used for missing data on self-report measures, all of which had < 10 % missing data. Five datasets were generated with missing values imputed. Results are reported on the pooled dataset.

3. Results

3.1. Participant characteristics

See Table 1 for a full description of participant characteristics. The final sample consisted of 48 participants (mean age = 28.60 years, *SD* = 8.41). Participants were balanced by sex ($n = 25$ females, 52.08 %) and were mostly non-Hispanic ($n = 38$, 79.17 %). Individuals with BDD reported an average of 3 body areas of concern, which included concerns about hair ($n = 12$), skin ($n = 11$), nose ($n = 4$), stomach/midsection ($n = 4$), legs ($n = 3$), overall face ($n = 3$), arms ($n = 3$), eyes ($n = 3$), chin/jaw ($n = 2$), nails ($n = 2$), neck ($n = 2$), chest area/upper body ($n = 2$), cheeks ($n = 1$), feet ($n = 1$), head ($n = 1$), height ($n = 1$), and lips ($n = 1$). Five healthy control subjects reported a previous history of a psychiatric disorder (2 with past alcohol abuse, 1 with past major depressive episode, 1 with past panic disorder with agoraphobia, and 1 with past alcohol abuse, alcohol dependence, and social anxiety disorder). There were no differences in oxytocin levels between healthy control subjects with a previous history and those without, $t(26) = -0.62$, $p = 0.54$. Seven individuals with BDD were taking concurrent psychotropic medications at a stable dose: sertraline ($n = 2$), fluoxetine ($n = 2$), escitalopram ($n = 1$), lorazepam ($n = 1$), and venlafaxine ($n = 1$).

There were no differences between BDD and HC on demographic variables. BDD and HC groups also performed comparably on social cognition tasks, except on the RMET, on which individuals with BDD performed better than HC, $B = 3.49$, $t = 2.66$, $p = 0.01$, $\text{eta}^2 = 0.14$. On other related measures of mood, anxiety, and attachment symptoms, there were significant differences between BDD and HC groups across nearly all of the measures, such that the BDD group had more impaired scores. There were no between-group differences in estradiol (in females) or free testosterone (in males). Therefore, these hormones were not used as covariates in subsequent analyses. There were also no group differences in cortisol levels.

Table 1
Participant Characteristics.

	BDD ($n = 20$)	HC ($n = 28$)	p
Demographic Variables			
Age (in years), *M* (SEM)	29.15 (1.76)	28.21 (1.68)	0.71
Sex (*n* (%))			0.73
Female	11 (55.00)	14 (50.00)	
Male[1]	9 (45.00)	14 (50.00)	
Race (*n* (%))			
Caucasian	13 (65.00)	16 (57.14)	0.97
Asian	3 (15.00)	5 (17.86)	
Black/African American	2 (10.00)	4 (14.29)	
More than one race	1 (5.00)	2 (7.14)	
Other	1 (5.00)	1 (3.57)	
Ethnicity (*n* (%))			0.17
Non-Hispanic or Latino	18 (90.00)	20 (71.43)	
Hispanic or Latino	2 (10.00)	7 (25.00)	
Unspecified	0 (0.00)	1 (3.57)	
Highest Level of Education (*n* (%))			0.30
High School Diploma	0 (0.00)	4 (14.29)	
2-yr degree	2 (10.00)	0 (0.00)	
Some college	4 (20.00)	4 (14.29)	
College graduate	6 (30.00)	9 (32.14)	
Some postgraduate	2 (10.00)	2 (7.14)	
Postgrad/professional degree	6 (30.00)	9 (32.14)	
Marital Status (*n* (%))			0.58
Single/Never Married	16 (80.00)	23 (82.14)	
Married (incl. common law)	1 (5.00)	3 (10.71)	
Living with Partner	2 (10.00)	2 (7.14)	
Divorced/Separated	1 (5.00)	0 (0.00)	
Living Situation (*n* (%))			0.81
Spouse/Partners/Children	3 (15.00)	5 (17.86)	
Parents	1 (5.00)	1 (3.57)	
Roommate	12 (60.00)	17 (60.71)	
Alone	3 (15.00)	5 (17.86)	
Other	1 (5.00)	0 (0.00)	
Clinical Variables			
Age of onset of BDD (in years)	15.70 (1.81)		
Clinician-rated and self-report measures			
BDD-YBOCS	24.40 (1.29)		
BABS	14.10 (1.05)		
BDD-SS	25.74 (2.39)	2.64 (0.77)	0.00
DASS Depression	4.80 (1.15)	1.07 (0.36)	0.01
DASS Anxiety	3.85 (0.87)	0.57 (0.23)	0.00
DASS Stress	5.58 (1.08)	1.64 (0.54)	0.00
BDI-II	12.55 (2.33)	2.57 (0.63)	0.00
PANAS Positive	28.20 (2.15)	31.26 (1.55)	0.24
PANAS Negative	22.10 (1.66)	13.21 (0.75)	0.00
ECR Avoidance	3.33 (0.25)	2.65 (0.21)	0.04
ECR Anxiety	4.55 (0.26)	3.22 (0.21)	0.00
Current Antidepressants (*n* (%))	7 (35.00)		
Additional Benzodiazepine	3 (15.00)		
Additional Beta Blocker	2 (10.00)		
Additional Anticonvulsant	1 (5.00)		
Current Comorbidity (*n* (%))			
Generalized Anxiety Disorder	7 (35.00)		
Major Depressive Disorder	5 (25.00		
Social Anxiety Disorder	5 (25.00)		
Eating Disorder Unspecified	3 (15.00)		
Specific Phobia	2 (10.00)		
Panic Disorder	2 (10.00)		
Obsessive-Compulsive Disorder	2 (10.00)		
Skin Picking Disorder	1 (5.00)		
Bulimia Nervosa	1 (5.00)		
Hypochondriasis	1 (5.00)		
Agoraphobia	1 (5.00)		
Posttraumatic Stress Disorder	1 (5.00)		
Olfactory Reference Syndrome	1 (5.00)		
Hormones			
Free testosterone (pg/mL) (males only)	4.14 (0.33)	3.79 (0.34)	0.50
Estradiol (pg/mL) (females only)	39.57 (3.91)	44.89 (6.45)	0.52
Cortisol (ug/dL)	12.07 (1.08)	11.04 (0.96)	0.52
Social Cognition Measures			
MEI	41.21 (1.61)	41.37 (1.19)	0.85
RMET	29.32 (0.68)	25.82 (0.98)	0.01
QSFED	57.47 (1.04)	58.04 (0.85)	0.68
QSFID	55.21 (1.30)	54.18 (1.57)	0.54

(*continued on next page*)

Table 1 (*continued*)

	BDD (n = 20)	HC (n = 28)	p
CFMT	54.42 (1.99)	53.18 (1.92)	0.67

Note. BDD = Body Dysmorphic Disorder; HC = Healthy Control; BDD-YBOCS = Yale-Brown Obsessive-Compulsive Scale Modified for BDD; BABS = Brown Assessment of Beliefs Scale; BDD-SS = Body Dysmorphic Disorder Symptom Scale; DASS = Depression Anxiety and Stress Scales; BDI-II = Beck Depression Inventory II; PANAS = Positive and Negative Affect Scales; ECR = Experience in Close Relationships Inventory; MEI = Morphed Emotion Identification; RMET = Reading the Mind in the Eyes Task; QSFED = Queen Square Face Emotion Discrimination; QSFID = Queen Square Face Identity Discrimination; CFMT = Cambridge Face Memory Test.

[1] One biologically male BDD participant identified as agender, and another identified as gender questioning.

3.2. Group differences in oxytocin levels

Mean serum oxytocin level across the entire sample was 1204 ± 61 pg/mL. Pooled fasting oxytocin levels were elevated in the BDD group compared to HC group, B = 259.86, t = 2.19, p = 0.03, eta^2 = 0.09 (Fig. 1). Controlling for concurrent use of medications did not change this result, B = 294.40, t = 2.14, p = 0.04, eta^2 = 0.10. There was no sex difference in oxytocin levels, B = 74.73, t = 0.63, p = 0.53, eta^2 = 0.01, and no group by sex interaction, B = -302.08, t = −1.27, p = 0.21, eta^2 = 0.03.

3.3. Association between oxytocin levels and measures of psychopathology and stress

Oxytocin levels correlated positively with increased BDD symptom severity on the clinician- administered BDD-YBOCS among all individuals with BDD, r = 0.51, p = 0.02, n = 20 (Fig. 2). This finding remained stable when controlling for concurrent use of medications, r = 0.50, p = 0.03, n = 20, and when controlling for the BDI-II and ECR Avoidant and Anxious subscales, r = 0.51, p = 0.04, n = 20. When examined separately for men and women, there were positive correlations in both sexes, which only achieved significance in women (r = 0.66, p = 0.03), but not men (r = 0.49, p = 0.19) with BDD.

As shown in Table 2, oxytocin levels did not correlate with performance on the RMET or any of the other social cognition tasks. There were no other significant associations between oxytocin and self-report measures of mood, anxiety, and attachment symptoms among HC individuals or those with BDD. Oxytocin levels did not correlate with indicators of stress, including cortisol levels and DASS stress or anxiety subscales, either in the full sample or in each group separately.

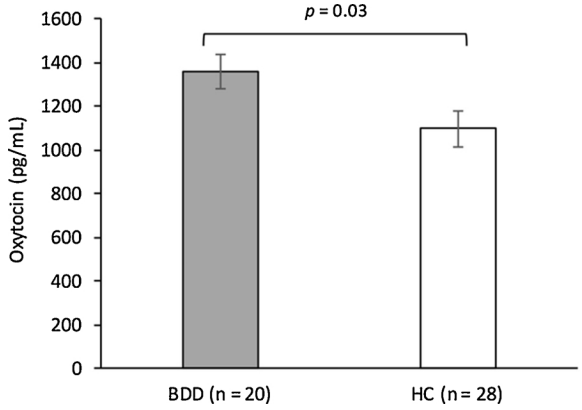

Fig. 1. Mean 1 -h pooled fasting oxytocin levels across groups. Oxytocin levels were higher in BDD, compared to HC.

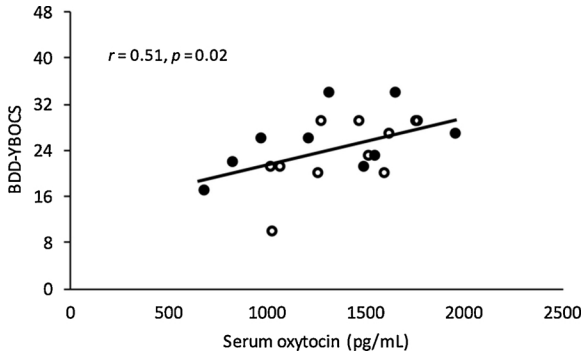

Fig. 2. Significant positive correlation between mean 1 -h pooled serum oxytocin concentrations and BDD symptom severity in the BDD group. Filled circles represent males; unfilled circles represent females.

Table 2
Associations Between Oxytocin Levels and Measures of BDD Pathology, Social Cognition, and Related Mood, Anxiety, and Attachment Symptoms, and Cortisol Levels in BDD.

Variable	r	p
BDD Pathology Measures		
BDD-YBOCS	0.51	0.02*
BDD-SS	0.07	0.78
Social Cognition Measure		
MEI	−0.25	0.30
RMET	0.15	0.54
QSFED	−0.08	0.74
QSFID	−0.34	0.15
CFMT	0.12	0.62
Subjective Mood, Anxiety, and Attachment Measures		
DASS- Dep	0.22	0.35
DASS- Anx	0.22	0.36
DASS- Stress	0.03	0.89
BDI-II	0.26	0.28
PANAS- Pos	−0.17	0.47
PANAS- Neg	0.10	0.67
ECR- Avoidant	0.03	0.90
ECR- Anxious	0.03	0.90
Hormones		
Cortisol	0.04	0.89

4. Discussion

This is the first study to assess endogenous oxytocin levels in BDD. A strength of our approach was the use of an integrated measure of oxytocin secretion based on frequent sampling over the course of one hour. We found that fasting oxytocin levels were elevated in BDD compared to controls, and oxytocin levels correlated positively with BDD symptom severity.

Although in the opposite direction of our hypothesis, our finding that pooled oxytocin levels were higher in BDD is consistent with previous studies demonstrating elevated basal levels of oxytocin in related psychiatric disorders, such as social anxiety disorder (Oh et al., 2018) and OCD (Leckman et al., 1994), using plasma and CSF, respectively; however, two studies in the same disorder populations examining the same biological fluids found no group differences in oxytocin levels (Altemus et al., 1999; Hoge et al., 2008). These divergent findings assessing unstimulated oxytocin levels even within the same disorder categories may be due to significant heterogeneity of psychiatric disorders between studies. Differences in the use of bioassays may also account for some of these discrepancies, as valid measurement of endogenous oxytocin is an area of active debate (Brandtzaeg et al., 2016; Leng and Sabatier, 2016; MacLean et al., 2019). One possible explanation for higher levels of oxytocin in BDD is that oxytocin plays a role in the stress response to reduce hypothalamic-pituitary-adrenal

axis activation and has established anxiolytic and antidepressant properties (Neumann and Slattery, 2016; Scantamburlo et al., 2007). A previous study measuring salivary oxytocin provided evidence that oxytocin (as well as cortisol) is released into peripheral circulation in response to psychosocial stress (de Jong et al., 2015). Elevated levels of oxytocin in BDD could therefore be in response to greater stress and anxiety symptoms. While this was the rationale for measuring cortisol levels, oxytocin levels did not correlate with cortisol levels nor any self-report measure of subjective mood, anxiety, or stress.

Another possibility is that BDD is associated with an increase in production of oxytocin to compensate for severe social avoidance and promote social interaction. Indeed, individuals with BDD display poor psychosocial functioning (Phillips et al., 2005b), and our data indicate that their relationships are characterized by anxious and avoidant attachment styles. However, we did not identify relationships between oxytocin levels and assessments of socioemotional functioning. Alternatively, the higher oxytocin levels and positive relationship between oxytocin and BDD symptom severity supports the possibility that high oxytocin levels may reflect increased vulnerability to BDD. Prospective studies are needed to determine whether high oxytocin levels are in response to stress or social avoidance and/or whether oxytocin contributes to BDD psychopathology. Future research could also examine changes in oxytocin levels in response to a controlled experimental social exchange, such as the Trust Game, to determine whether differences emerge within a symptom provocation context.

Our data indicate that there was a between-group difference in oxytocin levels and an association between oxytocin levels and BDD pathology. Sex did not impact these effects as there was no group by sex interaction and no sex difference in oxytocin levels. Examination of the correlations separately in each sex revealed large effect sizes, although the correlation only achieved significance in women with BDD. The lack of significant correlation in men with BDD may be due to our small sample size. BDD has a fairly equal sex distribution; however, there is some evidence that sex moderates the clinical features of BDD in terms of body areas of concern and repetitive behaviors (Phillips et al., 2006). It remains possible that oxytocin plays a role in the sex-specific manifestations of BDD. Future studies examining oxytocin levels in larger samples across both sexes are needed.

Interestingly, oxytocin appears to be a better marker of overall BDD psychopathology than social-cognitive deficits, and individuals with BDD displayed intact, if not better performance, across several domains of social cognition. Indeed, those with BDD performed better on the Reading the Mind in the Eyes Task, which assesses the ability to infer complex emotions of others from the eye region. These findings contrast with a body of research on emotion recognition biases in BDD (for a review, see Fang and Wilhelm, 2015), although differences may only be observed in self-referent versus other-referent contexts (Buhlmann et al., 2006, 2013). Our finding that individuals with BDD performed better than controls on the RMET contrasts with another study (Buhlmann et al., 2013) which showed no between-group differences, and may reflect sample differences, as the Buhlmann sample was more severe (greater BDD and depressive symptoms). Despite superior performance on the Reading the Mind in the Eyes Task in BDD, scores from this task did not correlate with oxytocin levels in the BDD group. Furthermore, the association between oxytocin and BDD pathology was only significant when using the BDD-YBOCS, rather than the BDD-SS, as an indicator of BDD pathology. Although both measures capture aspects of BDD symptom severity, the BDD-YBOCS is clinician-administered and widely used in BDD treatment studies, whereas the BDD-SS is a self-report measure that assesses the broad range of BDD symptoms. It is possible that there was only a significant association using the BDD-YBOCS because BDD is a highly heterogeneous disorder and the BDD-SS captures that heterogeneity by assessing several unique symptoms that may only affect a subset of individuals with BDD.

Our study had some limitations. Sample size was relatively small, especially for the BDD group; however, we identified important findings that call for larger studies. The cross-sectional study design also limited our ability to draw any causal inferences about the association between oxytocin levels and BDD pathology. Future prospective studies will be needed to clarify this relationship. There were additional limitations, which reflect the challenges of assessing oxytocin levels and the significant variability across studies in sample preparation and assay methods (MacLean et al., 2019). While optimization of measurement techniques for quantification and determination of biological activity of the oxytocin molecule (as well as precursors and degradation products) across different states is an important area for future investigation (Brandtzaeg et al., 2016; MacLean et al., 2019), here we used a commercially available ELISA to examine relative levels of oxytocin between groups and the relationship with clinical features (Lawson, 2017). There have also been mixed findings regarding the relationship between peripheral and central levels of oxytocin, with a recent meta-analysis showing that peripheral and central oxytocin concentrations are not correlated under baseline conditions (Valstad et al., 2017). Although this highlights a limitation of measuring peripheral levels of oxytocin and inferring potential relationships with central function, we did find a significant correlation between basal peripheral oxytocin and BDD symptom severity, which may indicate a relationship that warrants further investigation. Furthermore, measuring pulsatile parameters of oxytocin secretion may have more relevance to psychopathology than pooled or mean oxytocin levels. A previous study found that serum oxytocin pulse characteristics (e.g., pulse height and pulse mass) were strongly associated with socioemotional functioning in healthy men (Baskaran et al., 2017). Future research should examine whether pulsatile oxytocin secretion in BDD is a more sensitive biomarker of BDD psychopathology relative to pooled oxytocin levels.

5. Conclusions

We have demonstrated higher oxytocin levels among people with BDD, compared to healthy controls, and a positive association between oxytocin levels and BDD symptom severity. Future prospective studies in both sexes are needed to evaluate whether high basal peripheral oxytocin levels contribute to and/or result from clinical features of BDD.

Declaration of Competing Interest

A.F. has received salary support from Telefonica Alpha, Inc.

C.B. and F.P. have no financial disclosures to report.

R.J.J. has received salary support from Telefonica Alpha, Inc. She is paid as a faculty member of the Massachusetts General Hospital Psychiatry Academy for filming role plays for course content and for moderating the course discussion boards. She also receives book royalties from Hogrefe Publishing.

L.G. is on the Scientific Advisory Board for Sage Bionetworks, a nonprofit technology company, for which she receives a small honorarium. She is also a consultant for 23andme, a personal genomics company, and President and Board Chair for the Many Brains Project, a nonprofit technology company. She received no financial compensation for these roles. Finally, she receives research support from the NIH National Institute of Mental Health, National Institute of Aging, National Institute of Diabetes, Digestive and Kidney Disorders, National Cancer Institute, Brain & Behavior Research Foundation, NFL Players Association, and Broad Institute at MIT and Harvard.

E.A.L. is on the scientific advisory board and has a financial interest in OXT Therapeutics, Inc., a company developing an intranasal oxytocin and long-acting analogues of oxytocin to treat obesity and metabolic disease. E.A.L.'s interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflicts-of-interest policy.

S.W. has received research support in the form of free medication

and matching placebo from Forest Laboratories for clinical trials funded by the NIH. Dr. Wilhelm is a presenter for the Massachusetts General Hospital Psychiatry Academy in educational programs supported through independent medical education grants from pharmaceutical companies; she has received royalties from Elsevier Publications, Guilford Publications, New Harbinger Publications, and Oxford University Press. Dr. Wilhelm has also received speaking honorarium from various academic institutions and foundations, including the International Obsessive Compulsive Disorder Foundation and the Tourette Association of America. In addition, she received payment from the Association for Behavioral and Cognitive Therapies for her role as Associate Editor for the Behavior Therapy journal, as well as from John Wiley & Sons, Inc. for her role as Associate Editor on the journal Depression & Anxiety. Dr. Wilhelm has also received salary support from Novartis and Telefonica Alpha, Inc.

Acknowledgments

This work was supported by a Harvard University Mind Brain Behavior Interfaculty Initiative Award and National Institute of Mental Health Career Development Awards (K23 MH109593-04 and K24 MH120568). This work was also supported by the protocol nurses and administrative staff at the MGH Translational Clinical Research Center (TCRC) under Grant Number 1UL1TR001102. The authors would like to thank the following individuals for their assistance in preparing and conducting the study protocol: Dylan Abrams, Aishvarya Arora, Carolyn Davies, Eliza Davidson, Angelina Gomez, Eric Jenike, Dean Marengi, Helen Mizrach, Alexandra Shapiro, Charlie Suchin, and Alexandra Sullivan.

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