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Authors

Marazziti, Donatella

Carter, C Sue

Carmassi, Claudia

et al.

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Sex matters: The impact of oxytocin on healthy conditions and psychiatric disorders

Donatella Marazziti [a,b,*], C. Sue Carter [c,d], Claudia Carmassi [a], Alessandra Della Vecchia [a], Federico Mucci [e,f], Giovanni Pagni [g], Manuel G. Carbone [h], Stefano Baroni [a], Gino Giannaccini [i], Lionella Palego [i], Liliana Dell'Osso [a]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Italy
[b] Saint Camillus International University of Health and Medical Sciences – UniCamillus, Rome, Italy
[c] Kinsey Institute, Indiana University, Bloomington, IN, USA
[d] Department of Psychology, University of Virginia, Charlottesville, VA, USA
[e] Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Italy
[f] Department of Psychiatry, North-Western Tuscany Region NHS Local Health Unit, Lucca Zone, Lucca, Italy
[g] Department of Psychiatry, North-Western Tuscany Region NHS Local Health Unit, Lunigiana Zone, Aulla, Italy
[h] Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy
[i] Department of Pharmacy, University of Pisa, Pisa, Italy

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ABSTRACT

Oxytocin (OT) is involved in the regulation of physiological processes and emotional states, with increasing evidence for its beneficial actions being mediated by the autonomic and immune systems. Growing evidence suggests that OT plays a role in the pathophysiology of different psychiatric disorders. Given the limited information in humans the aim of this study was to retrospectively explore plasma OT levels in psychiatric patients, particularly focusing on sex-related differences, as compared with healthy controls. The patients studied here were divided into three groups diagnosed with obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) or major depressive disorder (MDD). Plasma OT levels were significantly different between healthy men and women, with the latter showing higher values, while none of the three psychiatric groups showed sex-related differences in the parameters measured here. The intergroup analyses showed that the OT levels were significantly higher in OCD, lower in PTSD and even more reduced in MDD patients than in healthy subjects. These differences were also confirmed when gender was considered, with the exception of PTSD men, in whom OT levels were similar to those of healthy men. The present results indicated that OT levels were higher amongst healthy women than men, while a sex difference was less apparent or reversed in psychiatric patients. Reductions in sex differences in psychopathologies may be related to differential vulnerabilities in processes associated with basic adaptive and social functions.

1. Introduction

Oxytocin (OT) is a nonapeptide primarily synthesized in paraventricular and supraoptic nuclei of the hypothalamus projecting to the posterior pituitary, the limbic system and various autonomic centers [1–3]. It is a pleiotropic hormone that plays a powerful and unique role in mammalian physiology, through the interaction with different receptors identified in vitro, such as the OXTR and three different types of arginine-vasopressin (AVP) receptors (AVPR1A, AVPR1B, AVPR2) [4–8].

The mistaken notion that OT was only important to one sex (female) and in one context (female reproduction), with no known role in male, might have decreased initial interest in this molecule [9]. However, studies first appearing in the 1990s broaden the spectrum of functions of this peptide to reveal pivotal roles for OT in social behaviors and the formation of adult social bonds in both sexes [10,11]. In addition, it is now evident that OT acts as a potent modulator of the immune system, even during development, and it plays a preminent anti-inflammatory role in the context of immune system function and homeostatic cellular processes. Oxytocin is released during the stress response and is

* Corresponding author. Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 57, 56100, Pisa, Italy.
E-mail address: dmarazzi@psico.med.unipi.it (D. Marazziti).

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an important modulator of anxiety and fear response, mainly with anxiolytic effects [12–17]. Elevated plasma OT in older women was significantly associated with gaps in social relationships, with less positive relationships with a primary partner, and with elevated cortisol levels [18]. Therefore, given its particular modulatory functions, OT links social behaviors and experiences together with the capacity to heal in the face of stress or trauma.

The OT-AVP system and its receptors show some sex-related differences depending on the brain region and species. Different studies carried out on several animal species, including humans, reveal more prominent effects of OT in females and more significant effects of AVP in males [19–21]. We should also mention that exogenous administration of OT influences paternal attachment, augments neural responses to toddlers responsiveness and attention towards children [22–24].

In rodents, the density of OT-immunoreactive axons tends to be higher in females [25]. Estradiol may increase the OXTR and affinity of the OXTR for OT, and while progesterone, especially during chronic exposure may decrease the functions of OT, especially in the amygdala [26–28]. In contrast, endogenous AVP synthesis and AVP receptors, especially of the V1a type, tend to be androgen-dependent, especially in brain areas related to social behavior and aggression [29,30]. Moreover, women had higher plasma OT levels than men and older adults had higher plasma AVP levels than young adults [31]. On the other hand [32], first described plasma OT levels in new fathers and mothers across the transition to parenthood in relation to maternal and paternal typical parenting behaviors without finding any differences between maternal and paternal OT at each time point [32].

The multiplicity of processes and functions modulated by OT lead to the hypothesis that OT may be involved in the pathophysiology of different psychiatric disorders, and in particular those that have been identified as sexually dimorphic. In general, in adulthood, women may generally be more dependent on estrogen and estrogen-OT interactions. The relationship between depression and OT levels is more commonly described in women [33–36] and some findings suggest that in the presence of deficiencies or dysregulation in either OT or its receptor, subjects may be more vulnerable to disorders, including symptoms of depression, characterized by either generalized anxiety or passive responses [37]. Negative correlations have been reported between plasma and cerebrospinal fluid (CSF) OT levels and the core symptoms of depression and suicidality [38,39], with some studies suggesting that the alleviating effect of social support could be mediated by OT [40–42]. Furthermore, OT levels in depressed women have been associated with the severity of both depression and anxiety symptoms [39]. Decreased CSF OT concentrations were also observed in women suffering from major depressive disorder (MDD) with a history of childhood abuse (particularly emotional abuse), suggesting that the enhancing effect of OT on social affiliation may play a crucial role in this condition [43]. One study, although not showing correlations between peripheral OT levels and symptoms of depression or suicidality, highlighted that methylation at OXTR CpG −924 was negatively correlated with depressive symptomology [44].

Scattered findings suggest that the OT might be also involved in the pathophysiology of obsessive-compulsive disorder (OCD) [45–47], both directly and through interactions with the serotonin system [48,49]. Elevated OT levels have been also putatively involved in the etiology of OCD repetitive behaviors. Some authors [50] reported that levels of OT in CSF were higher in OCD patients than in healthy controls and identified a positive correlation between higher CSF levels of OT and higher frequency of repetitive behaviors; however, negative findings are also available [51]. Studies on plasma OT levels, in OCD also have yielded conflicting results, with no apparent sex differences [52].

This literature is based on small studies and the presence or absence of sex differences needs to be examined more closely. For example, research in animals shows that pre-natal and early-natal exposure to varying levels of OT [53] or differential amounts of early nurture [54] can affect the expression of OXTR. Experiences such as these, mediated by OT or AVP, could be potentially related to the future expession of the repetitive behaviors that characterize OCD or other anxiety-related disorders.

OT is particularly likely to be implicated in the symptoms associated with post-traumatic stress disorder (PTSD) [55–58]. OT plays a role in stress responses, social reward, attenuation of memory consolidation and retrieval, decreasing of avoidance responses and reduction of passive avoidance behavior, all of which are altered in PTSD. Several studies in healthy individuals have reported that OT can decrease the magnitude of amygdala responses to aversive stimuli and increase resting state connectivity in corticolimbic brain regions [59–61]. Remarkably few direct comparisons of sex differences in OT in PTSD have been reported [62,63]. One recent study involving male policemen who developed PTSD after a severe trauma, found lower levels of salivary OT [64]. In women, the exposure to traumatic/stressful situations transiently increased OT levels, possibly associated with adaptive increases in pro-social and supporting behaviors [65,66]. The role of sex steroids, and especially estrogens in PTSD also deserves deeper study [67,68]. Interestingly, women, but not men, with high levels of post-stressor OT and the GG genotype of rs53576 felt the most positive affect after a stressor. On the other hand, men, but not women, with high levels of poststressor AVP and the 320 allele of the RS1 polymorphism reported more poststressor anger than noncarriers [69].

There is increasing evidence for a role of OT in neuropsychiatric conditions [70–72]. However, many of these studies do not analyze their data based on the sex of the subjects. The aim of this retrospective study was to explore sex-related differences in plasma OT levels in samples of psychiatric patients suffering from OCD, MDD and PTSD and to directly compare OT levels in these populations with those measured in an age-matched group of healthy neurotypical controls.

2. Subjects and methods

Ninety psychiatric outpatients of both sexes (45 men, M, and 45, W, mean age ± SD: 33.4 ± 9.4 years) at their first psychiatric consultation, were recruited at the psychiatric outpatient unit of the "Department of Clinical and Experimental Medicine", Section of Psychiatry, at University of Pisa and consecutively enrolled in this study. The diagnoses were carried out according to the criteria of the Diagnostic and Statistical Manual for Mental Disorders, fourth edition revised (DSM-IV-TR). Eligible subjects were first assessed through a clinical interview, and the resulting diagnoses were subsequently confirmed by the Structured Clinical Interview for DSM-IV, Patient Version 2.0 (SCID-I/P) [73]. Forty outpatients (20 men and 20 women) were suffering from OCD, 26 (13 men and 13) from PTSD, and 24 (13 men and 11 women) from MDD (Table 1).

Exclusion criteria for all recruited patients were: age <18 and >65 years; active cancer; heart, liver or kidney diseases; presence of haematological or neurological illnesses; a positive history for substance abuse; pregnancy and breastfeeding. Additional exclusion criteria were the use of psychotropic medications and of estrogenic or progestinic drugs; only nine patients reported occasionally taking benzodiazepines.

The severity of OCD was assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [74], that of MDD by the Hamilton Rating Scale for Depression (HRSD) [75], and that of the PTSD by the Impact for Event Scale revised (IES-R) [76]. The general severity of the symptomatology, regardless from the psychiatric disorder, was assessed by the Clinical Global Impression-severity (CGI-s) [77].

In the OCD group, 27 (15 men and 12 women) patients were single, and 13 (7 men and 6 women) were married. The age rage of the OCD patients was 23–37 (median age 29, mean +SD: 29.2 ± 7.3). Twelve patients were graduated, 24 had completed high school and 4 the primary school. The Y-BOCS total score of the patients was 30.5 ± 7.1, with no difference between men and women. Similarly, no gender differences were detected for the total scores of the Y-BOCS obsession (mean ± SD: 16.1 ± 3.0) and compulsion subscale (mean ± SD: 13.3 ± 4.1). The most

prevalent obsessions were those of contamination, doubting and symmetry, and the main compulsions were washing, checking and ordering.

In the PTSD group, 18 (8 men and 10 women) patients were married, six (4 men and 2 women) patients were single and two (1 men and 1 woman) were divorced. The age range of PTSD patients was 26–50 (median age 43.5, mean +SD: 40.3 ± 9.5 years). Nine patients had graduated from college, 11 had completed high school, and six had only attended primary school. The traumatic events reported by the sample were: severe car accident (7), physical violence (4), sexual violence (3), sudden death of a loved one (8), and natural disaster (4). The mean IES total score was 55 ± 15.

Sixteen patients (7 men and 6 women) of the MDD group were single, five (2 men and 2 women) were married and three were divorced (1 man, 2 women). The age range of MDD patients was 27–51 (median age 31, mean +SD: 33.0 ± 7.6 years). Nine patients had graduated from college, ten had completed high school, and one primary school only. The HRSD total score of the patients was 17.3 ± 5.0, with no difference between men and women.

The control group (HC) included ninety matched healthy, neurotypical volunteers (45 men and 45 women, mean age ± SD: 35.0 ± 6.4 years), selected on the basis of the absence of a personal or family history of major psychiatric disorders or medical diseases. No subject had ever regularly taken psychotropic or other drugs, as assessed by a detailed psychiatric examination. The women were selected on the basis of the presence of a normal menstrual cycle and no intake of contraceptive pills; their blood was drawn in the early follicular phase (between the second and the fifth days of the menses). The men had no history of genital disease or hypogonadism. All this information was derived from the collected medical history. Fifty-six HC (24 men and 32 women) were married, 29 were single (20 men and 9 women) and five were divorced (1 man and 4 women). Thirty-seven HCs were college graduates and 53 had completed high school.

After a complete description of the study, a written informed consent was obtained from each subject to participate in the study, previously approved by the Ethics Committee at Pisa University.

2.1. Assessment scales

2.1.1. Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

The Y-BOCS is a widely used instrument to assess obsessive-compulsive symptomatology. It is a clinician-administered semi-structured interview that contains 16 core items scored on a five-step Likert scale (0–4, higher scores indicating greater disturbance). While items 1 to 5 represent obsession-related dysfunctions, items 6 to 10 measure disturbances associated with compulsions. The remaining items are not disease-specific but do give valuable information for both differential diagnosis (especially insight) and treatment (e.g. avoidance). The total score is computed from the first 10 items, without items 1b and 6b. Compared to other scales evaluating OCD, this scale quantifies the severity of obsessive-compulsive symptomatology and the scale thoroughly taps major obsessions and compulsions on a checklist, thus providing further important qualitative information.

2.1.2. Hamilton Rating Scale for Depression (HRSD)

The HRSD provides a quantitative evaluation of the severity of the depressive condition shown by the patient and describes its changes, taking into account both the extent of the symptoms and their frequency. More specifically, the questionnaire rates the severity of depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. HDRS, in its most widespread version, consists of 21 items. Generally, the first 17 items are considered essential ones and the severity cut-off is defined on these, as follows: >25 severe depression; 18–24 moderate depression; 8–17 mild depression; <7 no depression.

2.1.3. Impact for Event Scale revised (IES-R)

The IES-R is a 22-item self-report measure (for DSM-IV) assessing subjective distress caused by traumatic events. It is a revised version of an older version, the 15-item IES [78]. The IES-R contains seven additional items related to the hyperarousal symptoms of PTSD, which were not included in the original IES. Items correspond directly to 14 of the 17 DSM-IV symptoms of PTSD. Respondents are asked to identify a specific stressful life event and then indicate how much they were distressed or bothered during the past seven days by each "difficulty" listed. Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The IES-R yields a total score (ranging from 0 to 88) and subscale scores can also be calculated for the intrusion, avoidance, and hyperarousal subscales.

2.1.4. Clinical Global Impression-severity (CGI-S)

The CGI-S is a questionnaire that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. The scale is comprised of three global scales (items): two of the items, "Severity of Illness" and "Global Improvement" are rated on a 7-point scale, while the third, "Efficacy Index", requires a rating of the interaction of therapeutic effectiveness and adverse reactions. Possible scores are: 1. Healthy patient; 2. Borderline; 3. Slightly ill; 4. Moderately ill; 5. Markedly ill; 6. Severely ill; 7. Very high severity level. In the specific case of our study, since there is no second endpoint for the evaluation of the subjects, we statistically analyzed only the first item ("Severity of illness").

2.2. Plasma preparation

Thirty ml of venous blood was withdrawn three times between 8 and 9 a.m. from fasting subjects who were sitting and relaxing in the same room at a constant temperature. The blood for OT assay (10 ml) was collected in vacutainers containing EDTA as anticoagulant, transferred to centrifuge tubes containing aprotinin (Sigma, Milan, Italy) (0.6 TIU/ml of blood) and gently mixed several times to inhibit the activity of proteinases. Blood was then centrifuged at 1600×*g* for 15 min at 4 °C and the ensuing plasma was collected and kept at −70 °C until the assay.

2.3. Extraction of peptides from plasma

On the day of the assay, 6 ml of each sample of plasma was acidified with 6 ml of buffer A (1% trifluoroacetic acid in H_2O) and centrifuged at 17,000×*g* for 20 min at 4 °C; after this centrifugation, the supernatant was collected. C-18 sep-columns were equilibrated by washing them with 1 ml of buffer B (60% acetonitrile in 1% trifluoroacetic acid) followed by buffer A (3 ml, 3 times). Acidified plasma solution was loaded into the pre-treated C-18 Sep-column; the column was washed slowly with buffer A (3 ml, twice) and the washing liquid was discarded. Oxytocin was then eluted with buffer B (3 ml, once) and collected into a polystyrene tube. The eluate was evaporated in a centrifugal concentrator (Speedvac), while the remaining sample was lyophilized by freeze dryer.

2.4. Oxytocin radioimmunoassay

Radioimmunoassay was performed by using Phoenix Pharmaceuticals Oxytocin RIA kit (Belmont, California, USA) following a previously described method [15]. The cross-reactivity of the OT antibody was 100% with OT and null with Lys-vasopressin, Arg-vasopressin, GH, alpha-ANP, Met-enkephalin, GRF, somatostatin, TRH, VIP, Pacap 27-NH2. The sensitivity of the assay, measured as IC_{50}, was 10–30 pg/tube. The intra-assay and inter-assay values were 9% and 11%, respectively. Lyophilized samples and standard OT were rehydrated with RIA buffer, and dilutions of standard OT were prepared (from 1 to 128 pg/tube). Primary rabbit anti-OT antibodies were added to each sample and each

standard, except for the non-specific binding tubes, and then the mixtures were stored for 24 h at 4 °C. ^{125}I-Oxytocin was added to mixtures which were subsequently stored for 24 h at 4 °C. Goat anti-rabbit IgG serum and normal rabbit serum were added to each tube; subsequently, tubes were centrifuged at 1700×*g* for 20 min at 4 °C. All the supernatant was carefully aspirated and pellets were counted by a gamma-counter (Wizard, PerkinElmer, Milan, Italy). All samples were assayed in duplicate. Standard curve and calculations of unknown samples were performed using Graphpad Prism3 software.

2.5. Statistical analyses

All demographic, clinical and laboratory data were presented for continuous variables in terms of mean ± standard deviation (SD), variation range (min and max values), or medians, when required. Categorial variables were expressed as frequencies (number) and percentages. The Kolmogorov-Smirnov test was used to determine normality of distribution of the variables. One-way analysis of variance (ANOVA) was used to analyze the intergroup differences. Comparisons for categorical variables were conducted by the use of $\chi 2$ test (or Fisher's exact test when appropriate). The correlations between different parameters, and between characteristics of the subjects and biological markers were explored by calculating the Pearson's correlation coefficient or Spearman rank correlation. All statistical analyses were carried out using SPSS, version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

3. Results

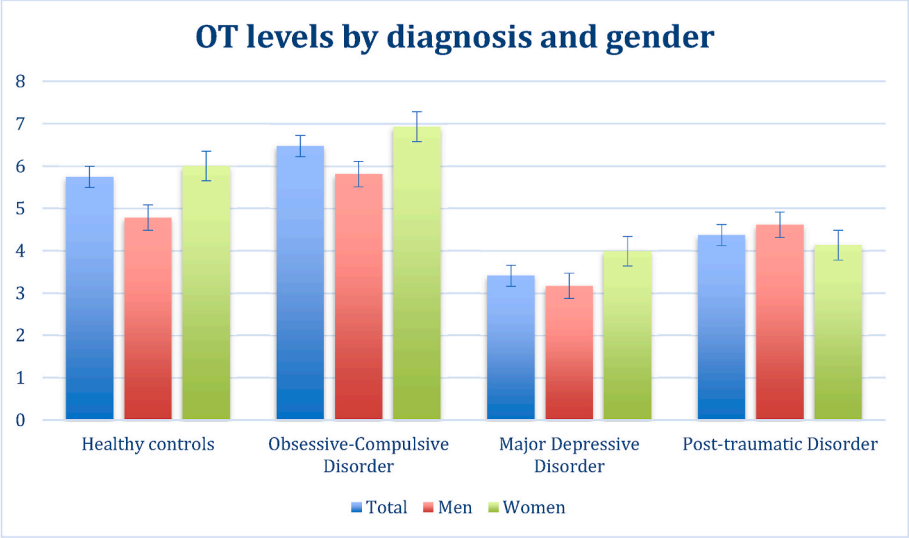
No significant age differences between psychiatric patients and healthy subjects, nor between men or women of each group were noted. The patients suffering from OCD had significantly higher plasma OT levels (reported as pg/ml, mean ± SD) in comparison to HCs (6.47 ± 1.41 vs 5.74 ± 1.99, p = 0.018), or PTSD (6.47 ± 1.41 vs 4.37 ± 1.62, p < 0.001) or MDD patients (6.47 ± 1.41 vs 3.41 ± 0.79, p < 0.001). Patients with PTSD had significantly lower plasma OT values than HCs (4.37 ± 1.62 vs 5.74 ± 1.99, p = 0.029). Plasma OT levels of MMD patients were lower than those of patients with PTSD (3.41 ± 0.79 vs 4.37 ± 1.62, p < 0.01).

Taking into account the sex of subjects (Fig. 1 and Table 2), plasma OT levels were significantly higher in healthy women than in men (6.00 ± 1.15 vs 4.78 ± 0.79, p < 0.001). Men diagnosed with OCD showed higher OT levels than men with PTSD (5.81 ± 1.36 vs 4.61 ± 1.36, p < 0.01) or MDD men (5.81 ± 1.36 vs 3.17 ± 1.42, p < 0.0005). Women with OCD women also had higher levels of OT than those diagnosed with PTSD (6.93 ± 1.15 vs 4.13 ± 1.15, p < 0.0005) or MDD (6.93 ± 1.15 vs 3.99 ± 1.74, p < 0.0005).

The differences between HC and psychiatric patients were maintained even when the two sexes were considered, except for PTSD. Indeed, women with PTSD showed significantly lower plasma OT levels than healthy women (4.13 ± 1.15 vs 5.33 ± 1.18, p < 0.001), while no difference was assessed between OT levels in PTSD and healthy men (4.61 ± 1.36 vs 4.83 ± 1.18). This suggests that the low OT vaues amongst PTSD were mainly due to female subjects.

Table 1
Mean age ±SD in healthy control subjects (HC) and in OCD, PTSD and MDD patients.

Groups	Age, years	M/F differences
Total healthy controls (90)	35.0 ± 6.4	
men (45)	35.1 ± 7.5	t = 0.138, p = 0.891
women (45)	34.9 ± 6.2	
Total psychiatric patients (86)		
Total OCD (40)	29.2 ± 7.3	
men (22)	29.3 ± 7.7	t = 0.090, p = 0.929
women (18)	29.1 ± 7.0	
Total PTSD (26)	40.3 ± 9.5	
men (13)	40.6 ± 9.7	t = 0.164, p = 0.871
women (13)	40.0 ± 8.9	
Total MDD (20)	33.0 ± 7.6	
men (10)	35.4 ± 7.3	t = 1.371, p = 0.187
women (10)	31.2 ± 6.4	
Total patients (176)		



Legend. OT = oxytocin; SEM = standard error of the mean (reported on the bar graph).

Fig. 1. Oxytocin levels in each group, divided by diagnosis and gender.
Legend. OT = oxytocin; SEM = standard error of the mean (reported on the bar graph).

Table 2
Plasma OT levels (pg/ml, mean ± SD) and sex-related differences in healthy controls (HC), OCD, PTSD and MDD patients.

Groups	Plasma OT (pg/mL, mean ± SD)	M/F differences
Total HC (90)	5.74 ± 1.99	
men (45)	4.78 ± 0.79	$t = -2.410$, $p < 0.001$
women (45)	6.00 ± 1.15	
Total psychiatric patients (86)		
Total OCD (40)	6.47 ± 1.41	
men (20)	5.81 ± 1.36	$t = -0.501$, $p > 0.1$
women (20)	6.93 ± 1.15	
Total PTSD (26)	4.37 ± 1.62	
men (13)	4.61 ± 1.36	$t = 0.854$, $p > 0.1$
women (13)	4.13 ± 1.15	
Total MDD (20)	3.41 ± 0.79	
men (10)	3.17 ± 1.42	$t = -1.006$, $p > 0.1$
women (10)	3.99 ± 1.74	

4. Discussion

The present retrospective and thus preliminary study explored plasma OT levels in healthy control (HC) subjects and in patients suffering from three different psychiatric disorders (OCD, PTSD and MDD) particularly evaluating possible intra- and intergroup sex-related differences. Our findings showed that plasma OT levels of healthy subjects were higher in women than in men. However, these differences were no longer apparent in individuals with OCD, PTSD or MDD. In fact, women with PTSD had levels of OT that were lower than those in men.

The finding of higher levels of OT in healthy, comparatively young women versus men replicates previous findings [31]. This association is also consistent with the assumption that females are more dependent on OT than men [79]. In addition, steroids, such as estrogen, progesterone and testosterone, can influence OT, AVP and the expression of their receptors [80–83]. In rodents, estradiol enhances OXTR affinity for OT, while chronic progesterone may decrease OT binding, especially in the amygdala [26–28].

Interestingly, when comparing plasma OT levels between men and women suffering from one of the three psychiatric disorders were considered, no significant difference emerged. However, specific considerations have to be made. In our PTSD group, although plasma OT levels were significantly lower than that of HC, this difference was mainly due to values in female patients. This finding is in contrast with results of a previous study showing that women with a history of physical abuse were characterized by increased OT levels under acute stress [84], or with the report of decreased OT levels in male policemen [64]. The heterogeneity of these findings may be due to the variety and severity of traumas experienced by the assessed patients and individual differences in adversity across the lifespan [85]. Factors such as these need to be considered in the interpretation of variations in OT.

Traumas related to sociality may be of particular relevance to later production of OT or the OXTR. For example, a study evaluating the predictive value of OT on PTSD symptoms following a car accident led to negative results [86]. The nature of traumatic experiences, including physical abuse, may be especially critical in women. In present study, of the PTSD patients seven out of thirteen women had a history of prior physical or sexual violence. The small size of our sample precluded an analysis the effect of different traumas on OT, but these are likely to be of importance.

Understanding the role of functional role of OT will be increased by measures of the expression of the OXTR. There are indications that OXTR gene polymorphisms and OXTR gene methylation have some value in the prediction of OT's function or OT synthesis [87,88]. For example, preliminary evidence for female-specific associations between OXTR methylation and early life adversity and socio-affective functioning has been reported [89,90].

In the present study, MDD patients showed significant lower plasma OT levels than those in healthy subjects and this difference remained significant when both the two sexes were compared with those of HC. Moreover, MDD patients showed the lowest plasma OT values amongst diagnostic groups. It is well known that MDD is characterized by a hyper-reactivity of the HPA axis [91,92], with loneliness and life events playing a decisive role in the development of this disorder [93–97]. More specifically, past studies found higher OT to be associated with both better social interaction and reduced activity in the HPA axis [98]. Negative correlations were also found between OT and both depressive symptomatology and suicidality [38,39]. Even for MDD, as already noted in PTSD, OXTR gene polymorphisms seem to play a significant role in the development of the disorder, since the different alleles have been associated with different levels of psychological resources, optimism, self-esteem [99], and reward dependence [100]. Particularly, the minor A allele has been associated with greater depressive symptomatology in MDD patients [99] and higher physiological and subjective stress reactivity [101]. Therefore, different OT levels in MDD patients may be influenced by OXTR gene polymorphisms, although no studies explored as yet this interdependence.

Different considerations have to be made for the OT values of patients with OCD that were significantly higher when compared to healthy subjects. Brain areas involved in the pathophysiology of OCD circuit, such as the orbitofrontal cortex, caudate and accumbens nuclei seem to be influenced by serotonin as well as by OT; OT and serotonin that have been found to interact anatomically and functionally in both the CNS and periphery [49]. As mentioned above, OT levels are putatively involved in the pathophysiology of OCD behaviors, as supported by animal data [50,102–104], but also by high CSF and plasma OT levels in OCD patients [50]. Interestingly, OT levels were negatively related to the OCD symptom severity, as assessed by the Y-BOCS total score, rather than to specific symptoms [105]. This might be due to the presence of anxiety generally associated with the OCD, and by the anxiolytic activity of OT. On the other hand, anxiety may be generated by obsessions, perceived as intrusive and uncomfortable, while performing compulsions would reduce the anxiety levels. Although dimorphism has been reported for the frequency of both obsessions and compulsions [106], the overall prevalence of OCD has been generally reported to be similar in the two sexes. However, a recent review highlighted that women exhibited OCD 1.6 times more commonly than men, with lifetime prevalence rates of 1.5% in women and 1.0% in men [107]. Again, the typically elevated OT levels belonging to the peripartum period seemed to be associated with an increased risk for the onset or the worsening of OCD [108–110]. This would suggest that women might be particularly at risk for some OCD subtypes more related to homonal changes, but the mechanisms for this remain to be determined.

Epigenetic studies have suggested an association between OXTR hypermethylation and symptoms severity in OCD [111]. Further investigations concerning epigenetic alterations in the OXTR seem necessary in OCD, while considering the possible relationship between methylation of the OXTR and circulating OT levels. Furthermore, vulnerability to psychopathological disorders/symptoms may occur following events that might occur during critical periods in early development and later along the life spam [112]. Such vulnerabilities have been associated with a single nucleotide polymorphism (SNP) rs53576 in the OXTR gene, which maps to the third intron (a noncoding region). The rs53576 appears to be a promising genetic marker of individual differences in social behavior, stress reactivity, and psychopathology. The minor A allele has been associated with vulnerabilities to psychiatric and social disorders and maladaptive outcomes [99–101, 113]. By contrast, the G allele has been associated with positive social behaviors, including sociality [114], seeking emotional support when

distressed [115], and being more likely to benefit from social support [116]. For example, individuals with an A allele and less secure attachment reported more social anxiety than G homozygotes [117], while among individuals with an A allele, a perceived negative social environment was associated with significantly increased PTSD symptoms. Sex differences in OXTR gene polymorphisms [87] and in DNA methylation [118] have been observed to affect stress-responses in a sex-dependent manner. Female-specific associations between OXTR methylation and psychopathology, early life adversity and socio-affective functioning have been reported [89,90]: this could be related to sex differences in psychobiological responses to stress [119] and to the higher prevalence of PTSD among women.

Finally, in the present study significant OT differences emerged from intergroup comparisons. Patients with OCD showed higher plasma OT levels than those with PTSD and MDD; this statistical significance remained even when the comparison was performed by gender. This is in agreement with the fact that OT in OCD patients was significantly higher than in HC, while OT in patients suffering from MDD or PTSD was significantly lower than in their healthy counterparts. In a comparison between patients with PTSD and those with MDD, both groups with lower OT values, when compared to HC, revealed significantly higher OT values in the PTSD group; however, this difference disappeared when the comparison was made between women. As mentioned, in this study women with PTSD showed the largest difference in mean OT value compared to their healthy counterparts, thus showing, together with female MDD the lowest value among all four groups of enrolled women in this study.

Based on research primarily conducted in rodents, we can speculate that the differences seen here between the two sexes also might be based in part on sex differences in peptide receptors, especially for AVPR and OXTR [83]. However, before strong conclusions can be drawn regarding the role of OT in psychiatric disorders, additional understanding of the human OXTR is needed [120,121]. Better methods also are needed for assessing the role of sex and experience across development which could affect sex differences in vulnerability to disorders.

The origins of the difference described here may reflected sex differences in vulnerability to manage basic adaptive and social functions and mild stresses, which could become more serious and manifest as disease states. Whether this arises as a cause or consequence of vulnerability in the OT system remains to be determined.

Growing evidence suggests the importance of the role of the oxitocinergic system, including availability of the peptide as well as the methylation status of the OXTR gene, to alter vulnerability to different types of responses to trauma. These in turn have consequences for behavioral and social responses across the lifespan, supporting the value of measures of DNA methylation [122]. Although not available here, future studies should include a detailed medical and social history of the patients with the inclusion of significant social relationships and trauma across the life span and especially during childhood [85].

Limitations in this study should be acknowledged. First, the retrospective nature and the size of the sample. Secondly, OT levels were measured in plasma, and the importance of this measure to central nervous system function is not well understood. However, parallel modifications in plasma and central OT have been reported in a variety of studies [27,123], leaving open the possibility that peripheral OT levels may be useful markers of the CNS concentrations of this neurohormone [47,124,125]. Furthermore, we did not evaluate the presence of young children in the recruited subjects considering that the plasma values of OT would seem to be related to the parent-child interactions [126]. Finally, the menstrual cycle-related fluctuations in OT levels should be considered as a potential bias in the female population [127]. The major strengths of the study were that the two sexes were equally represented in our sample, the patients were all within a limited age range, all of them were drug-free and, within each subgroup, patients were all suffering from the only diagnosed psychiatric disorder.

In summary, the relationships among components of the OT system and sex differences in these disorders, are complex. The present study revealed that the circulating levels of OT tend to become similar in men and women when comparisons are made in those suffering from a psychiatric disorder, increasing or decreasing in the two sexes depending on the type of pathology. Therefore, it is conceivable that in psychopathological conditions, such as those explored in this study, OT assumes greater importance as a marker of dysfunctions of the regulation of the HPA axis or of inflammatory processes.

Sex differences in psychiatric disorders presumably reflect the combined influence of genetics, epigenetics, endocrinology and other experiences. For example, women may have been more likely to experience childhood abuse [128]. Future investigations of the role of the OT system in psychiatric conditions should take into consideration the levels of circulating sex hormones, particularly in women. Circulating AVP levels should be considered as well, given its role in stress management, particularly in men. At the same time, other major hormones including prolactin and cortisol may be sexually-dimorphic and could have prognostic value. It is important to recognize that OT also is a component of the immune and inflammatory systems [3]. There is increasing evidence implicating excess inflammation in both psychiatric conditions and general health [129].

Awareness of the importance of studying sex differences in the OT system is relatively recent but growing [3,72]. However, differences in the OT system, such as those described here, as well as measures of AVP and its receptors suggest that a deeper understanding this system could offer clues to mechanisms underlying either the sexually dimorphic vulnerability or resilience to psychiatric disorders. This knowledge in turn may suggest novel interventions to prevent or treat such disorders, with consequences that differ in males and females.

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Authors contributions

D. Marazziti: conceptualization, investigation, methodology, writing – original draft and review and editing.
S. Baroni: investigation, methodology.
L. Palego: investigation, methodology.
L. Dell'Osso: supervision.
C. Carmassi: investigation, methodology.
G. Giannaccini: supervision.
F. Mucci: investigation, methodology, editing.
G. Pagni: investigation, methodology.
A. Della Vecchia: investigation, methodology.
M.G. Carbone: data curation, formal analysis, visualization, writing – original draft and review and editing; **C.S. Carter**: writing review and editing.

Declarations of interests

None.

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