



Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol



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ABSTRACT

The neuropeptide oxytocin (OT) promotes social behavior and attenuates stress responsivity in mammals. Recent clinical evidence suggests OT concentrations may be dysregulated in major depression. This study extends previous research by testing whether: 1) OT concentrations vary systematically in depressive disorders with and without hypercortisolemia, 2) gender differences in OT concentrations are observed in depressed vs. healthy control participants, and 3) OT concentrations are predictive of clinical phenotypes. Plasma OT concentrations of psychotic major depressive (PMD; $n = 14$: 10 female, 4 male), non-psychotic major depressive (NPMD; $n = 17$: 12 female, 5 male), and non-depressed, healthy control ($n = 19$: 11 female, 8 male) participants were assayed at 2000, 2400, 0400, and 0800 h. Plasma cortisol concentrations were quantified at 2300 h, and clinical phenotypes were determined. As expected, PMD participants, compared to NPMD and healthy control participants, showed higher plasma cortisol concentrations. Although both depressed groups showed similar OT concentrations, a significant interaction effect between group and gender was observed. Specifically, depressed females exhibited lower mean OT concentrations than depressed males. Further, depressed vs. healthy control female participants exhibited lower mean OT concentrations, whereas depressed vs. healthy control male participants showed a trend in the opposite direction. OT concentrations were also predictive of desirability, drug dependence, and compulsivity scores as measured by the Million Clinical Multiaxial Inventory-III. All findings were independent of cortisol. These data suggest that OT signaling may provide a mechanism by which to better understand female-biased risk to develop depressive disorders and that plasma OT concentrations may be a useful biomarker of certain clinical phenotypes.

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1. Introduction

Individuals with depressive disorders often exhibit social difficulties, anxiety symptoms, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Heuser et al., 1994). A common feature of HPA axis dysregulation is hypercortisolemia, which is present in 40–60% of depressed patients (Gold et al., 1986; Parker et al., 2003). Depressive disorders are also twice as prevalent in female compared to male patients (Nestler et al., 2002; Young, 1998).

The pathophysiology of depressive disorders and enhanced female risk to develop them are not well understood. It has been hypothesized that the neuropeptide oxytocin (OT) may play a role in these phenomena (Frasch et al., 1995). OT is a neuropeptide of hypothalamic origin with broad ranging central and peripheral nervous system effects. OT is released during positive social interactions (Knox and Uvnas-Moberg, 1998; Young et al., 2008), and exhibits anxiolytic properties in preclinical animal models (Amico et al., 2004). OT also exerts a tonic inhibitory influence over the HPA axis (Neumann et al., 2000). However, stressful social experiences, which are frequent precipitants of depressive disorders, activate the HPA axis. Often these experiences involve social isolation or loss, which may decrease OT signaling, thereby diminishing OT's ability to inhibit HPA axis drive. Females may be particularly vulnerable under these stressful circumstances, as they

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respond to social rejection (Stroud et al., 2002) and marital conflict (Kiecolt-Glaser et al., 1996, 1998) with greater HPA axis responses compared to men.

Preliminary research has shown that some depressed patients exhibit lower OT concentrations compared to healthy controls and that OT concentrations are lower in patients with moderate compared to mild depression (Frasch et al., 1995; Garcia et al., 2011; Ozsoy et al., 2009). Several pilot studies have concomitantly measured cortisol and OT concentrations in major depressed patients (Garcia et al., 2011; Parker et al., 2010), but no research has evaluated OT concentrations in patients with psychotic major depression (PMD), who typically exhibit greater depressive severity, and who are more likely to exhibit hypercortisolemia than patients with non-psychotic major depression (NPMD) (Belanoff et al., 2001).

In addition to the well-described roles of OT biology in human behavioral functioning, there is emerging evidence that OT concentrations are also associated with an array of clinical phenotypes and personality traits. For example, cerebrospinal fluid (CSF) OT concentrations are associated with a history of aggression (Lee et al., 2009), childhood trauma (Heim et al., 2009), and suicide intentionality (Jokinen et al., 2012). CSF OT concentrations are likewise negatively correlated with anxiety concentrations in patients with major depression (Scantamburlo et al., 2007) and plasma OT concentrations are lower in female patients with borderline personality disorder compared to healthy female controls (Bertsch et al., 2013). Mothers who used cocaine during pregnancy have lower plasma OT concentrations and greater hostility and depressed mood, as well as less social support and fewer adaptive strategies for dealing with stressful life events compared to cocaine naïve mothers (Light et al., 2004). In contrast, higher plasma OT concentrations are associated with measures of positive personality traits including increased extroversion in healthy male and female participants (Andari et al., 2012) and secure attachment and lower compulsive temperament in first-time mothers (Strathearn et al., 2009, 2012). Increased plasma OT concentrations are also associated with secure attachments and lower plasma cortisol and anxiety concentrations in healthy premenopausal women (Tops et al., 2007).

The present study extends previous research efforts in several respects. We measured plasma OT and cortisol concentrations in both male and female PMD, NPMD, and healthy control participants to test whether OT concentrations differ in participants with PMD vs. NPMD, or in depressed participants with and without hypercortisolism (regardless of depressive subtype). We also sought to examine whether female and male depressed participants differed in OT concentrations, and whether cortisol concentrations influenced these differences. Finally, we explored whether OT concentrations were associated with depression severity and anxiety symptomology (Hamilton Depression Rating Scale), as well as personality and clinical syndromes (Million Clinical Multiaxial Inventory-III) in depressed participants.

2. Materials and methods

2.1. Study participants

Adult participants were recruited through Stanford University Medical Center, as well as through online and print advertisements, as part of a larger research program, which investigates HPA axis physiology in depressive disorders. The present study was initiated after the completion of two recruitment rounds of a larger parent study, and resulted in available samples from 50 participants: 14 PMD (10 female, 4 male), 17 NPMD (12 female, 5 male), and 19 healthy controls (11 female, 8 male). Participants enrolled in the present study did not overlap with those in our previously

published OT and depression study (Parker et al., 2010). However, participants' cortisol data have been reported previously (Keller et al., 2006; Schatzberg et al., 2013). This research was conducted in accordance with the Declaration of Helsinki, and the Stanford University Institutional Review Board approved the study design. Informed written consent was obtained from all participants after the study procedures had been fully explained.

All PMD and NPMD participants met DSM-IV-TR criteria for a current major depressive episode, with or without psychotic features and provided Hamilton (1960) Depression Rating Scale (HDRS) scores ranging from severe to very severe depression. PMD participants were required to have a minimum score of 5 on the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). This subscale consists of the following four items: conceptual disorganization, suspiciousness, hallucinations, and unusual thought content. Healthy control participants were required to have a score <6 on the HDRS, have no psychotic symptoms as measured by the BPRS positive symptom subscale, and have no history of Axis I disorders as determined by the Structured Clinical Interview for DSM-IV-TR (First et al., 1997). Depressed participants were allowed to remain on psychiatric medications (see Table 1) provided the dose had not been adjusted in the last week. Healthy control participants were free of psychiatric medications. Additional study exclusion criteria for all participants were as follows: electroconvulsive shock therapy or substance abuse problems in the last six months, current drug use (evaluated by urinary toxicology screening), major medical illness, history of seizures, major head trauma, abnormal clinical laboratory tests, unstable or untreated hypertension, cardiovascular disease, endocrine disorders, pregnancy, or lactation.

2.2. Blood collection procedures

Participants were admitted to the Stanford University Hospital General Clinical Research Center at 1500 h. At 1600 h, an intravenous line, kept patent with saline infusion, was started in one arm and 4 mL of whole blood was drawn into heparinized vacutainer tubes once every hour between 1800 and 0900 h. Participants were required to be supine in bed 15 min prior to each blood sample collection. No food or sleep restrictions were imposed. Blood samples were subsequently centrifuged and the plasma fraction was stored at -70°C prior to hormone quantification. Blood aliquots were available for OT analyses at four time points (2000, 2400, 0400, and 0800 h).

2.3. Plasma hormone quantification

Plasma OT concentrations were quantified using a commercially available enzyme immunoassay kit (Enzo Life Sciences, Inc.,

Table 1
Concomitant psychiatric medications for participants with non-psychotic major depression (NPMD) and psychotic major depression (PMD).

	NPMD (N = 14)	PMD (N = 13)
No psychiatric medications	2	8
Antidepressant only	3	4
Antidepressant and antipsychotic	1	0
Antidepressant and anxiolytic	1	1
Antidepressant and mood stabilizer	0	1
Antidepressant, antipsychotic, and anxiolytic	3	0
Antidepressant, antipsychotic, and mood stabilizer	3	0
Antipsychotic and mood stabilizer	1	0
<i>Breakdown of psychiatric medications</i>		
Any antidepressant	10	6
Any antipsychotic	8	0
Any anxiolytic	4	1
Any mood stabilizer	4	1

Farmingdale, NY). This kit has been validated for use in humans, and is highly specific and exclusively recognizes OT and not related peptides (Carter et al., 2007). Per Enzo Life Sciences literature, the limit of assay sensitivity where the curve is no longer linear is 10 pg/mL. Sample extraction and concentration procedures were initiated by thawing plasma samples in an ice bath before acidification with 0.1% trifluoroacetic acid (TFA). Acidified samples were then centrifuged at 17,000g for 15 min at 4 °C. Phenomenex Strata-X columns (Phenomenex Inc., Torrance, CA) were activated with 4 mL of HPLC grade methanol followed by 4 mL of molecular biology grade water. Following column activation, the sample supernatants were applied and drawn through the columns by vacuum. Peptides were then eluted by applying 4 mL of pre-elution buffer (89:10:1 water:acetonitrile:TFA) followed by 4 mL of elution buffer (80:20 acetonitrile:water). Elutes were evaporated at room temperature using compressed nitrogen, and reconstituted in assay buffer prior to quantification. Samples were assayed in duplicate with a tunable microplate reader for 96-well format according to manufacturer's instructions. A trained technician without knowledge of experimental conditions performed all assays. Intra- and inter-assay coefficients of variation were below 10%.

Plasma cortisol concentrations were quantified for all participants using the Access Immunoassay System (Beckman Coulter, Chaska, MN) as part of the larger parent study. The sensitivity of this assay is 0.4 ug/dL (11 nmol/L). Cortisol concentrations in our study were evaluated at 2300 h, a time well-validated for determination of hypercortisolemia (Boscaro et al., 2001; Raff et al., 1998).

2.4. Phenotypic measurements

Depression severity and anxiety symptomology were determined using the HDRS total score and the HDRS anxiety subscale, respectively. The HDRS is a widely used and well-validated, investigator administered measure of symptom severity and determination of clinical subtypes for depression (Hamilton, 1960). Personality characteristics and clinical syndromes were evaluated with the Million Clinical Multiaxial Inventory (MCMI)-II or -III. These characteristics correspond to Axis II diagnoses in the DSM-IV. The MCMI was administered to depressed participants only, as it was standardized and developed for exclusive use in clinical populations (Million et al., 2009). In addition to assessing a wide range of personality disorders and clinical syndromes, the MCMI includes three indices that modify a participant's Base Rate scores: Disclosure, Desirability, Debasement; and, two random response indicators: Validity and Inconsistency.

2.5. Statistical analyses

The plasma OT data were severely skewed, following an exponential distribution. For use as an independent (predictor) variable, we took the mean of the log of the 2000, 2400, 0400 and 0800 h measures (which prevents a single data point skewing the mean). For use as a dependent (predicted) variable, we calculated the arithmetic mean of the four time points, and then modeled both the mean and the skewed error distribution directly in a Generalized Linear Model (GLM; gamma error distribution, reciprocal link function) implemented using JMP v10 for Windows, and PROC GENMOD in SAS v9.3 for Windows as needed for detailed post-hoc tests. This approach is preferable to simple transformation and modeling in a least-squares framework, particularly because it is more agnostic and flexible in accommodating the error distribution of the data (Littell et al., 2002). The 2300 h plasma cortisol data showed the same skew, and thus were log transformed for use as a predictor, and treated in the same GLM framework for use as a dependent variable.

We first tested whether Group (PMD, NPMD, and healthy control) and Gender (female, male), predicted 2300 h plasma cortisol concentrations. This analysis is essentially a positive control as PMD patients are known to show elevated 2300 h cortisol concentrations over NPMD patients (Belanoff et al., 2001). Group was nested within Depressed, to explicitly test whether Depressed and Non-depressed participants differed on average; and then whether NPMD and PMD participants differed from each other; Gender and all interactions were included. Least-squares means and Bonferroni-corrected orthogonal planned contrasts were calculated for post-hoc-testing. Assumptions of the model were tested graphically. In addition, this model estimated overdispersion (no significant evidence for overdispersion was observed).

An identical analysis was used to predict mean plasma OT; and then also with 2300 h cortisol included as a covariate, yielding identical results. The simpler model is presented in the Results section. The post-hoc tests, and model-fit tests discussed above were employed.

Finally, the predictive relationships of plasma OT and cortisol concentrations to measures of 1) depressive severity (HDRS), 2) anxiety symptoms (HDRS anxiety subscale), and 3) personality dimensions (MCMI base rate scores) were each tested with the same multiple linear regression models implemented as a GLM in JMP v10 for Windows. These analyses excluded healthy controls, because they either scored low and without variation, or because no score could be obtained on the instrument. The models were blocked by Group, Gender, and their interaction, and the log of the 2300 h plasma cortisol, and its interaction with Group. We tested for an overall effect of the mean of the log of the plasma OT concentration, and its interaction with Group (i.e., whether the effect of OT differed in PMD and NPMD participants). This model therefore tested within each blocking factor for consistent effects of OT across the blocking factors (e.g., testing whether the effect of OT within each gender is consistent for both genders). The interaction explicitly tests whether the effect of OT is different in the two patient groups. Bonferroni planned contrasts were calculated as required for post-hoc tests. The assumptions of GLM were tested graphically, and no transformations were required.

3. Results

Demographic and clinical characteristics for PMD, NPMD, and healthy control groups are summarized in Table 2. Because age differed significantly by group [$F_{2,41} = 3.889$; $p = 0.028$], with NPMD participants being older than healthy control participants ($p = 0.027$; no other groups differed significantly), age was included as a statistical covariate in subsequent analyses as appropriate.

Of the 50 participants with available plasma samples, one participant was omitted for a missing plasma OT value. We also excluded all female participants prescribed estrogen due to the known modulatory effects of estrogen on OT (Ochedalski et al., 2007) and cortisol (White et al., 2006) signaling. These exclusions yielded a final sample size of 44 participants [13 PMD (9 female, 4 male), 14 NPMD (9 female, 5 male), and 17 healthy controls (9 female, 8 male)] for the analysis.

As expected, 2300 h cortisol concentrations differed by group. Specifically the PMD participants showed significantly higher concentrations than the NPMD participants [Group-nested-within-depressed Likelihood Ratio (LR) $\chi^2 = 7.76$; $p = 0.0053$; see Table 2], and further post-hoc tests showed that healthy controls did not differ from NPMD, but did differ from PMD participants. No other significant main or interaction effects were observed.

Initial descriptive statistics and subsequent follow up analyses revealed that PMD and NPMD participants did not differ in plasma OT concentrations [Group-nested-within-depressed LR $\chi^2 = 0.14$;

Table 2
Participant demographics and clinical characteristics.

	HC (N = 17)	NPMD (N = 14)	PMD (N = 13)	Test
Age	37.12 (12.71) ^{ab}	47.57 (11.99) ^a	35.69 (12.22) ^b	$F_{41,2} = 3.889$; $p = 0.028$
Education	15.62 (1.62) ^a	15.29 (1.44) ^a	15.15 (3.00) ^a	$F_{41,2} = 0.203$; $p = 0.817$
Gender				
Male	8	5	8	$LR\chi^2 = 0.899$; $p = 0.638$
Female	9	9	9	
HDRS	0.71 (1.21) ^a	22.14 (3.70) ^b	31.31 (6.12) ^c	$F_{41,2} = 237.6$; $p < 0.001$
HDRS Anxiety	0.47 (1.01) ^a	14.57 (3.27) ^b	15.54 (3.86) ^c	$F_{41,2} = 135.9$; $p < 0.001$
BPRS	18.94 (1.56) ^a	31.86 (4.29) ^b	47.75 (6.62) ^c	$F_{40,2} = 153.7$; $p < 0.001$
BPRS Positive Symptom Scale	4.18 (0.53) ^a	4.36 (0.74) ^a	11.83 (1.99) ^b	$F_{40,2} = 179.5$; $p < 0.001$
11pm plasma cortisol (µg/dL)	2.32 (1.54) ^a	2.71 (2.40) ^a	6.50 (6.45) ^{b,d}	$F_{40,2} = 4.916$; $p = 0.012$

HC, healthy control; NPMD, non-psychotic major depression; PMD, psychotic major depression; HDRS, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale.

Means with the same superscript are not significantly different according to Tukey's post-hoc test.

^d One PMD participant had a missing 11pm plasma cortisol value.

$p = 0.7125$]. Instead, the only predictor of plasma OT concentrations was a highly significant interaction between depressed group and gender [Depressed*Gender $LR\chi^2 = 9.54$; $p = 0.0020$]. Males and females showed opposite patterns between depressed and non-depressed participants. Depressed females had significantly lower plasma OT concentrations than healthy control females [Healthy Control Females vs. Depressed Females: $LR\chi^2 = 6.76$; $p = 0.0093$; Bonferroni critical alpha correction set at 0.025]. Male participants generally showed greater OT variability, which rendered some post-hoc tests non-significant [Healthy Control Males vs. Depressed Males: $LR\chi^2 = 3.52$; $p = 0.0605$; Bonferroni critical alpha correction set at 0.025]. Male and female depressed participants significantly differed [Depressed Males vs. Depressed Females: $LR\chi^2 = 7.33$; $p = 0.0068$; Bonferroni critical alpha correction set at 0.025], but their control counterparts did not [Healthy Control Males vs. Healthy Control Females: $LR\chi^2 = 3.14$; $p = 0.0762$; Bonferroni critical alpha correction set at 0.025] (see Fig. 1).

For the phenotypic data we only report significant results for OT, or its interactions, since the presence of cortisol in the model did not alter the findings as mentioned above. The MCMI Desirability Score increased with higher mean log plasma OT [$F_{1,12} = 5.470$; $p = 0.0375$; Fig. 2a]. The MCMI Drug Dependence Base Rate Score decreased with higher mean log plasma OT ($F_{1,12} = 6.428$; $p = 0.0262$; Fig. 2b). Finally the MCMI Compulsive Base Rate Score, was predicted by the oxytocin*group interaction ($F_{1,12} = 9.498$; $p = 0.0095$; Fig. 2c). For this last result, post-hoc analysis showed that OT positively predicted compulsivity in the PMD group only [$F_{1,12} = 17.19$; $p = 0.0014$; Bonferroni critical alpha correction set at 0.025], but not the NPMD group [$F_{1,12} = 0.14$; $p = 0.1361$; Bonferroni critical alpha correction set at 0.025].

4. Discussion

This pilot study was designed to investigate whether plasma OT concentrations differed in the context of hypercortisolemia in PMD, NPMD, and healthy control participants. We secondarily tested the relationship between plasma OT concentrations and clinical and personality syndromes in depressed participants. As expected, PMD

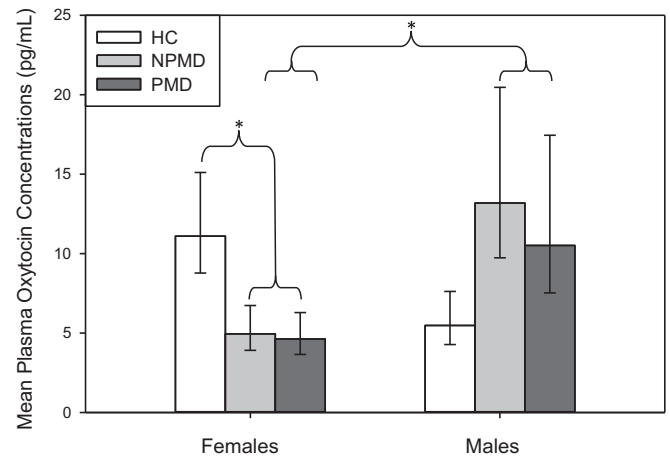


Fig. 1. Mean plasma oxytocin (OT) concentrations differ by group and sex. Post-hoc tests revealed that depressed females have lower OT concentrations than healthy control females, and depressed females have lower OT concentrations than depressed males. Data show fitted means and standard errors. * indicates a significant finding after correction for multiple comparisons ($p < 0.025$). HC, healthy control; NPMD, non-psychotic major depression; PMD, psychotic major depression.

participants exhibited significantly higher cortisol concentrations compared to NPMD and healthy control participants. However, PMD and NPMD participants did not differ in plasma OT concentrations. Interestingly, subsequent analyses revealed a significant group by gender interaction effect, such that depressed females exhibited lower OT concentrations compared to depressed males, irrespective of psychotic status. Further, depressed females, irrespective of psychotic status, exhibited lower OT concentrations compared to healthy control females. Depressed males, irrespective of psychotic status, exhibited a strong trend (before controlling for multiple comparisons), toward higher plasma OT concentrations compared to healthy control males. These findings were all independent of cortisol concentrations. A positive relationship was found between OT concentrations and MCMI Desirability scores for both male and female depressed participants, irrespective of psychotic status. Further, an inverse relationship between OT concentrations and MCMI Drug Dependence Base Rate scores was found for both male and female depressed participants, irrespective of psychotic status. Finally, OT concentrations were positively correlated with MCMI Compulsivity Base Rate scores in PMD, but not NPMD, participants.

The findings that OT concentrations: 1) differed significantly between female and male depressed participants; and, 2) were decreased in depressed females but increased (non-significantly) in depressed males compared to gender-matched healthy controls were not predicted. One post-hoc explanation is that in females, OT plays its previously demonstrated role of promoting social bonding (Lim and Young, 2006; Pedersen et al., 1982; Pedersen and Prange, 1979; Witt et al., 1992), and when females experience social isolation or loss, as frequently occurs prior to onset of depression (Bruce and Hoff, 1994), they experience diminished OT release. In contrast, OT may function as a stress hormone in males, as exogenous OT suppresses cortisol release in response to psychological stress when paired with social support in males (Heinrichs et al., 2003). This suggests that males may experience elevated OT release as a mechanism to reduce stress by promoting social behavior, increasing social support and suppressing cortisol release. This interpretation may help to explain the disparity in findings from previous studies examining plasma OT in depression, which have shown both elevated (Parker et al., 2010) and diminished (Frasch et al., 1995) plasma OT concentrations in depressed

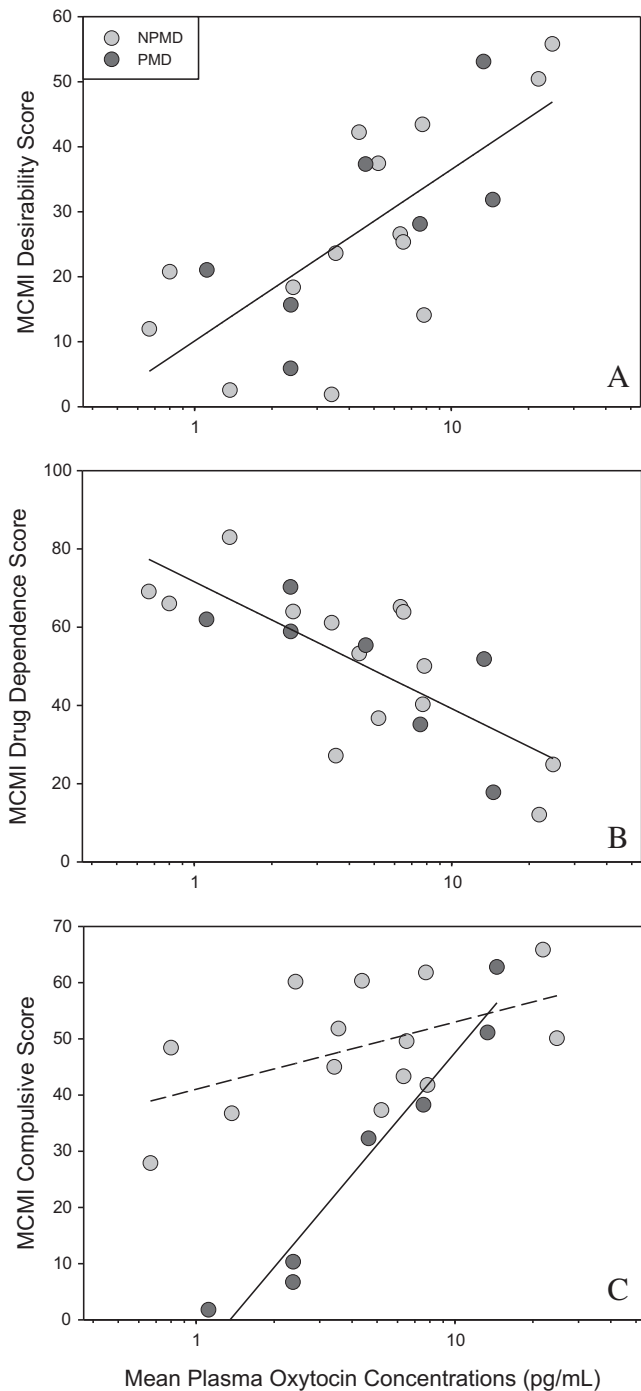


Fig. 2. Mean plasma OT concentrations: positively predict MCM Desirability scores in depressed participants (Panel A), negatively predict MCM Drug Dependence Base Rate scores in depressed participants (Panel B), and positively predict MCM Compulsivity Base Rate scores in PMD, but not NPMD, participants (Panel C). To correct for skew, mean plasma OT concentration is calculated as the mean of logged titers. To correct for the controlling variables in the analysis, the regression line is partialled (controlled) for other variables in the analysis, and calculated at the mean value of those variables. Similarly, data are shown as residuals from this mean regression line. NPMD, non-psychotic major depression; PMD, psychotic major depression.

participants. These previous studies consisted of small sample sizes, and were not powered to examine gender differences in OT concentrations, raising the possibility that the gender most represented in each study was perhaps responsible for driving the observed effects.

Although PMD and NPMD females presented with and without hypercortisolemia, respectively, they did not differ in OT concentrations, with both groups exhibiting equally diminished OT concentrations compared to healthy control female participants. There are two possible explanations for these findings. First, OT biology may be differentially regulated in females with PMD vs. NPMD. Specifically, the hypercortisolism that characterizes PMD may suppress OT release, whereas in NPMD, low circulating OT concentrations may be regulated via a cortisol-independent (and as yet unknown) mechanism. In contrast, it is also possible that diminished OT concentrations occur via cortisol-independent mechanisms in females for both depressive disorders. The available data unfortunately do not allow us to differentiate between these two possibilities, and indicate a clear need for follow up studies to rigorously test these competing hypotheses.

OT concentrations were significantly correlated with depressed participants' concentrations of Desirability scores on the MCM. This item is one of the "Modifying Indices" of the MCM and aims to measure a participant's response style to determine whether they have a propensity to present themselves in a positive light, essentially controlling for the subjective nature of this self-report measure (Million et al., 2009). Interestingly, it has been hypothesized that intranasal administration of OT may inflate a person's desire to report socially relevant information in a positive manner, thus altering their responses on self-report measures and interview questionnaires (Guastella and MacLeod, 2012). Our findings of a positive correlation between endogenous OT concentrations and increased MCM Desirability scores suggest that higher plasma OT concentrations represent a heightened drive to be viewed positively by others, at least for depressed participants. This finding also aligns with the established evidence that OT is critical in the expression of prosocial and affiliative behaviors (Young, 2009).

Our finding of an inverse relationship between OT plasma concentrations and MCM Drug Dependence scores are supported by increasing evidence that suggests dysregulation in OT signaling may play a significant role in the development of substance abuse problems and associated psychosocial issues, including depression (see Carson et al., 2013; McGregor and Bowen, 2012; McGregor et al., 2008 for review). For example, chronic administration of cocaine to pregnant and post-partum rats results in aberrant mothering behavior and increased aggression toward a resident intruder and these behavioral changes are associated with decreased OT concentrations in the medial preoptic area, ventral tegmental area, and hippocampus, as well as reduced OT receptor binding density in the ventral medial hypothalamus and the bed nucleus of the stria terminalis (Jarrett et al., 2006; Johns et al., 1997a,b). Importantly, this research is supported by evidence in humans. As outlined in the Introduction, women who used cocaine during pregnancy show blunted plasma OT concentrations, experience increased hostility and depressed mood, and have less social support and adaptive coping strategies for stressful life events than do healthy non-cocaine using mothers (Light et al., 2004). In other relevant preclinical studies repeat cocaine self-administration results in decreased hippocampal and hypothalamic OT concentrations, chronic exposure to opiates decreases central OT synthesis (You et al., 2000), and chronic exposure to alcohol is associated with degeneration of hypothalamic magnocellular OT containing neurons in both humans and rats (Silva et al., 2002; Sivukhina et al., 2006).

The finding that OT concentrations were positively correlated with MCM Compulsivity scores in PMD, but not NPMD, participants are intriguing. Preclinical studies have shown that both central and peripheral injections of OT to rodents result in repetitive and compulsive grooming behavior (Sarnyai, 1998). Further, Leckman et al. (1994) provided evidence for elevated CSF OT

concentrations in patients with obsessive–compulsive disorder (OCD) compared to patients with Tourette's syndrome and healthy controls. They further showed that CSF OT concentrations were positively correlated with current severity of OCD symptoms. However, given the evidence that higher plasma OT concentrations and intranasal administration of OT are associated with reduced positive symptoms in schizophrenia it is difficult to posit why plasma OT might be related to compulsivity in PMD, but not NPMD, participants (Pedersen et al., 2011; Rubin et al., 2010).

5. Limitations and conclusions

While producing interesting results, our study has several limitations. First, we did not experimentally control menstrual cyclicity, which is problematic given the known interaction of female reproductive hormones and OT on modulating the stress response (Ochedalski et al., 2007; Taylor et al., 2006). This study was also limited by the availability of social behavioral data, which precluded detailed analysis of OT concentrations in relation to social functioning. In addition, much like other studies in this field (Frasch et al., 1995; Garcia et al., 2011; Parker et al., 2010) our sample size was relatively small, particularly for males, so may not have been statistically powered to find significant relationships between OT concentrations in both males and females. Research with more participants, especially males, is necessary to bring greater clarity to gender effects on OT biology in depression. Research with more PMD participants is also necessary in order to determine whether low OT and high cortisol concentrations are associated. Finally, central and peripheral OT concentrations can be independently regulated under certain conditions (Landgraf and Neumann, 2004; Ludwig and Leng, 2006) thus leaving the possibility that clinical symptoms in our study population reflect dysregulation in brain OT systems that are not reflected in plasma samples. Future studies would benefit from assessing the relationship between concomitantly collected blood and CSF samples to more precisely determine the role of OT biology in depressive disorders.

In conclusion, these findings further implicate a role for dysregulated OT biology in patients with major depression, and extend this knowledge for the first time to patients with psychotic major depression. Evidence from this study indicates that OT signaling may provide a mechanism by which to better understand female-biased risk to develop depressive disorders, and suggests that intranasal OT “replacement” therapy may be efficacious in female patients with known impairments in OT signaling. Finally, data from this study suggest that plasma OT concentrations may be a useful biomarker for the presence of certain clinical and personality syndromes.

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Contributors

All authors read and approved the final manuscript. Kaeli Yuen, Dr. Alan Schatzberg, and Dr. Karen Parker conceptualized the theoretical framework for the research presented in this paper. Dr. Jennifer Keller and Dr. Schatzberg oversaw data collection for the parent study which was conducted by Dr. Keller, Dr. Anna Lembke,

Heather Kenna, and Dr. Lakshika Tennakoon in Dr. Schatzberg's laboratory. Shellie Hyde and Ms. Yuen prepared biological samples and conducted hormone assays in Dr. Parker's laboratory. Ms. Yuen and Ms. Hyde also entered experimental data, created the statistical database, and helped write the methods section of this manuscript. Dr. Joseph Garner, Dr. Dean Carson, and Dr. Parker conducted the statistical analyses, Dr. Garner wrote the statistical analysis section and the experimental results sections, and Dr. Carson created the figures and table. Ms. Yuen, Dr. Parker, and Dr. Carson wrote the first draft of the manuscript. Dr. Schatzberg, Dr. Parker, and Ms. Yuen provided financial support for the project.

Conflict of Interest

Ms. Yuen, Dr. Garner, Dr. Carson, Dr. Keller, Dr. Lembke, Ms. Hyde, Ms. Kenna, Dr. Tennakoon, Dr. Schatzberg, and Dr. Parker report no biomedical financial interests or potential conflicts of interest.

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