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The influence of depressive symptomatology and perceived stress on plasma and salivary oxytocin before, during and after a support enhancement intervention

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Summary Oxytocin (OT) activity increases in response to stress as well as to warm social contact. Subclinical depression is associated with higher stress but less reward from social contacts. The present investigation was intended to examine whether husbands and wives with high depressive symptomatology scores have increased plasma and salivary OT that may be mediated partly by higher perceived stress, and also to assess whether an intervention to convey partner support through “warm touch” may reduce effects of depressive symptoms on OT. In this study, 34 healthy married couples (n = 68) ages 20–39 provided self reports of depressive symptoms (CESD) and stress (Perceived Stress Scale) before being randomly assigned to a 4-week intervention study enhancing partner support through “warm touch”, or to a “behavior monitoring” control group. Plasma oxytocin levels were obtained pre- and post-intervention, while salivary oxytocin was taken at home during week 1 and week 4. Results revealed that subjects with higher depressive symptoms scores had higher plasma OT levels at pre-intervention, and higher salivary OT levels at home during week 1 (p < .05). Plasma OT results were moderated by gender such that plasma OT levels were highest among females high in depressive symptomology. Higher perceived stress was also linked to both higher depressive symptomatology (r = + .65, p < .0001) and plasma OT (p < .05) and a significant mediator. During the intervention, salivary OT remained elevated among subjects high in depressive symptomatology in the control group but not the intervention group. At post-intervention, plasma OT levels in subjects with vs. without depressive symptomatology no longer differed. Results indicate that subclinical depression is associated with elevated plasma and salivary OT levels, which may be mediated in part by increased stress. OT differences linked to subclinical depression were minimized by the warm touch intervention.

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1. Introduction

The role of oxytocin (OT) in formation of pair bonds is well established in non-human mammalian species (Carter, 1998; Young and Wang, 2004). For this reason, OT has received considerable recent attention in human research focused on family relationships and attachment quality. On the surface, however, the findings appear paradoxical. Some studies have observed higher plasma OT levels in men and women reporting more supportive relationships with spouses or parents (Gordon et al., 2008; Grewen et al., 2005; Light et al., 2005; Tops et al., 2007a; Turner et al., 1999); however, two of these same studies and several others also reported that higher OT levels were associated with anxiety or distress about social or romantic attachments (Marazziti et al., 2006; Taylor et al., 2006)(Gordon et al., 2008; Hoge et al., 2008; Taylor et al., 2010; Tops et al., 2007b).

One way to integrate these reports linking higher OT linked to both positive relationships and to ambivalent or distressing relationships is to consider the multiple roles of OT activity. In addition to its role in attachment and bonding, OT has been repeatedly shown in animal models to be activated by stress and anxiety-inducing stimuli, and thereby modulates and inhibits both sympathetic nervous system and hypothalamic-pituitary-adrenal stress activity (Amico et al., 2004; Ring et al., 2006; Windle et al., 2004). Helping to synthesize these two aspects of OT activity are studies indicating that endogenous or exogenous OT administration reduces anxiety behaviors in rodents via activation of OT receptors on serotonergic neurons (Slattery and Neumann, 2010; Waldherr and Neumann, 2007; Yoshida et al., 2009) and enhances inhibition of central amygdale by diazepam (Viviani et al., 2010). Such studies have led to suggestion that OT administration might also be beneficial as adjunctive treatment for social anxiety disorder (Guastella et al., 2009; Rotzinger et al., 2010).

In human depression, it is equally plausible that plasma OT levels would be low due to reduction in the rewarding aspects of social contacts or elevated due to increase in perceived stress. Recent research has been relatively consistent, however, in showing that most patients meeting criteria for major depressive disorder demonstrate elevated levels of plasma OT (Cyranowski et al., 2008; Parker et al., 2010; Scantamburlo et al., 2007). In the most extensive study of depression, Cyranowski et al. (2008) found that although the average plasma levels of OT were higher in unmedicated female depressed patients than controls, the difference was due to a subgroup of those with depression who showed huge pulsatile increases in OT even during quiet isolation while other patients did not. To date, however, no investigations have examined subclinical depression and whether it is also related to increased vs. decreased OT. Furthermore, no study has clarified whether effects of depression on OT are primarily linked to increased perceived stress levels, or whether increased perceptions of stress have separate and independent effects on OT activity.

Previously, we (Holt-Lunstad et al., 2008) studied OT, sympathetic and blood pressure changes produced by a 4-week intervention to increase support expressed through “warm touch” vs. a monitoring-only control condition in 34 married couples. The present report uses the data from this investigation to examine the following hypotheses: (1) that subclinical depression in married women and/or men is associated with increased plasma OT prior to the start of intervention; (2) that higher perceived stress is linked to both higher depressive symptoms and to higher OT, and may be a partial mediator of the relationship between the other 2 factors; (3) that the “warm touch” intervention reduces differences in OT associated with subclinical depression and/or perceived stress, providing evidence that this type of intervention is effective in normalizing physiological responses among stressed or mildly depressed individuals.

2. Method

2.1. Participants

Participants and procedures have been described in detail previously (Holt-Lunstad et al., 2008). To summarize briefly, 34 healthy married couples (n = 68) married 6 months or more were recruited from the community (age: mean = 25.2; SD = 3.8 years, range 20–39 years) and completed the screening and one month protocol. Couples were randomized into two groups, with 20 couples in the intervention group and 14 couples in the “monitoring only” control group. Recruitment of subjects and study protocol were approved by the university IRB committee.

2.2. Procedures

After randomization, couples in both groups underwent similar physiological assessment procedures before and after the 4-week intervention/behavioral monitoring period. Plasma OT was obtained once pre- and post-intervention. The effects of the intervention on OT activity were also assessed by comparing salivary OT obtained at home once during week 1 and twice during week 4 of the intervention/monitoring period. After consent was obtained, participants completed a packet of questionnaires that assessed standard variables that may influence health (e.g., demographics, health history) as well as depressive symptoms (Center for Epidemiological Studies Depression Scale or CESD) and recent life stress (Perceived Stress Scale). These questionnaires were completed once at the pre-intervention testing. OT measures: a pretreatment blood draw for plasma OT obtained via venipuncture was made after each couple sat close together for 5 min holding hands. For salivary OT, saliva samples were obtained at home on 3 occasions: saliva sample 1 was taken during the first week of the intervention/monitoring period, while samples 2 and 3 were both taken during the fourth week of the intervention/monitoring period, on different days. The intervention couples were instructed to obtain all three saliva samples at home on evenings when they practiced the warm touch techniques, while the controls were simply told to collect their samples during evenings spent at home. All couples were called by a research assistant during this time and reminded to do this. Participants were instructed to freeze the saliva samples immediately, and then all three frozen samples were returned to the lab at the time of the post-intervention procedure.
2.2.1. Outline of intervention, home practice and post-intervention testing protocol

Couples randomized to the intervention group were asked to come into the lab in groups of 3–5 couples, for two 1-h training sessions. During the first session (week 1 of the intervention) couples were trained in Rosen Method Listening Touch where one increases awareness of the partner’s mood and body state through touching their partner’s neck, shoulders and hands, first while the partner was seated in front of them and then while both partners stood together back to back, gradually initiating a slow rocking motion. Then, they were given an audio recording to guide them in practicing these techniques at home, and were instructed to practice for 30 min 3 times/week for 4 weeks, and to keep records of when they practiced and their mood state before and after practice. During the second session (week 2 of the intervention) couples watched a short video of actors showing examples of sensitive and insensitive touch, followed by a second video demonstrating neck, forehead and shoulder massages. Couples were then asked to follow along with the massage video, practicing with their spouse under supervision of a trained staff member. Couples were given the option either to add massage to their practice or to replace the listening touch practice with massage during weeks 2–4. In the Control Group, subjects were told not to change anything about their normal behavior with their spouse and to simply keep a diary of their physical affection and mood. They were asked to report this once a week for 4 weeks. For both the intervention and control groups, monitoring of warm touch had to be recorded online on a fixed schedule to prevent confabulation errors associated with retrospective recall.

2.3. Measures

2.3.1. Medical and demographic information (Volunteer Health Questionnaire)

Subjects completed an in-house form assessing all relevant health variables, plus occupation, education, and total family income.

2.3.2. Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D includes 20 clinically derived items and appears to be a reliable and valid measure of depression (Radloff, 1977). In a nationwide survey of 2500 participants, the scale’s reliability showed high consistency, ranging from .75 to .95 (Cronbach’s alpha).

2.3.3. The Perceived Stress Scale (PSS)

This widely used scale is a ten-item assessment designed to measure perceived stress exposure and severity over the past month. It has been demonstrated to have adequate psychometric properties and is related to other stress, health, and satisfaction measures (Cohen et al., 1983).

2.3.4. Oxytocin sampling and bioassay procedures

As previously described, a pre- and post-treatment plasma sample for OT was obtained directly from a single-stick venipuncture after 5 min of close warm couple contact, and the 3 home saliva samples for OT were obtained by using unstimulated passive drool collected into 4 ml plastic tubes. Participants were asked to spit into the tube until full. Samples were immediately frozen at the subjects’ homes, transported still frozen to the lab and then shipped to the University of North Carolina for assay using enzyme immunoassay (EIA) methods using an OT EIA kit from Assay Designs (Ann Arbor, Michigan, USA). For salivary OT, the methods used were similar to those developed for salivary OT and validated by Carter et al. (2007), with the addition of an extraction step that was required because Assay Design is now using a new and different OT antibody from the one they used. This new OT antibody now requires an extracted sample, because as stated in the new kit instructions, this new antibody gives much lower precision without an extracted sample. The extraction reduces matrix interference and, through evaporation, concentrates the sample 3.2 times, which is very similar to the 4.0 times concentration produced by Carter’s full dry-down procedure (Carter et al., 2007). In this study, the extraction efficiency was 101.6% and intra assay variability was 4.8% obtained from both saliva and plasma samples, since all of these samples were extracted and assayed in the same batch at the same time. Saliva OT and plasma OT have been shown to similarly discriminate breast-feeding from bottle-feeding mothers of infants, and to correlate reliably with each when obtained in the same time period (Grewen et al., 2010).

2.4. Primary analyses

We used Proc Mixed (SAS Institute; Singer, 1998; Little et al., 1996) to estimate random intercept models with random effects for couples. Kenny and colleagues (Kenny et al., 2006) proposed a model of dyadic data analysis that uses the dyad as the unit of analysis. This model suggests that a person’s independent variable score affect both one’s own dependent variable score (i.e., actor effect) and the partners’ dependent variable score (partner effect). As such, analyses directly model the interdependence of husbands’ and wives’ data. In our analyses, gender and intervention condition were first centered at their grand mean before inclusion into the model. Separate analyses were performed examining the impact of each of the psychological variables (e.g., depressive symptomatology and stress), the intervention, gender and their statistical interactions on plasma and salivary oxytocin levels.

Depressive symptomatology was treated categorically based on empirically derived clinical cut-offs, such that CES-D scores ≥8 indicate presence of subclinical or clinical depression. (Cohen et al., 2010). CESD scores among this sample ranged from 1 to 32 (mean = 9.02; median = 7.5). Approximately half of our sample (49.3%) had a CESD scores ≥8, of which 7 participants (roughly 10% of total sample) had scores ≥16 (clinical depression). We found no significant gender difference for either CESD scores (p = .89) or for depression classification (p = .63). The mean CESD score for males was 9.32 (sd = 6.91) and the mean for females was 8.72 (sd = 6.45). Because no such clinical cut-offs exist for stress, the total PSS score was treated continuously. For salivary OT, all samples were obtained at home after the intervention or monitoring period had begun. Because we wanted to examine whether a single week of enhanced warm contact was sufficient to increase OT activity, we first com-
pared the influence of the psychological variables at week 1 salivary OT levels. Then, to examine whether additional practice of the techniques would further alter effects of depressive symptomatology on OT activity, group differences in the mean of samples 2 and 3 obtained during the final week of the intervention or monitoring period were examined before and after controlling for week 1 OT levels. Correlations between measures were computed as Pearson product-moment correlations. For pre-intervention baseline characteristics of our groups see Holt-Lunstad et al. (2008). All analyses were two-tailed and data are reported in un-standardized regression coefficients.

3. Results

3.1. The influence of depressive symptomatology on oxytocin

We find a significant effect of depressive symptomatology on plasma OT \( F = 11.69; p < .01 \), such that those high in depressive symptoms had significantly higher plasma OT than those low in depressive symptoms (see Fig. 1). There was also a significant gender effect \( F = 4.39; p < .05 \) such that females had significantly higher plasma OT \( (M = 11.23; sd = 1.15) \) than males \( (M = 8.06; sd = 1.17) \). There was also a significant depressive symptomatology by gender interaction on plasma OT \( (F(1,31) = 4.71; p < .05) \). The simple effects reveal that depressed women had the highest OT compared to depressed men or non-depressed women (see Fig. 2).

We also found a significant main effect of depressive symptomatology on salivary OT taken during the first week of the intervention \( (F(1,25) = 9.13; p = .01) \) such that when controlling for gender, high depressive symptomatology was associated with higher salivary OT than non-depressed (see Fig. 3). We found no main effect of gender nor a gender by depressive symptomatology interaction for salivary OT \( (p > .10) \).

3.2. The influence of stress as a potential mediator

A second aim is to examine whether greater perceived stress may explain why depressive symptomatology influences OT and physiological stress activation. We found that self-reports of the severity of perceived stress and depressive symptomatology are significantly correlated \( (r = .65; p < .0001) \). Therefore, we repeated our analyses examining effects of perceived stress on plasma and salivary OT.

We found a significant effect of perceived stress for plasma OT \( (b = .42; F = 9.74; p < .01) \) such that higher stress was associated with higher OT. Since we hypothesized that higher stress was a potential mediating factor in the relationship between depressive symptomatology and OT, we re-examined the relationship between depressive symptomatology and pre-intervention plasma OT after controlling for perceived stress. Adjusting for stress substantially weakened the effect of depressive symptomatology on plasma OT so that it was no longer significant \( (p > .10) \). Further, the Sobel’s test of mediation was significant \( (2.16; SE = .12; p = .02) \), suggesting that the association between depressive symptomatology and plasma OT may be partly mediated by perceived stress. There was no significant effect of stress on week 1 salivary OT \( (p > .20) \).

3.3. The influence of the warm touch enhancement intervention

3.3.1. During the intervention

Salivary OT was first obtained during the initial week of the intervention, not prior to the intervention as was done for
plasma OT. For week 1 salivary OT, there was a significant depressive symptomatology by condition interaction \((F = 8.22; p = .02)\). Similar to the plasma OT finding, among the control group those high in depressive symptoms had significantly higher salivary OT than those low in depressive symptoms \((p < .05)\). In the intervention group, after just 1 week of training and home practice, salivary OT did not differ significantly between the high and low depressive symptomatology subjects. This effect was most pronounced among the women with high depressive symptomatology scores (see Fig. 4).

The main effect of depressive symptomatology on salivary OT that was significant during week 1 of the intervention was no longer significant at week 4 \((p = .17)\). In contrast, the interaction between depressive symptomatology and intervention condition remained significant \((F(1,11) = 4.82; p = .05)\) such that differences in depressive symptomatology persisted in the control condition but did not differ in the intervention condition. When we adjusted week 4 salivary OT for week 1 levels, the interaction was no longer significant \((p > .20)\), suggesting that there was no further enhancement of the effect of the intervention on depressive symptomatology group differences in salivary OT between weeks 1 and 4.

3.3.2. Post-intervention

Initial differences in plasma OT based on depressive symptomatology or perceived stress were no longer present at the completion of the intervention \((p > .20)\). Likewise, there were no significant main effects or interactions involving depressive symptomatology or stress on any of the post-intervention assessments adjusting for pre-intervention levels \((p > .20)\) (Table 1).

### 4. Discussion

Consistent with prior studies involving patients with major depressive disorder (Cyranowski et al., 2008; Parker et al., 2010; Scantamburlo et al., 2007), the present investigation found that married men and women with subclinical depression as indexed by high CESD scores had higher pre-intervention levels of plasma OT than those with low scores. Although present in men as well, this effect was particularly pronounced among the married women with high symptoms of depression. Men and women with higher depressive symptomatology scores also had higher week 1 salivary OT levels.

As predicted, higher perceived stress scores were jointly related to both pre-intervention plasma OT and to depressive symptomatology score. The Perceived Stress Scale quantifies the individual’s feelings of being exposed to stressful life events during the past month. The significant test of mediation supports the interpretation that the elevated OT in the depressive symptomatology group was in part due to increased stress. As described previously, OT increases during stress have been observed in animal models (Amico et al., 2004; Ring et al., 2006; Windle et al., 2004). Among mothers of infants, we have likewise observed significant increases in plasma OT immediately following psychological stressors (Light et al., 2000; Greven and Light, submitted for publication). The elevated OT activity thus may be a response to excessive stress effects experienced in subclinical depression that outweigh any influence of the social or bonding aspects of the environment.

In subjects randomized to the warm contact enhancement intervention, depressive symptomatology group differences in salivary OT levels were no longer significant as early as the first week of the intervention, and this finding was true during the last week as well. In the control condition, however, subclinical depression was related to higher salivary OT during both weeks 1 and 4. Furthermore, there were no significant differences in plasma OT levels between high and low depressive symptomatology groups at post-intervention controlling for pre-intervention levels.

Altogether, these findings suggest that the warm touch enhancement intervention had a measurable beneficial effect in lowering stress-enhanced OT among the men and women with subclinical depression. This adds to the findings of the beneficial physiological changes previously reported for this intervention (Holt-Lunstad et al., 2008), which in

![Figure 4](image-url)  
**Figure 4** Week 1 salivary oxytocin according to intervention group and level of depression.

### Table 1 Sample characteristics prior to intervention by group assignment and depression level.

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Low DS n = 19</td>
<td>Low DS n = 15</td>
</tr>
<tr>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Age 26.04</td>
<td>24.07</td>
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<tr>
<td>BMI 24.49</td>
<td>24.25</td>
</tr>
<tr>
<td>Stress 19.37</td>
<td>21.26</td>
</tr>
<tr>
<td>Plasma OT 8.03</td>
<td>5.75</td>
</tr>
<tr>
<td>High DS n = 21</td>
<td>High DS n = 13</td>
</tr>
<tr>
<td>M</td>
<td></td>
</tr>
<tr>
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<tr>
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<tr>
<td>Stress 25.38</td>
<td>29.78</td>
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<tr>
<td>Plasma OT 11.86</td>
<td>15.74</td>
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<table>
<thead>
<tr>
<th>p-Value</th>
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<td>p = .47</td>
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<td>Plasma OT</td>
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<td>p = .15</td>
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DS: depressive symptomatology; Low DS = CESD scores < 8; High DS = CESD ≥ 8; M: mean; SEM: standard error of the mean; BMI: body mass index; p-values are based on two-tailed tests. p-Value reflects the significance of the interaction between depression and group assignment.
addition to increased salivary OT levels also included decreased sympathetic activity in both husbands and wives as indexed by lower salivary alpha amylase throughout a 24 h sampling period and lower 24 h ambulatory blood pressure in the men. It is important to note that our original report stated that there were increases in salivary OT but no reliable increase in plasma OT in the intervention group vs. the controls following the month of warm touch home practice. When we re-analyzed that result controlling for depressive symptom score, we found that the intervention group did show reliably greater post-intervention plasma OT compared to the control group. It is thus extremely important in studies of this kind to assess and control for depressive symptomatology and/or stress, which otherwise might obscure the effects of social contact and support on OT activity. Furthermore, the present study confirms that individuals who are higher in depressive symptoms can respond beneficially to this type of warm touch based support enhancement intervention. As post hoc analyses, we found that the husbands with high as well as low depressive symptoms showed similar reductions in ambulatory BP, and women and men with and without subclinical depression showed similar reductions in salivary alpha amylase after the intervention.

As described earlier, the association between OT and stress may appear paradoxical. Elevations in oxytocin are linked both to reductions in stress as well as an indicator of stress. For instance, there are data to demonstrate that elevations in OT are linked to relaxation and calm (McCarthy, 1995), that OT inhibits stress-induced HPA response, and is associated with affiliative behavior (Scantamburlo et al., 2009). Conversely, studies have linked elevations in OT to relationship distress in women (Taylor et al., 2006, 2010; Turner et al., 1999) and is found experimentally in animals (Grippo et al., 2009). To reconcile such divergent findings it has been argued that OT may restore biological balance through reciprocal modulation (Legros et al., 1982; Scantamburlo et al., 2009). Thus, OT may increase in response to stress as a counterbalance — to calm the physiological system and promote affiliative connection. Given that social withdrawal is characteristic of depression, elevations in OT found among those high in depressive symptoms may be a corrective response to trigger increased affiliation.

We acknowledge several important limitations to our study. First, because our measurements were of peripheral OT, it is unclear to what extent OT in the periphery is reflective of central OT. Additionally we used a fairly homogeneous population of young, healthy married couples that was primarily Caucasian and educated. Therefore, whether the effects we found would be generalizable to other populations would require further study, including those with major depressive disorder or subclinical postpartum depression. In patients with a clinical diagnosis of major depression, based on several recent reports, it appears equally likely that this population may have lower OT (Ozsoy et al., 2009; Garcia et al., 2010) as to have higher OT levels than controls (Park et al., 2010). Even when dealing with subclinical depression, findings from different samples may differ. When our own research group studied new mothers with vs. without subclinical postpartum depression (Light et al., 2010), we found that those with higher depression scores showed marginally decreased leukocyte gene expression of OT receptors while the OT prepropeptide levels were unchanged and serotonin receptor 1-a and 1-d expression was increased. Another potential limitation is that we only assessed stress and depression at the pre-intervention assessment so we cannot determine whether the intervention may have led to reductions in perceived stress or depressive symptomology. Further, the Perceived Stress Scale does not differentiate social from non-social stressors. Research reveals that social stressors have more of an influence on the HPA and thus more toxic than non-social stressors (Dickerson and Kemeny, 2004), therefore it is possible that oxytocin may be particularly sensitive to social stressors. Finally, we acknowledge that in some instances, current perceived stress and/or anxiety levels may be equally important or more important to consider. For example, in unmarried young adults, Keri and Kiss (2011) observed that plasma OT levels were more strongly associated with state anxiety than with depressive symptom scores.

Men and women with subclinical depression may be an important high risk group to examine as they may be predisposed to multiple unfavorable conditions. For instance, in a prospective study among older adults it was found that among those with subclinical depression at the outset of the study, 84% were clinically depressed at a 33 month follow-up (Cohen et al., 2010). Research among a community cohort of women found that post-partum major depression could significantly be predicted by prior depressive symptoms and not breastfeeding at an 8-week follow up (Davey et al., 2008). There is also a well-documented association between depression and cardiovascular disorders (Grippo and Johnson, 2009; Mosovich et al., 2008; Van der Kooy et al., 2007). Depressive symptoms have also been significantly predictive of subclinical atherosclerosis (Seldemijr et al., 2010; Spitzer et al., 2008). Intervening among those with subclinical depression may prevent the transition to severe and persistent depression; and possibly reduce risk for cardiovascular outcomes.

Our findings support the hypothesis that dysregulated OT may be a biomarker of emotional distress which characterize major depression (Parker et al., 2010). These findings extend prior studies by demonstrating that the disruption in OT associated with depressive symptomatology may be strongest among women. Sexual dimorphism has been widely documented in response to both acute and chronic stressors (Grippo et al., 2007; Klein and Corwin, 2002; McCormick et al., 2005). Sex differences are also seen in prevalence, presentation, etiology of depression (Grigoriadis and Robinson, 2007). However, despite relative sex differences, depression affects both men and women; thus, examining OT among both sexes may provide further understanding the pathophysiological mechanisms.

This study is the first known study to submit that an intervention may be effective in “normalizing” disruptions in OT levels due to depression in humans. Prior research found that although depression was associated with deregulated serum oxytocin levels relative to controls, anti-depressant and electroconvulsive shock therapy did not significantly alter oxytocin levels among those with either major depression or bipolar disorder (Ozsoy et al., 2009). In mice, however, it was found that sexual activity and mating reduced depressive behaviors in wild type male mice that was not seen in OT receptor-deficient mice (Matsushita et al., 2010). Oxytocin was reported to have had an antidepressant-like
effect. Although our intervention involved non-sexual touch, the couple’s massage component of the intervention may mimic such intimate physical affection. Given the prevalence of treatment resistant depression (Hughes and Cohen, 2009), successful intervention among those high risk prior to developing chronic depression may be particularly important to examine further. Overall, these findings have implications for the role of oxytocinergic mechanisms as potential interventions that target this regulatory peptide in the management and treatment of depressive disorders.

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Conflict of interests

All authors declare that we have no conflicts of interests to declare.

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