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A heartfelt response: Oxytocin effects on response to social stress in men and women

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ABSTRACT

Background: Animal research indicates that oxytocin is involved in social behavior, stress regulation, and positive physiologic adaptation. This study examines whether oxytocin enhances adaptive responses to social stress and compares effects between men and women.

Methods: Hypotheses were tested with a placebo-controlled, double-blind experiment. Social stress was induced. Changes in cardiovascular reactivity, affect, and behavior were assessed.

Results: Participants given oxytocin, relative to placebo, responded to social stress with a *challenge* orientation characterized by a benign pattern of cardiovascular reactivity. Gender differences emerged. Men given oxytocin reported less negative affect and had greater vagal rebound, while women given oxytocin reported more anger and had better math performance following social stress.

Discussion: Findings indicate oxytocin stimulates an approach-oriented cardiovascular profile during social stress, suggesting mechanisms by which oxytocin might improve physical health. However, before considering oxytocin as therapeutic or uniformly enhancing health, greater understanding of possible gender differences in effects is needed.

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1. Introduction

Positive social relationships have consistently been associated with better health, although the neurobiological underpinnings of these observed effects are not well understood. Animal research has indicated that oxytocin, a neuropeptide produced in the supraoptic and paraventricular nuclei (PVN) of the hypothalamus, is involved in social bonding, stress regulation, and positive physiologic adaptations that may be linked with greater longevity and successful aging (Depue and Morrone-Strupinsky, 2005; Knox and Uvnas-Moberg, 1998; Taylor et al., 2000; Uvnas-Moberg, 1997). Because of its potential role in promoting positive human social behavior, recent research has focused on whether oxytocin may lead to improved social and emotional functioning for a range of disorders including autism, schizophrenia, and anxiety or depression (Averbeck, 2010; Bartz and Hollander, 2008; Bartz et al., 2010). Moreover, given its apparent anti-stress effects, some investigators

have posited that oxytocin may reduce stress-related physiologic consequences such as decreasing heart rate and blood pressure, and have speculated important links between oxytocin and cardiovascular health (Knox and Uvnas-Moberg, 1998). However, knowledge of the effects of oxytocin in healthy humans remains limited and some recent research has suggested that effects may not be uniformly prosocial or stress-reducing (De Dreu et al., 2010; Miller, 2010; Shamay-Tsoory et al., 2009). Moreover, gender differences in these stress-related effects have been speculated but never directly tested in humans. Therefore, in this study we provide one of the first direct tests of the hypothesis that oxytocin facilitates a positive, adaptive profile of physiological responses during highly stressful situations in healthy men and women.

Interest in a clinical application for oxytocin comes from positive results in basic science studies. Pre-clinical research on the neurobiology underlying social bonding and engagement suggests that oxytocin facilitates bonding and approach behaviors partly by inhibiting stress-related maladaptive cognitive, affective, and biological activation (Depue and Morrone-Strupinsky, 2005; Porges, 2003a). In animals, oxytocin modulates sympathetic and parasympathetic nervous system activity (SNS, PNS), and more generally is involved in cardiovascular regulation (Higa et al., 2002; Petersson and Uvnas-Moberg, 2007; Uvnas-Moberg, 1997). Such effects, if

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applicable to humans, could promote health by reducing potentially toxic direct effects of stress-related neuroendocrine and autonomic activation.

Several recent studies in men found that exogenously administered oxytocin reduced fear-related activation in the amygdala, reduced cortisol levels and distress in response to social stress, increased prosocial behaviors, and modulated social memory (Heinrichs et al., 2003, 2004; Kirsch et al., 2005; Kosfeld et al., 2005). These results led investigators to propose oxytocin as a key hormone underlying positive social experience and prosocial behavior, and their related health benefits, which could perhaps portend a role as a therapeutic agent (Uvnas-Moberg, 1997).

However, despite early promising evidence, one recent study found that exogenously administered oxytocin increased parasympathetic and sympathetic cardiac control under resting conditions only among individuals who did not report feeling lonely (Norman et al., 2011). Other research has found that under certain conditions oxytocin may actually enhance negative responses to social stress in humans (Bosch et al., 2005; Shamay-Tsoory et al., 2009). The animal literature has suggested that oxytocin is more potent in the presence of higher estrogen levels, leading investigators to hypothesize that effects of oxytocin will be stronger in women than men. However, among female animals, higher levels of oxytocin are associated with more aggression and willingness to attack along with less fear (Campbell, 2008). Further, a number of studies in humans suggest that higher peripheral levels of oxytocin serve as a marker of greater distress among women (Cyranowski et al., 2008; Hoge et al., 2008; Taylor et al., 2010). To date, little experimental data are available on the effects of exogenously administered oxytocin in women or whether oxytocin alters subjective, hormonal, cardiovascular, and behavioral responses to social stress uniformly in both men and women.

One critical distinction that might assist in the interpretation of whether oxytocin is stress-buffering or not is a more precise definition of what are the features of harmful versus beneficial stress responses. Not all stress reactions are equal. By differentiating acute stress reactions that facilitate goal-directed behavior and are characterized by benign physiological reactions from stress reactions that impair performance and have harmful consequences, we might gain traction on the question of how oxytocin modulates acute stress reactions.

Several theories have identified psychological antecedents and physiological consequences that differentiate “good” stress from “bad” stress responses (e.g., Dienstbier, 1989; Frankenhaeuser, 1986; Henry, 1986). One theory that integrates Dienstbier’s “physiological toughness” theory and Lazarus and Folkman’s stress appraisal theory in the context of acute stressful situations is the biopsychosocial model of challenge and threat (for a review see Blascovich and Mendes, 2010). In this model both challenge and threat states occur during acute “stressful” situations; however, the states differ in their antecedent appraisal process and subsequent downstream cardiovascular reactivity. For example, “challenge states” occur when individuals appraise their resources as exceeding the demands of the task, whereas “threat states” occur when situational demands are perceived to exceed resources. Importantly, these psychological states have different profiles of cardiovascular responses. Even though both states are characterized by SNS activation, challenge is characterized by increases from a resting state in cardiac output (CO, the total volume of oxygenated blood the heart pumps in a minute) and decreases in total peripheral resistance (TPR) – vasodilation. Threat is characterized by little or no increase in CO and increases in TPR – vasoconstriction. Furthermore, in some contexts, SNS activation is greater in challenge than threat states, consistent with Dienstbier’s idea of physiological toughness, which suggests that larger increases in SNS activation

to novel situations is related to effective coping and better performance (see also Jamieson et al., 2010).

Benefits in cognitive performance, emotional status and health have been identified as following from challenge states. For example, challenge, relative to threat, states have been associated with better decision making (Kassam et al., 2009), higher status (Scheepers et al., 2012), more approach-oriented behavior and increased positive affect (Mendes et al., 2008). Larger increases in sympathetic activation (commonly measured using changes in ventricle contractility, a relatively pure measure of sympathetic activation, or changes in catecholamine levels) also tend to produce better performance in physical and cognitive tasks. For example, a recent study of students preparing to take the GRE assigned participants to either a *stress reappraisal* manipulation, which encouraged participants to interpret their physiological arousal during test-taking as a beneficial reaction that would help them perform better during the exam, or a no-instruction control condition. Reappraisal participants exhibited a larger increase in sympathetic activation (measured with salivary alpha amylase) immediately before taking a practice GRE and performed better at the math exam than those who were assigned to the control condition. Indeed, consistent with the challenge and threat framework, the greater the SNS increase the better the math performance. Furthermore, the reappraisal participants, compared to control, earned higher GRE exam scores when they took the actual test in the following months (Jamieson et al., 2010).

Individual differences also align in expected directions with experiencing threat or challenge during acute stress episodes. People who believe more strongly in a just world (Tomaka and Blascovich, 1994), individuals with high, stable self-esteem (Seery et al., 2004), and non-lonely individuals (Cacioppo et al., 2002) typically exhibit cardiovascular reactivity consistent with challenge states during acute stressful tasks more than individuals who self-report lower on these constructs. Individual differences in the neurobiological milieu have also been linked to challenge and threat states. In a recent paper, individuals with higher left, relative to right, frontal cortical activity (a neurological pattern previously linked to positive affect and well-being) were more likely to respond to a stressful situation with challenge appraisals and “challenge” reactivity (higher CO and lower TPR) (Koslov et al., 2011).

These patterns of benign “challenge” responses may accumulate over time to more positive health outcomes. In a recent examination of more than 1500 participants from the Framingham sample (Jefferson et al., 2010), increased cardiac output, one of the primary cardiovascular determinants of “challenge” states, was associated with decelerated brain aging—individuals with greater cardiac output had increased brain volume and showed increased cognitive processing speed in older adulthood. These researchers speculated that increased oxygenated blood produced by the heart may have long-term protective effects in the brain.

Recovery from stressful situations might also provide a more precise picture of the stress modulating role of oxytocin. One promising measure of recovery from stressful situations is *vagal rebound* or the extent to which vagus nerve activity returns to resting levels or even “over-shoots” resting levels after suppression of the vagal brake (Porges, 2007). Whereas lower levels of heart rate variability during a stressful task might indicate attentional control or distress, once a stressor has ended, an adaptive response is for the vagus nerve to re-establish control and slow down heart rate. Vagal rebound is measured with heart rate variability responses during recovery from an acute stressor.

In our experimental paradigm, we rely on these distinctions in cardiovascular responses during and recovery from acute stressful situations to examine the role of oxytocin in modulating stress responses. Using a placebo-controlled double-blind experiment

with a sample of healthy men and women recruited from the community, we tested the hypothesis that oxytocin facilitates adaptive stress responses during and following an acute social evaluation by examining: (1) changes from baseline to stress exposure for ventricle contractility (VC: measured as pre-ejection period multiplied by -1 so that increases in sympathetic nervous system are represented as increased VC) and cardiac output (CO); and (2) vagal rebound. We hypothesized that if oxytocin promotes positive responses to social stress, individuals exposed to exogenously administered oxytocin relative to placebo would exhibit a pattern of cardiovascular reactivity consistent with challenge states (increased VC and CO) during a highly stressful social evaluation. To provide converging evidence of challenge states we videotaped participants during the stress task, and trained observers (blind to condition) to code these recordings for specific *challenge* and *threat* behavior that occurred during the stress task. We predicted that oxytocin participants would exhibit more positive affect and behavior and possibly better performance than placebo participants. Following the stressor, we expected that oxytocin participants would show greater vagal rebound immediately following the completion of the stress task. Finally, we hypothesized that oxytocin would be associated with less self-reported negative affect under conditions of stress. Although we predicted these general positive effects of oxytocin for both men and women, we also tested whether gender moderated any of the responses.

2. Methods

2.1. Overview

This placebo-controlled, double-blind experiment employed a between-subjects factorial design, using a 2 (men vs. women) \times 2 (oxytocin vs. placebo) design. Participants were randomized to receive either intranasal oxytocin spray or placebo (saline) nasal spray. Social stress was induced using the Trier Social Stress Test (TSST), which prior work has suggested reliably activates the hypothalamic–pituitary–adrenal axis and the SNS (Kirschbaum et al., 1993). Baseline measures of estradiol were obtained via saliva samples. Primary outcomes were cardiovascular (CV) reactivity, objective behavior during the stress task coded by observers unaware of the oxytocin condition, and self-reported affective responses. Details of the study design have been previously published (Kubzansky et al., 2009). This protocol was approved by the Institutional Review Boards at the two institutions overseeing the research: Harvard School of Public Health and Brigham and Women's Hospital.

2.2. Participants

Participants between the ages of 25 and 65 years were recruited from the community. Interested participants completed an initial telephone screening and were scheduled for a lab appointment. Upon arrival participants completed a face-to-face screening, designed to determine individuals' health status and adherence to study day instructions. Individuals who had any known medical condition (including mental disorders) or were taking any type of medication (including birth control pills) were excluded. Further exclusions included obesity, pregnancy, breastfeeding, smoking, heavy alcohol use, and drug abuse (as assessed by validated instruments, the CAGE and the RAGS, Ewing, 1984; Sobell et al., 1999). Premenopausal women were asked to participate during the follicular phase of the menstrual cycle, a time when hormone levels are relatively low and stable (Symonds et al., 2004). Participants were asked to abstain from food and liquids (except water) for 4 h prior to participation in the experiment and from exercise, caffeine, and alcohol during the 12 h prior to participation. Eligible individuals completed consenting procedures and a brief final screen after arrival at the laboratory. This was conducted by a physician who obtained a medical history, performed a physical exam, and administered a pregnancy test for women. Eligible participants who continued with the protocol received monetary compensation for participation as well as transportation costs.

A total of 99 healthy participants completed the study, including 49 men and 50 women. Participants were 68% Whites and 32% non-Whites with an age range of 21–63 years (mean = 33, standard deviation {SD} = 10.7). Levels of educational attainment ranged from high school degree or GED equivalent to graduate school degree (83% had a college degree or higher).

2.3. Procedure

Primary informed consent was obtained directly from participants upon arrival at the laboratory; however, consent for the social stress tasks was delayed until just prior to oxytocin or placebo administration to avoid anticipatory stress in the

baseline resting period. After the brief final screening eligible participants completed baseline questionnaires assessing demographics and relevant individual attributes (e.g., trait anxiety). Participants then had a quiet period, followed by a baseline measure of cardiovascular responses and collection of a saliva sample for determination of estradiol (Jennings et al., 1992; Piferi et al., 2000). We used the cardiovascular baseline responses to create physiological "reactivity" scores (see below).

After a brief description of the stress tasks, consent to continue with the protocol was obtained. Then participants received a single dose of either 24 IU oxytocin or placebo intranasally. Studies with other peptides (melanocortin, vasopressin which is closely related in structure to oxytocin, and insulin) administered intranasally have found that they are absorbed within 30 min as assessed by peptide levels in the cerebrospinal fluid (Born et al., 2002). Other experimental work with intranasal oxytocin in humans has consistently utilized an absorption period ranging between 40 and 50 min (Heinrichs et al., 2003; Kosfeld et al., 2005; Shamay-Tsoory et al., 2009). The stress tasks were initiated 40 min after oxytocin or placebo administration with a brief 5-min period during which participants prepared for the first stress task. Immediately prior to performing this task, a state mood measure was obtained.

The TSST generally requires participants to perform two separate tasks in front of an audience: a 5-min public speaking task and a 5-min mental arithmetic exercise. Both tasks were conducted in front of a stoic audience (consisting of two women) and in the presence of a video camera conspicuously videotaping the performance. Participants were told that their performance would be evaluated by audience members and reviewed (via videotape) by other trained professionals. After performing the speech task, participants were asked to perform an arithmetic task (counting backwards from 996 by steps of 7), which was described as being related to mental ability and general intelligence. Prior to performing this task, state mood measures were administered again. State mood and post-task measures were also obtained a final time after completion of the math task. Autonomic nervous system responses were monitored throughout the procedure. At the completion of the protocol, the experimenter debriefed participants and paid them for participation.

2.4. Measures

2.4.1. Autonomic nervous system (ANS)

Sympathetic and parasympathetic measures were recorded noninvasively according to established guidelines (Sherwood et al., 1990). We measured electrocardiography (ECG100C) and impedance cardiography (NICO100C) and integrated the signals with an MP150 system (BIOPAC Systems Inc, Goleta, CA). Sensors to measure ECG were applied in a modified lead II configuration and impedance cardiography was obtained using four mylar bands that completely encircled the neck and chest area. A 4 mA AC current at 100 kHz was passed through the outer bands, and z_0 and dz/dt were recorded from the inner bands. All signals were filtered on-line and collected at 1000 Hz.

We used HRV (2.5) and IMP (3.0) modules from Mindware Technologies (Gahanna, OH) to edit and score the physiological parameters of interest, specifically respiratory sinus arrhythmia (RSA, a measure of heart rate variability), cardiac output (CO), and pre-ejection period (PEP). PEP, a chronotropic measure of the strength of the contractile force of the heart, provides a sensitive index of sympathetic control of the heart (Brownley et al., 2000). Impedance data were ensemble averaged with 1-min epochs and each waveform was verified and edited as needed. Visual inspection was conducted by research assistants who completed extensive training in the second author's lab and all scored data were confirmed by a post-doc level research scientist and the second author. Inspection of the waveforms focused on detecting ectopic beats and accurate Q, R, S placement in the ECG trace, and accurate detection of the B-, X-, and Z-points (aortic valve opening, aortic valve closing, and dz/dt max, respectively) on the dz/dt waveform. We did not rely on available B-detection algorithms (e.g., Lozano et al., 2007), but rather only accepted waveforms in which we could visually confirm a B-point.

Stroke volume (SV) was estimated using the Kubicek equation (see Sherwood et al., 1990) and the subsequent cardiac output (CO) in liters per minute was calculated by multiplying heart rate (HR) \times (SV/1000). PEP was calculated as the time interval in ms between the Q-point of the ECG and the B-point of the dz/dt signal, such that greater PEP decreases indicate a sympathetic nervous system response. For ease of interpretation, we calculated ventricle contractility by multiplying PEP reactivity by -1 so that increases in ventricle contractility indicate increases in sympathetic activation or faster time between contraction and valve opening.

HRV was also scored in 1-min bins. The HRV module detrended the data using a first order polynomial to remove the mean and any linear trends, cosine tapered the data, submitted it to Fast Fourier Transformation, and took the natural log integral of the high frequency power (.15–.40 Hz) as an index of RSA. This method is generally accepted as an optimal noninvasive measure of cardiac vagal control (Berntson et al., 1997, 1993; Cacioppo et al., 1994). After scoring all data, a random subsample of data was selected to re-score. Inter-scorers reliability exceeded 90% for all measures of interest.

We also attempted to collect continuous blood pressure responses given the previous data on TPR differences between challenge and threat states. Unfortunately, we used a tonometric blood pressure device that estimated blood pressure from the radial artery using a sweep technology. Though the device met hospital standards, it is extremely sensitive to movement; when participants move their arms or wrists, it can produce highly variable estimates of questionable validity (see Berntson et al.,

2007; Mendes, 2009). Even with our best efforts to restrain participants' wrists during the TSST, we observed highly variable and invalid blood pressure responses (ranging from 40 mmHg to 190 mmHg) due to movement artifact. Because of these problems we did not analyze the blood pressure responses nor could we estimate TPR, which requires blood pressure responses.

Based on our hypotheses and the valid data collected, we focused on reactivity (i.e., changes from baseline to stress task) of three autonomic nervous system parameters: CO, VC, and RSA. We calculated change scores for each minute at baseline and during the stress tasks. We used the last minute of the baseline period because that is typically the time when autonomic parameters are at their most quiescent state. To examine post-stress autonomic changes, we subtracted the last minute of the stress task period from the first minute of the post-stress exposure period (i.e., recovery time after completion of stress tasks).

2.4.2. Estradiol

Saliva samples were collected using IBL sampling devices and the methodology described by Kirschbaum and Hellhammer (1989). Estrogen was evaluated from a saliva sample obtained at baseline. Before assaying for free estradiol, samples were thawed and spun at 3000 rpm for 10 min to obtain clear saliva with low viscosity. The free estradiol concentrations in saliva were analyzed with a time-resolved immunoassay with fluorescence detection. The limit of detection was 0.3 pg/mL and the inter- and intra-assay coefficients of variance were below 14% and 15%. A random sample of 20% of the samples was assayed in duplicate and reliability was 0.98.

2.4.3. Psychological measures

Anger and anxiety were assessed with the Spielberger State-Trait Personality Inventory (STPI) (Spielberger, 1998). Trait measures assessed stable individual differences in the frequency and intensity with which individuals experience these negative emotions. State measures assessed how anxious, angry or depressed individuals felt while in the laboratory. Subscales all have demonstrated validity and had high internal consistency reliability in this study (all trait $\alpha > 0.77$; all state $\alpha > 0.84$). State positive and negative affect were measured using subscales from the Positive and Negative Affect Schedule which prior studies have indicated is both valid and reliable (Watson et al., 1988). These subscales had high internal reliability in this study (all $\alpha > 0.84$). State measures were obtained at four time points: baseline, immediately prior to performing the speech task, immediately prior to performing the math task, and then directly after completion of the math task. For each state measure, scores from the baseline condition were compared with task condition or post-task scores to indicate affective response to the stress exposure.

2.4.4. Behavioral observation and coding

Research assistants ($N = 4$; 2 men and 2 women) were trained to code the videotaped speech and math tasks. Training consisted of a group instructional session, followed by everyone scoring the same 30 participants and determining reliability across those participants. Inter-rater reliability was high (agreement within 2 points ranged from 82% to 100% for all variables). Once consistency was established, each study participant's performance was scored by a single coder. Each participant's behavior was scored during the first stress task using established and reliable coding schemes for challenge and threat emotions and behaviors (Mendes et al., 2008). The challenge construct comprised 11 questions including how comfortable, strong, confident, enthusiastic, interested, clear, and alert the participant appeared, as well as how much eye contact they made with the evaluators, how animated they were during the speech, the intensity of their gestures, and how much somatic activity they exhibited during the speech ($\alpha = 0.92$). The threat construct was created using 8 items including how anxious, agitated, distressed, jittery, and tense the participant appeared, as well as how rigid the participants held their body, how curled into themselves they became during the speech (trying to appear smaller), and how much they froze ($\alpha = 0.80$).

Performances were also scored according to the quality of speech and performance on the math task. Speech quality was operationalized according to whether it seemed well structured and given in a clear and animated way ($\alpha = 0.90$). An objective measure of math performance quality was derived by rating participants on how many numbers they were able to get correct and how clear and consistent they were while engaging in the counting task ($\alpha = 0.85$).

2.4.5. Covariates

Height and weight was obtained by the physician during the final screening, with participants wearing socks and clothing, from which body mass index (weight/height²) was calculated. Age, race/ethnicity, and years of education were obtained by self-report on the baseline questionnaires.

2.5. Data analysis

Initial analyses evaluated effectiveness of the randomization procedure by considering distribution of demographic and trait anger, anxiety, negative and positive affect across oxytocin and placebo groups, using t -tests or chi-square tests as appropriate. Affective, cardiovascular, and behavioral outcomes were considered using a series of two-way (oxytocin \times gender) analyses of variance (ANOVA) or analyses of co-variance (ANCOVA) when inclusion of covariates in the models was required. As most covariates did not differ across gender or oxytocin condition, they were not

Table 1

Distribution of study variables across oxytocin and placebo groups at baseline.

Study variable	Oxytocin $n = 48$		Placebo $n = 51$		p -Value
	M	SD	M	SD	
Demographics					
Age (years)	32	10.2	34	11.2	0.34
BMI (kg/m ²)	23.9	2.8	23.6	3.1	0.62
Educational attainment (years)	16.6	3.0	16.6	2.1	0.93
Affect (sum score)					
Trait negative affect	16.4	5.3	14.7	4.8	0.09
Trait positive affect	22.5	24.4	24.6	6.8	0.12
Trait anxiety	23.0	6.6	21.6	5.7	0.25
Trait anger	21.7	7.6	19.9	6.4	0.21
Physiological ^a					
CO (L/min)	7.2	2.3	6.8	2.1	0.44
PEP (ms)	112.2	11.8	110.1	10.9	0.38
RSA (ms ²)	6.5	1.1	6.2	1.3	0.25
Estradiol (pg/mL)	3.9	3.0	4.1	3.3	0.76

^a Average over 6 min of baseline. CO indicates cardiac output; PEP indicates pre-ejection period (we use this measure to calculate ventricle contractility); RSA indicates respiratory sinus arrhythmia.

included in the reported models with several exceptions. Because cardiovascular outcomes may be particularly sensitive to age, all reported analyses with this outcome use ANCOVA and adjust for age. Similarly, because the performance tasks are highly sensitive to education levels, all reported analyses of performance outcomes use ANCOVA and adjust for education level.

Subjective responses were measured once per time period, and thus we assessed change between relevant time periods using each time period score. Of note is that cardiovascular and affective measures were taken at each of the two stress exposure tasks. However, findings at the two time points were virtually identical. Thus for parsimony when considering effects of stress exposure, we report the findings taken during the initial stress exposure period (the speech task).

For each analysis, we considered whether the interaction between gender and oxytocin was significant. In addition, we report effect sizes as Cohen's d statistic, calculated as the difference between the two relevant group means divided by the pooled standard deviation (i.e., the root mean square of the two standard deviations). Small, medium, and large effects sizes for d are estimated as .20, .50, and .80, respectively (Cohen, 1992). We also conducted all analyses using ANOVAs with repeated measures, but findings were identical, and for ease of interpretation we report the two-way ANOVAs or ANCOVAs. Statistical tests were two-tailed and conducted at the .05 level of significance. In addition, to identify potential outliers on each outcome, all variables were examined and individuals who had extreme values (>2.5 SDs above the mean) were set to missing for that particular outcome (n 's range from 0 to 4 depending on the outcome). Additionally some physiological data were unscorable because of faulty sensors, movement artifacts, loss of signal, or noisy signals (8–22% of data are missing for each study interval; impedance parameters have more missing data than others). Thus, data for each outcome have variable degrees of freedom, but missing data were not related to oxytocin administration and thus should be considered to be missing completely at random. Data presented in figures include means and standard error of the means.

3. Results

3.1. Initial analyses

Participants in the oxytocin and placebo groups did not differ significantly according to any of the baseline (pre-oxytocin manipulation) variables, although there was a slight trend for individuals randomly assigned to receive oxytocin to have slightly higher negative affect at baseline ($p = 0.09$) than those receiving placebo (see Table 1). Men and women also did not differ significantly on any of the baseline demographic or affect variables with the exception that men had a trend toward higher trait anger than women (men $M = 22.0$, $SD = 7.6$ versus women $M = 19.5$, $SD = 6.3$, $t(96) = 1.76$, $p = 0.08$). Women had higher estradiol levels than men, although the difference was not statistically significant (men $M = 3.6$, $SD = 2.8$ versus women $M = 4.3$, $SD = 3.4$, $t(97) = -1.19$, $p = 0.24$). Men also had significantly higher CO, higher PEP and lower RSA than women (CO: men $M = 8.1$, $SD = 1.8$ versus women $M = 6.0$, $SD = 2.0$, $t(82) = 4.93$, $p < 0.01$; PEP: men $M = 114.8$, $SD = 11.1$ versus women $M = 108.2$, $SD = 10.8$, $t(82) = 2.75$, $p < 0.01$; RSA: men $M = 6.1$,

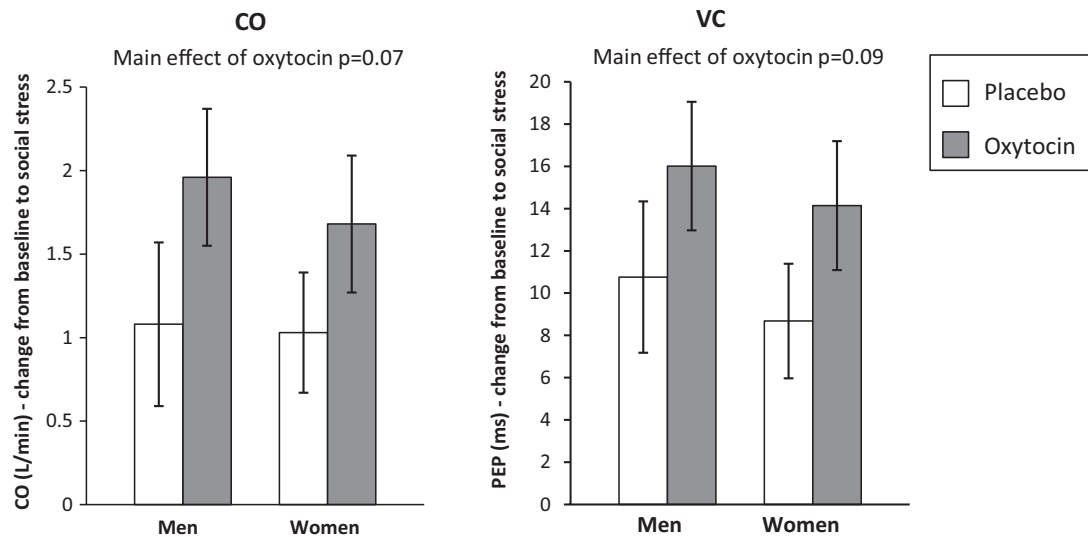


Fig. 1. Effect of oxytocin on cardiac activity during stress exposure.

$SD=1.4$ versus women $M=6.6$, $SD=1.0$, $t(89)=-2.16$, $p=0.03$). A manipulation check suggested that all participants found the TSST “stressful” with a mean score above the median of the range (1–5), $M=2.89$, $SD=1.05$, significantly different from 0, $t=27.35$, $p<0.001$, and a marginal gender difference whereby women found the task slightly more stressful than men ($p=0.09$).

3.2. Effect of oxytocin on autonomic responses to stress exposure and stress recovery

Consistent with our hypothesis that oxytocin participants would exhibit a *challenge* response to the stressful task, participants given oxytocin, compared to placebo participants, exhibited a trend toward greater increases in CO ($F(1, 68)=3.31$, $p=0.07$, $d=0.47$), and VC (indicating more sympathetic activation; $F(1, 71)=2.98$, $p=0.09$, $d=0.45$) (Fig. 1). No effect of oxytocin on RSA reactivity during the stress task was observed. Neither the main effect for gender nor the gender by oxytocin interaction was significant for any of the stress reactivity variables.

We then examined vagal rebound following the stress task. Oxytocin participants differed from placebo participants ($F(1, 82)=3.83$, $p<0.05$, $d=0.37$) showing greater vagal rebound (Fig. 2). Again the main effect for gender or the interaction was not significant.

Given the possible potentiating role of estrogen on the influence of oxytocin we tested whether estradiol was an effect modifier of any of the observed effects. However, all effects of oxytocin on stress response reported above were unchanged when ANCOVA's took account of estradiol. Thus, effects of oxytocin on autonomic response to stress did not depend on endogenous levels of estrogen either within or across gender.

3.3. Effect of oxytocin on task performance and behavior

As challenge and threat states have been linked to more positive behavior and performance outcomes, we then turned to the behavioral coding to determine if the effects of OT were evident in participants' behavior and performance. Using the challenge and threat constructs separately, we observed a trend for oxytocin to produce less threat and more challenge behavior (Fig. 3): Threat: $F(1, 86)=3.26$, $p=0.07$, $d=0.33$; Challenge: $F(1, 85)=3.52$, $p=0.06$, $d=0.32$. As in previous work, the threat construct was correlated

with the challenge construct ($r=0.71$, $p<0.001$), so we created a single index in which higher scores indicated greater *challenge* behavior ($\alpha=0.91$). This combined index produced an effect significant for the oxytocin manipulation, $F(1, 86)=4.24$, $p=0.04$, $d=0.36$. Participants who were given oxytocin were rated by observers as exhibiting more *challenge* and less *threat* behavior during the speech task than placebo participants (Fig. 3).

We then examined performance on the math task. We did not observe an oxytocin main effect but there was a gender main effect – on average men performed better than women on the math task, $F(1, 87)=4.22$, $p=0.04$, $d=0.46$. However, this main effect was qualified by a gender \times oxytocin interaction trend, $F(1, 87)=3.54$, $p=0.06$. Women given oxytocin performed better ($M=4.06$; $SE=.26$) than women given placebo ($M=3.33$; $SE=.23$), $d=0.63$, but men given oxytocin or placebo did not differ, $d=0.17$ (Fig. 3). No effect of oxytocin on speech quality was evident.

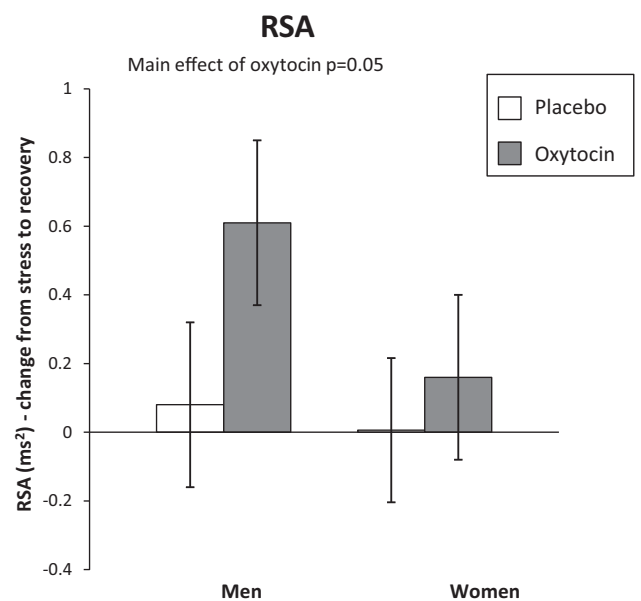


Fig. 2. Effect of oxytocin on vagal rebound during stress recovery.

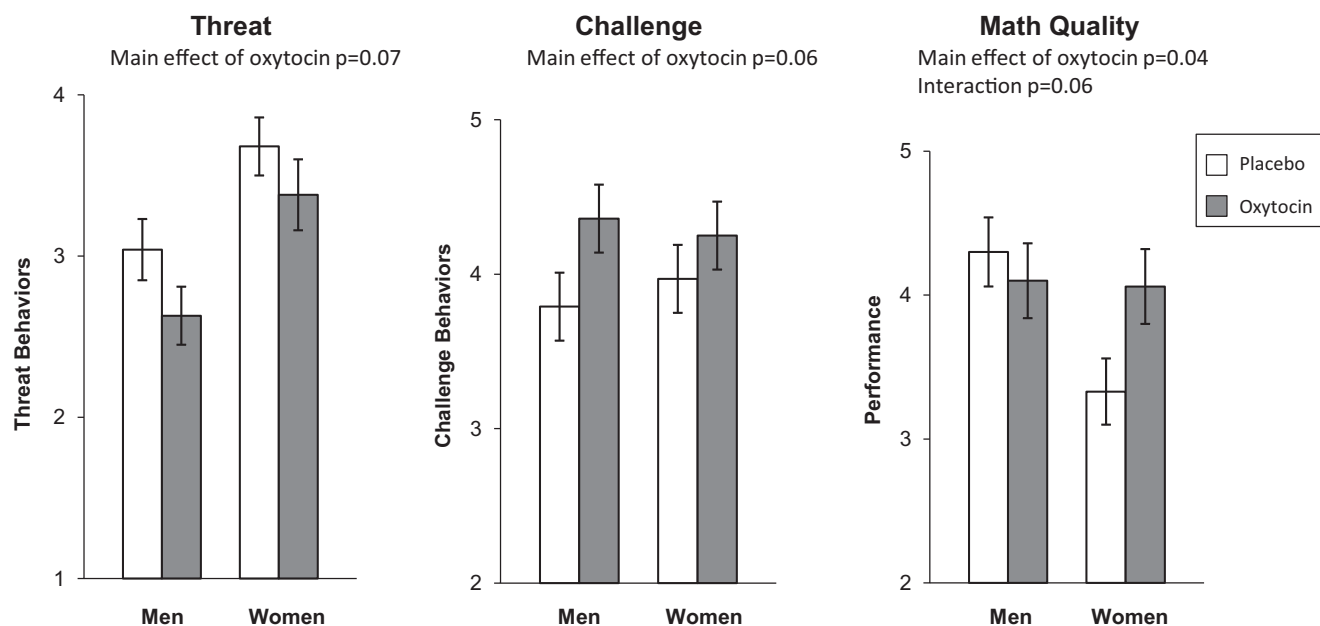


Fig. 3. Effect of oxytocin on task performance and behavior.

3.4. Effect of oxytocin on affective responses to stress exposure

Effects of oxytocin on CO and VC during stress exposure suggest that oxytocin facilitates a more adaptive *challenge* response to an acute stressor and promotes healthy recovery as indicated by greater vagal rebound. Behavioral coding provided converging evidence that oxytocin promoted positive social behavior and for women better math performance. We then examined participants' self-reported affective states. In response to oxytocin, men had significantly lower negative affect scores immediately following the stress task compared to men given placebo, $d=0.71$. In contrast, women given either placebo or oxytocin exhibited similar increases in negative affect, $d=0.14$ (Fig. 4). This two-way interaction of gender-by-oxytocin on negative affect was significant comparing baseline to immediately prior to the stress exposure, $F(1, 92)=4.83$, $p=0.03$, or to post-stress, $F(1, 92)=4.78$, $p=0.03$.

Given the importance of specific negative affect for a range of health outcomes (Kawachi et al., 1996; Kubzansky et al., 2006) we explored the patterning of specific emotions in more detail. Findings for anger followed the same pattern as those for negative affect and yielded a substantial gender by oxytocin interaction. For example, relative to men given placebo, men given oxytocin had greater decreases in anger, $d=0.24$, whereas women given oxytocin had greater increases in anger than women given placebo, $d=0.65$, comparing baseline to stress exposure $F(1, 88)=3.72$, $p=0.06$ and findings were similar when considering baseline to post-stress, $F(1, 88)=6.61$, $p=0.01$ (Fig. 4). Findings for anxiety were similar to those of anger but less pronounced and less consistent. Finally, positive affect decreased over the course of the study in all groups, until recovery when women given oxytocin reported continued reduction in positive affect but men given oxytocin reported increased positive affect, gender \times oxytocin interaction $F(1, 94)=6.89$, $p=0.01$. Overall, oxytocin appeared to mitigate self-reported distress in response to stress exposure among men, but amplified anger among women.

4. Discussion

This is the first study to examine effects of oxytocin on response to social stress across a number of domains in both men and women. Findings indicate an effect of oxytocin on physiologic activation that is highly consistent with prior theorizing and empirical animal studies, suggesting that oxytocin enhances biological readiness to approach or engage in social interaction under stressful conditions. Other work has highlighted the importance of the ANS (both PNS and SNS) in facilitating social engagement (Porges, 2003b) and for providing a broad picture of the quality of an individual's functioning. We observed cardiovascular and behavioral indicators consistent with the idea that oxytocin would be associated with a positive or *challenge* state under conditions of social stress. Additionally we found that following the stress task participants provided oxytocin showed a healthier recovery profile as indexed by greater vagal rebound. Taken together, the ANS and behavioral findings suggest that oxytocin facilitated a more positive response to a psychological stressful evaluation for both men and women. Recent work identifies oxytocin as a central cardiovascular modulatory peptide (Higa et al., 2002; Martins et al., 2005) and indicates key cellular mechanisms by which oxytocin modulates sympathetic and parasympathetic activity in response to social stress. Animal studies indicate that oxytocin is involved in mediating cardiopulmonary input into the nucleus of the solitary tract (NTS) and integrating these inputs with centrally mediated responses like stress (Higa et al., 2002; Peters et al., 2008). Oxytocin projections from the PVN of the hypothalamus selectively innervate the NTS and act on second-order neurons involved in regulating cardiac function (Higa et al., 2002). Research examining effects of oxytocinergic neurons projecting to the NTS under various conditions demonstrates that oxytocin modulates baroreflex control of heart rate by augmenting vagal outflow (Braga et al., 2000; Higa et al., 2002). Together with findings from the present study, these experiments suggest an important pathway by which oxytocin may modulate social stress response.

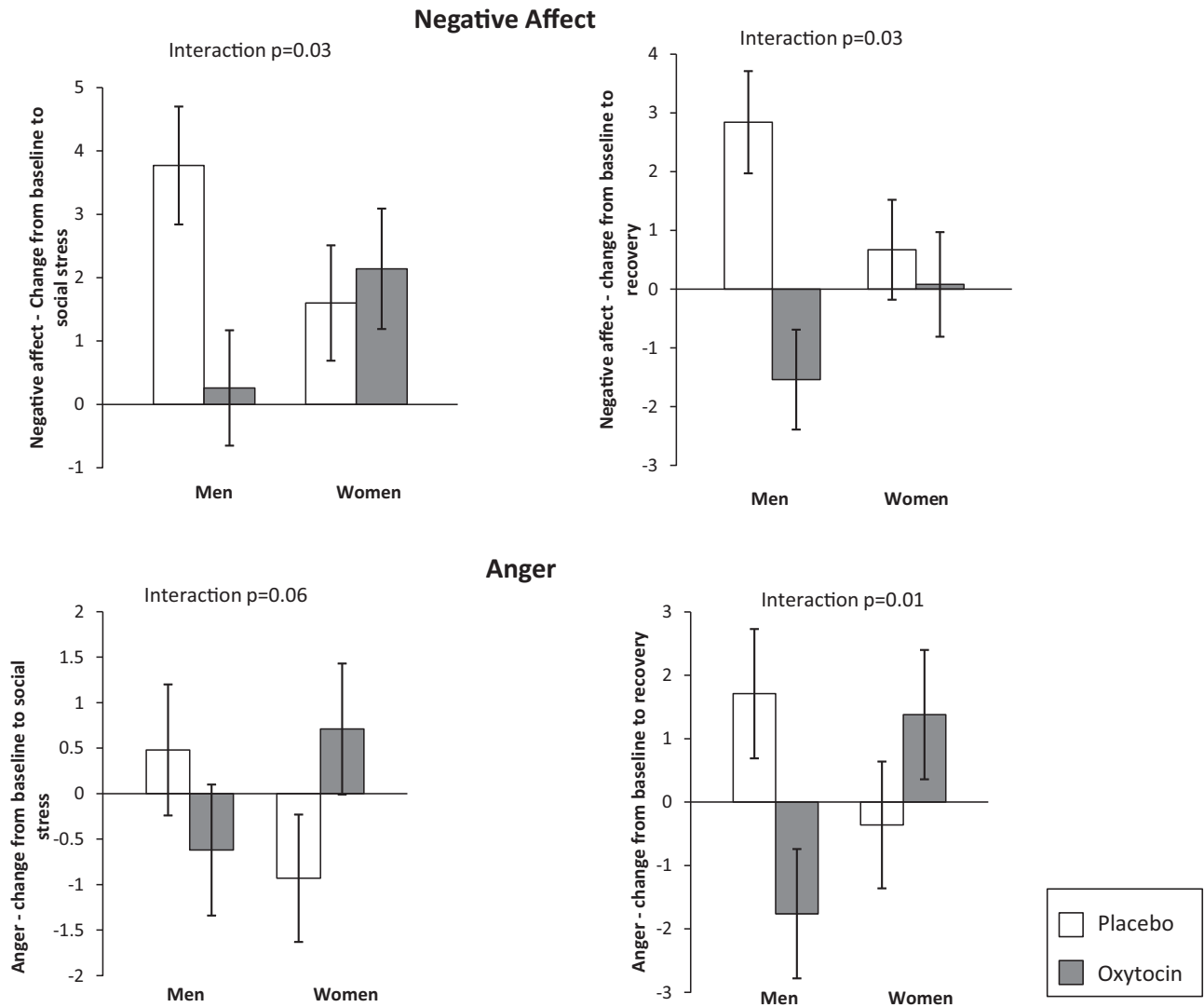


Fig. 4. Effect of oxytocin on negative affect and anger during stress exposure and recovery.

However, we also observed some gender differences, particularly when examining self-reported affect responses to the stress task. Consistent with prior work considering response to stress exposure, men given oxytocin reported less distress (Heinrichs et al., 2003). However, we found a different effect in women. Women given oxytocin reported more distress and specifically more anger. Interestingly, among the negative emotions, anger is unique in that it is an approach-related emotion and part of the appetitive system (Carver and Harmon-Jones, 2009; Harmon-Jones and Allen, 1998), and has been linked to challenge profiles of reactivity (higher CO and lower TPR, Mendes et al., 2008). Women given OT also performed objectively better on the math task than women given placebo. The performance finding might very well be expected given that anger is often associated with improved cognitive performance (see Lerner and Tiedens, 2006). Oxytocin may be associated with multiple approach-related emotion states. Thus, while oxytocin generally influenced a sense of challenge and readiness to engage, men and women may differ in how they engage with their social environment and in their subjective response to social demands. The increased cardiovascular activation that often characterizes challenge responses was associated with more positive states for men but with less positive states for women who reported more anger following the social evaluative stress. Because anger may be associated with short-term benefits in performance

or other tasks (Lerner and Tiedens, 2006) but long-term harm when it extends to more ruminative processes, more work is needed to determine health-related effects of oxytocin and their similarity across men and women. However, the gender differences in anger may also be due to floor effects for women who presented with lower rates of anger than men at baseline allowing women more room to have an anger reaction.

Prior studies with intranasal oxytocin have suggested that oxytocin modulates activation of the amygdala and fear-related behavior and autonomic activity (Domes et al., 2007). Other work, however, has suggested that in certain situations (e.g., intergroup competition) this reduced threat response may correspond with more positive feelings toward one's own group but more hostility and aggression toward non-group members (De Dreu et al., 2010). Our finding supports this more complex understanding of oxytocin effects, suggesting that rather than uniformly increasing prosocial behavior and positive feelings, oxytocin may well increase sensitivity to and willingness to engage with the social context and social agents in part by attenuating a sense of social threat (Shamay-Tsoory et al., 2009). If this is true, then perhaps in the present study under conditions of enhanced sensitivity, men and women – who both exhibited higher levels of social approach behavior – attended to different social cues or differentially interpreted similar cues, leading to a differentiated set of emotional and behavioral

responses. Thus, it may be that men in our study perceived this Trier task more positively than women. An interesting test of this hypothesis might be to administer oxytocin to men and women under conditions of stress that men perceive more negatively and women perceive more positively. If oxytocin increases sensitivity to the social context, then under these conditions we might expect to see the gender difference observed in the present study reversed, such that women's responses are more positive relative both to women with placebo or to the men. What is clear is that one should not assume either that the effects of oxytocin are uniform across multiple parameters or that they are similar for men and women.

Our study has some important limitations as well as strengths. Due to equipment malfunction we were unable to measure (and then calculate) two key aspects of cardiovascular function, blood pressure and total peripheral resistance. This tempers our strong interpretation that OT was associated with a *challenge* relative to *threat* profile of stress reactivity. However, in most challenge and threat studies, CO and TPR show similar effect sizes and given that CO is used to calculate TPR (the TPR formula is [mean arterial pressure]/[cardiac output]) this is not particularly surprising. We have no reason to believe that valid blood pressure data would lead us to a different conclusion here, but given the failure of our blood pressure device, we acknowledge that this is a critical limitation. Moreover we were unable to assess peripheral levels of oxytocin and compare those with levels of oxytocin absorbed via nasal spray administration because assays of peripheral oxytocin are thus far somewhat unreliable. Further, peripheral oxytocin levels may not correlate with cerebrospinal fluid levels of oxytocin. The design of the current study did not allow for measurements of oxytocin levels in the cerebrospinal fluid. Some of our findings showed trends but fell just short of conventional significance perhaps due to limited cell sizes. Finally due to concerns about habituation to the stress task we used a between-subjects design, which meant we could not compare effects of oxytocin and placebo within the same participants.

However, this study also has significant strengths. Effect sizes were generally in the moderate range (trend or significant Cohen's *d* effect sizes ranged from 0.32 to 0.71). In addition, the experimental double-blind placebo-controlled design enhances our confidence that oxytocin genuinely modulates cardiovascular response to acute stress in humans. Our volunteer sample was relatively highly educated and therefore may not be fully representative of the general population. However, recruitment from the community and inclusion of participants with a broad age range, suggests that results may be generalizable beyond young men, the population most frequently considered in other experimental studies with oxytocin. In fact, we view our inclusion of both men and women to be a particular strength of this investigation. Finally, effects of oxytocin across a range of biological, behavioral, and subjective responses were considered, thereby permitting a more comprehensive consideration of the range and consistency of effects.

In sum, our results suggest that oxytocin strongly influences CO and sympathetic activation during a stressful task, and heart rate variability following a stressful task in humans, supporting the idea that the oxytocinergic system modulates responses to stress and influences the social engagement system. This finding has interesting implications when considering oxytocin as a potential therapeutic agent, especially when coupled with research linking higher levels of CO to slower brain aging (Jefferson et al., 2010) and research linking higher heart rate variability and lower levels of distress with reduced risk of cardiovascular and other diseases (Chida and Hamer, 2008; Everson-Rose and Lewis, 2005; Kiecolt-Glaser et al., 2002; Thayer and Lane, 2007). However, our findings that in the context of social evaluative stress, oxytocin facilitated a generally positive social experience for men, but a less uniformly

positive experience for women, add complexity when considering the potential health benefits of oxytocin.

Because of its potential for mitigating maladaptive biological and psychological responses to stress, oxytocin has been proposed as a key biological substrate that may underlie resilience. Our results show that oxytocin may underlie resilience processes and the ability to build and sustain social relationships, but its effects may not be uniformly positive and prosocial. Before broadly considering oxytocin as a therapeutic or uniformly enhancing health, greater understanding of the conditions under which it is most beneficial is needed.

Conflict of interests

The authors declare they have no conflict of interests.

Authors' contributions

All authors contributed to the design and coordination of the study and have read, commented on, and approved the manuscript.

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