Gender differences in oxytocin-associated disruption of decision bias during emotion perception

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\textbf{A B S T R A C T}

Oxytocin is associated with differences in the perception of and response to socially mediated information, such as facial expressions. Across studies, however, oxytocin’s effect on emotion perception has been inconsistent. Outside the laboratory, emotion perception involves interpretation of perceptual uncertainty and assessment of behavioral risk. An account of these factors is largely missing from studies of oxytocin’s effect on emotion perception and might explain inconsistent results across studies. Of relevance, studies of oxytocin’s effect on learning and decision-making indicate that oxytocin attenuates risk aversion. We used the probability of encountering angry faces and the cost of misidentifying them as not angry to create a risky environment wherein bias to categorize faces as angry would maximize point earnings. Consistent with an underestimation of the factors creating risk (i.e., encounter rate and cost), men given oxytocin exhibited a worse (i.e., less liberal) response bias than men given placebo. Oxytocin did not influence women’s performance. These results suggest that oxytocin may impair men’s ability to adapt to changes in risk and uncertainty when introduced to novel or changing social environments. Because oxytocin also influences behavior in non-social realms, oxytocin pharmacotherapy could have unintended consequences (i.e., risk-prone decision-making) while nonetheless normalizing pathological social interaction.

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\textbf{1. Introduction}

Accumulating studies document changes in the perception of and response to socially mediated information, including emotion perceived from faces, associated with intranasal administration of oxytocin in humans (see meta-analyses by Van IJzendoorn and Bakermans-Kranenburg, 2012; Shahrestani et al., 2013). For example, Domes et al. (2007b) found that oxytocin increased men’s accuracy for difficult mental state attributions on the Reading the Mind in the Eyes task. Bartz et al. (2010) found that oxytocin rescued “empathic accuracy” of men who scored toward the high end of the normal range on the Autism Spectrum Quotient self-report questionnaire. Although studies report oxytocin-associated increases in accuracy of facial emotion perception, there appears to be variation in the effect of oxytocin across different facial expressions. Guastella et al. (2008) found that oxytocin increased accuracy of men’s recall of previously seen faces depicting happiness but not angry or neutral faces. Marsh et al. (2010) found that oxytocin increased accuracy of men’s and women’s categorization of faces depicting happiness, but not anger, disgust, fear, sadness, or surprise. In contrast, however, Di Simplicio et al. (2009) reported that oxytocin increased accuracy of men’s categorization of neutral faces and depictions of surprise, but not of happiness. Similarly, Fischer-Shotty et al. (2010) found that oxytocin increased accuracy of men’s categorization of depictions of fear, but not of happiness. Lischke et al. (2012) found that oxytocin reduced the intensity of expression at which men identified depictions of angry and fearful faces but did not significantly affect accuracy of labeling faces as happy, angry, sad, or fearful. Thus, across studies the effects of oxytocin on emotion perception have been inconsistent (reviewed by Bartz et al., 2011; Graustella and MacLeod, 2012).

Generalizing across social cognition studies, oxytocin may improve the “salience” of social stimuli, and a variety of possible mechanisms have been identified including effects on initial stimulus appraisal, attention, behavioral motivation, and memory (see, e.g., Bartz et al., 2011; Kemp and Guastella, 2011; Churchland and Winkielman, 2012; Graustella and MacLeod, 2012). Individual differences, internal to the perceiver, and situational differences,
such as aspects of study design, may account for some of the variation across emotion perception studies (Bartz et al., 2011; Graustella and MacLeod, 2012; Lischke et al., 2012).

Nonetheless, one consideration missing from studies of the effects of oxytocin on emotion perception is a characterization of emotion perception as a decision. Outside the laboratory, affective judgments about another person (e.g., Is that person angry at me? Do I trust that person?) involve interpretation of perceptual uncertainty (e.g., scowls do not always indicate anger) and assessment of behavioral risk (e.g., there are different costs to inferring an instance of anger when it does not exist, a “false alarm,” vs. missing an instance of anger when it does exist, a “missed detection”). Differences in the decision-like characteristics implemented by different study designs and analytic approaches could contribute to the apparent inconsistency of oxytocin’s effects. Although the results of emotion perception studies are often characterized as “improved” perception, generalization across studies or to perception outside the laboratory remains challenging. This difficulty arises, in part, because many studies have not sufficiently distinguished among various measures of performance, which include accuracy (proportion of trials answered correctly), conformation to a consensus norm, response bias, perceptual sensitivity, and decision optimality. For example, accuracy on the Reading the Minds in the Eyes task is a measure of congruence with a sample norm rather than a measure of performance over items that have objectively correct or incorrect answers (Baron-Cohen et al., 2001). Additionally, accuracy, even when it does reflect objective performance, is a function of sensitivity (ability to discriminate perceptual differences) and response bias (propensity to judge percepts as one alternative vs. another); high sensitivity and neutral bias both contribute to high accuracy (Macmillan and Creelman, 1991). Further, “accurate” perception (maximizing proportion correct) does not necessarily imply “optimal” perception (maximizing net benefit earned); it is the value earned from correct decisions, not the number of correct decisions, that is ultimately important. In environments where the costs of false alarm and missed detection differ, perceivers maximize net benefit by matching their behavior to the biased cost structure (Lynn et al., 2012), even though such bias can reduce accuracy.

In light of the inconsistencies in how emotion perception is conceptualized and measured, the results of oxytocin studies that utilize economic decision-making games may be relevant to understanding oxytocin’s effect on emotion perception. In the social economic “trust” game, “investors” decide how much money to transfer to a partner, the “trustee.” Trustees have the option to return the investment, with interest, or keep some or all of the investment and interest for themselves. Studies using the trust game indicate that oxytocin attenuates aversion to the risk of economic loss. Kosfeld et al. (2005) found that oxytocin increased the magnitude of men’s investments. Investors given oxytocin appeared less averse to the risk that their partner in the game might respond to the investment selfishly. Behavior between oxytocin and placebo groups did not differ in a non-social version of the game. Kosfeld et al. did not provide feedback to investors about whether or not trustees responded to the investment fairly or selfishly, indicating that the difference in “trust” was not based on learning from trial to trial.

Mikolajczak et al. (2010) directly manipulated men’s perception of risk in the trust game. While they found that oxytocin attenuated aversion to the risk of monetary loss, they also established a lower bound to the effect. Among men provided with vignettes (prior to the game) describing trustees as trustworthy, men given oxytocin made larger investments than those given placebo (replicating Kosfeld et al., 2005). However, men provided with vignettes describing trustees as untrustworthy invested little money, regardless of oxytocin treatment. This finding indicates that if risk is great enough, oxytocin does not noticeably alter risk perception.

Contrary to (Kosfeld et al., 2005; see also Baumgartner et al., 2008), in a non-social version of the game, Mikolajczak et al. (2010) found that men who received oxytocin invested more than men who received placebo. Mikolajczak et al. (2010) showed that this “non-social” difference between studies lay in the different investment risk that participants inferred from the task instructions for the non-social game. Perception of economic risk may therefore be a salient domain of oxytocin’s activity, regardless of whether the risk has a social component.

Optimizing decisions (i.e., maximizing net benefit accrued over a series of decisions) involves learning from the outcomes of one’s past decisions. Baumgartner et al. (2008) found that oxytocin caused the magnitude of men’s investments in the trust game to remain unchanged following feedback that trustees had behaved selfishly. Men receiving placebo reduced their investment magnitude under the same conditions. Therefore, while the reduced risk aversion caused by oxytocin does not require feedback about the outcomes of one’s decisions in order to become established (Kosfeld et al., 2005), the reduction also appears immune to the consequences of poor decisions.

Although the results of studies utilizing this economic game are framed in the social terms of “trust” and risk of “betrayal”, more generally the economic loss resulting from poor decisions (e.g., the feedback provided by Baumgartner et al., 2008) may also be viewed as aversive feedback (i.e., punishment, as opposed to reward). Further evidence for a link between oxytocin and the perception of aversive feedback comes from a study utilizing aversive conditioning. Petrovic et al. (2008) initially elicited low ratings of how sympathetic individual faces appeared by pairing the faces with electric shock. Men who then received oxytocin (subsequent to the aversive conditioning) re-rated the faces as more sympathetic than did men who received placebo. Oxytocin, then, appears to reduce negatively valenced affective value associated with a stimulus, providing an explanation for why the effects of aversive feedback about one’s decisions are attenuated by oxytocin (i.e., Baumgartner et al., 2008).

Risk can be quantified with two parameters: estimated payoff value (e.g., magnitude of aversive feedback), and the estimated likelihood of accruing the payoff. Oxytocin may be decreasing either or both to bring about attenuated risk aversion. Although the two studies that involved aversive conditioning (Baumgartner et al., 2008; Petrovic et al., 2008) did not investigate oxytocin’s effects in these terms, a study of pain perception (Singer et al., 2008) may be relevant to understanding oxytocin’s effect on risk sensitivity. Singer et al. (2008) found that oxytocin reduced amygdala activation elicited by painful electric shock in men, which suggests that oxytocin may attenuate risk aversion by reducing the influence of negatively valent stimulation (e.g., the perceived relevance of aversive feedback), rather than the estimated likelihood of accruing the aversive feedback.

1.1. The current study

In sum, emotion perception may be viewed as a decision made under conditions of uncertainty and risk. Nonetheless, prior studies of emotion perception have not modeled this uncertainty and risk. Prior studies involving risk indicate that oxytocin attenuates risk aversion, but have not investigated emotion perception. Prior studies utilizing aversive stimulation and conditioning indicate that oxytocin’s influence on risk aversion could result from reducing the influence of aversive feedback on subsequent behavior. To bring together these elements and characterize oxytocin’s effects on emotion perception from a
decision-making perspective, we utilized a task that combines perceptual uncertainty with behavioral economics in a signal detection framework (Lynn et al., 2012).

In signal detection theory, response bias is strongly influenced by the risk parameters, payoff magnitude and likelihood (Green and Swets, 1966). Achieving optimal bias requires that the perceiver accurately “estimate” these parameters and adjust (bias) his or her categorization behavior accordingly. We used the probability of encountering angry faces and the cost of misidentifying them as not angry to create a biased perceptual environment. We measured the effect of oxytocin on optimality of emotion perception bias in this environment.

Notably, almost all prior emotion perception studies of oxytocin from which our hypothesis has been drawn have examined men only. An exception is Domes et al. (2010), who studied women only. Domes et al. found, in an fMRI study, that for women, oxytocin-associated activity in the amygdala elicited by angry faces differed from that reported in prior studies of men. In women, oxytocin did not change amygdala activity in response to angry faces (Domes et al., 2010), while in men, oxytocin has led to reduced activity (e.g., Domes et al., 2007a). We included men and women in our sample but analyzed gender as a factor, in addition to oxytocin treatment condition.

Available data thus supported the hypothesis that men receiving oxytocin (vs. placebo) would under-estimate the cost of misidentifying angry faces as not angry and/or the probability of encountering angry faces (relative to not angry faces), such that oxytocin would be associated with a more neutral-going (sub-optimal) bias when learning to judge scowling faces as angry or not. To explore the possibility that the effects of oxytocin on risky emotion perception decisions might differ by gender, we included gender as an analysis factor.

2. Methods

2.1. Participants and procedure

Forty participants (age M = 44.0 ± 10.32 [S.D.]; years, 40% women, 75% Caucasian) free of psychiatric illness were recruited. Prior to administration of double-blind oxytocin/placebo, participants received a medical screening (see Supplementary Material), and completed the first of three Affect Grids (Russell et al., 1989), a brief measure of affective state scored on dimensions of pleasure-displeasure and arousal-sleepiness. Under supervision, participants then self-administered 30 IU of double-blind intranasal oxytocin (10 sprays at 3 IU oxytocin per spray; Syntocinon<sup>®</sup>, Novartis Corporation) or placebo spray with a metered-dose pump actuator (oxytocin: n = 22, 9 women; placebo: n = 18, 7 women; see Supplementary Table S1).

Following drug/placebo administration, participants spent 25 min working on puzzles screened for neutral affective content to provide a standardized experience while waiting for the drug to be absorbed. After this period, participants completed a second Affect Grid (Watson et al., 1988), the Liebowitz Social Anxiety Scale (Heimberg et al., 1999), the Quick Inventory of Depressive Symptoms (Rush et al., 2003), the Perceived Stress Scale (Cohen et al., 1983), the State-Trait Anxiety Inventory (Spielberger et al., 1970), and an assessment of the treatment-blind to determine whether participants believed they took the active drug or placebo.

2.2. Emotion perception task

We designed a task to capture key features of uncertainty and risk inherent to emotion perception decisions. In social interactions, perceivers are faced with uncertainty about the state of a social partner. The uncertainty exists because, for example, sometimes people look angry when they are not (e.g., when they are concentrating), and sometimes people do not look angry when they in fact are (e.g., when they are hiding their emotions). In addition to uncertainty, the judgment (e.g., that the person is or is not angry) entails risk: the behavior of the perceiver, in light of his or her judgment, has consequences on subsequent social interactions. Benefits and costs accrue to the perceiver—for example, the social interaction may be facilitated or interrupted as a consequence of the perceiver’s judgment and subsequent actions (and in more extreme circumstances, the perceiver may be threatened). To capture these elements of uncertainty and risk in emotion perception, we used a computational, utility-based signal detection framework (Lynn et al., 2012). In this framework (Fig. 1), faces that depicted expressions ranging from relaxed to strongly scowling comprised two categories: “angry” (targets) and “not angry” (foils). Uncertainty was implemented by creating distributions of targets and foils that shared exemplars (i.e., the distributions overlapped on the perceptual domain). Targets were M = 60 ± 15% (1 S.D.) scowl intensity. Foils were M = 40 ± 15% (1 S.D.) scowl intensity. Risk was created by earning or losing points for correct vs. incorrect categorization of targets and foils.

Correct detection (categorizing a target as “angry”) earned 10 points. Correct rejection (categorizing a foil as “not angry”) earned 10 points. Missed detection (categorizing a target as “not angry”) cost 10 points. False alarm (categorizing a foil as “angry”) cost 3 points. Additionally, the base rate of targets was 0.6 (60% of trials were targets). The combination of relatively high missed detection cost and relatively frequent targets dictated a liberal optimal bias (optimal c = −0.6 at maximum sensitivity of d = 1.33). That is, a tendency to categorize faces as angry was required to maximize points earned. Face stimuli comprised posed neutral and scowling expressions from 1 male and 1 female photographic model. We digitally blended the 0% scowling (neutral, relaxed-face) and 100% scowling faces of a given model to generate a series of 11 “morphs” that ranged from 0% to 100% scowling in 10% steps (Lynn et al., 2012; see also Supplementary Material).

Over 230 trials, participants attempted to optimize their categorization of the faces, answering the on-screen prompt “Is this person angry?” by pressing keyboard buttons labeled “Yes” and “No.” Trials were presented on a computer monitor and began with a centered white fixation cross on a black screen (300 ms duration). Faces remained on-screen for 750 ms. The prompt followed the face, and remained on-screen until the participant’s response. Participants earned and lost

Fig. 1. A utility-based signal detection framework for emotion perception. Three signal parameters (similarity of target [“angry”] and foil [“not angry”]) signal distributions, decision payoffs [costs and benefits implemented as points earned or lost], and the base rate of occurrence of targets relative to foils) combine to yield a utility function (Lynn et al., 2012). The point of maximum utility locates the optimal decision criterion position (dashed drop line). Responding to faces of scowl intensity > criterion as “angry” will maximize net benefits accrued over a series of decisions (e.g., maximize points earned over trials). The left-of-center criterion location indicates a tendency to categorize faces as angry, called “liberal” response bias. The y-axis for the target and foil signal distributions (probability density) is not shown.
points for correct or incorrect answers, and received immediate on-screen feedback ("Yes – that was right." or "No – that was wrong."). points earned for the current trial, and cumulative points earned). Following the feedback was a 300 ± 100 ms inter-trial interval (black screen). We recorded response button choice, points earned, and response time (from a USB keyboard) for each trial. Trials for which response times were less than 300 ms were excluded from analysis due to the high probability of their containing motor errors. We calculated bias (response times were less than 300 ms were excluded from analysis due to the high inter-trial interval (black screen)). We recorded response button choice, points trial, and cumulative points earned). Following the feedback was a 300 ms black screen.

4. Results

We found associations between drug condition, response bias, and scores on the Perceived Stress Scale (PSS, which measures “stress” over the last month) and State-Trait Anxiety Inventory (Trait total score, STAI-T, which measures anxious tendencies “in general”), uncorrected for multiple comparisons across the other questionnaire scores and symptom assessments (Table 1). No such associations were found for the other affect questionnaires. Lacking pre-treatment ratings on the PSS and STAI-T scores, however, we could not distinguish possible effects of oxytocin on self-reported stress and anxiety from sampling differences at baseline. In light of the possibility of baseline differences in stress and anxiety between treatment groups, we evaluated the effect of oxytocin and gender on bias and sensitivity using PSS and STAI-T as covariates. The covariates did not interact significantly with the treatment and gender factors on bias or sensitivity outcomes, indicating that the covariates met the homogeneity of slopes assumption for Analysis of Covariance (ANCOVA).

We found a significant interaction of treatment and gender on response bias (Table 1, Fig. 2; ANCOVA, $F(1,32)=4.1, P<0.049$, partial $\eta^2=0.11$, power = 0.51), without main effects, controlling for stress and anxiety in this non-psychiatristically ill sample. In line with our hypothesis, men who received oxytocin exhibited significantly less liberal (less optimal) bias than those who received placebo (follow-up ANCOVA among men, $F(1,20)=5.0, P<0.037$, partial $\eta^2=0.20$, power = 0.57). Women’s bias was not significantly affected by oxytocin (follow-up ANCOVA among women, $F(1,12)=0.6, P>0.465$, partial $\eta^2=0.04$, power = 0.11). Within each treatment group, bias of men and women did not differ significantly (follow-up ANCOVA among oxytocin group, $F(1,22)=3.0, P>0.098$, partial $\eta^2=0.14$, power = 0.38; follow-up ANCOVA among placebo group, $F(1,18)=2.8, P>0.116$, partial $\eta^2=0.17$, power = 0.35). There were no effects of treatment or gender on sensitivity.

4. Discussion

We hypothesized that oxytocin administration would be associated with insufficient decision bias in emotion perception in men. Consistent with this view, we found that men given oxytocin exhibited a relatively suboptimal (less liberal) response bias compared to men given placebo when participants attempted to optimize their decisions in response to experimenter-defined values of target-foil similarity, payoffs (points earned/lost), and “anger” base rate. Men given oxytocin appeared less able to calibrate their emotion perception to the signal detection parameters that cause bias (i.e., payoffs, base rate, or both). As a learning experiment, our results suggest that oxytocin may impair men’s ability to optimally adapt their emotion perception (e.g., judgments of anger from faces) to differences in risk and uncertainty that characterize different social contexts.

We found no effect of oxytocin on women judging scowling faces as “angry” in our study. This result is congruent with studies showing no effect of oxytocin-associated activity in the amygdala elicited by angry faces in women (Domes et al., 2010) but reduced activity in men (e.g., Domes et al., 2007a). It is unlikely, however, that our null finding with faces depicting anger for women would generalize to all social perceptions. Domes et al. (2010), for example, did find that oxytocin increased women’s amygdala response to facial depictions of fear. Furthermore, although the literature is sparse, oxytocin-related differences in social perception between men and women appear to be varied. For example, Marsh et al. (2010) found that oxytocin increased accuracy for perceptions of happiness in both men and women, while Fischer-Shoffy et al. (2013) found that oxytocin increased accuracy for the perception of kinship in women but not men, and for the perception of competitive relationships in men but not women.

Our results point to a computational mechanism by which oxytocin could affect social approach – withdrawal motivation, which Kemp and Guastella (2011) used to characterize oxytocin’s effects in social and affective domains of experience. Namely, the increased social approach or reduced withdrawal motivation attributed to oxytocin may arise because events are perceived as less likely to be threats (reduced base rate), or if they are threats, less costly to endure (reduced missed detection cost).

We found that oxytocin impaired emotion perception under conditions requiring bias (i.e., requiring attention to costs and base rate). This result indicates one mechanism by which oxytocin produces the increased accuracy (i.e., proportion of trials responded to correctly) reported in prior emotion perception studies and supported by meta-analysis (Shahrestani et al., 2013). Emotion perception studies typically implement unbiased perceptual environments: the base rates of different emotion depictions are equal and any costs or benefits of categorizing
a face as one emotion or another are not specified, so effectively equal. Participants bring their own idiosyncratic bias to any perceptual task (one imputus for the initial development of SDT; Green and Swets, 1966). Our results suggest that oxytocin could neutralize that bias to some extent, relative to placebo. Mathematically, neutral bias necessarily results in greater accuracy than liberal or conservative bias in unbiased environments (Supplementary Fig. S2). Thus, the neutralization of bias by oxytocin can explain the higher accuracy associated with oxytocin in neutrally-biased environments. Notably, in environments that demand non-neutral bias, such as the present study (and, we believe, many decisions outside the laboratory) unbiased decision-making is in fact suboptimal decision-making. Ultimately, it is not the number of correct decisions one makes (i.e., accuracy) that is important, but the balance of correct and incorrect decisions one achieves (i.e., bias), in light of their benefits and costs. Accuracy, as a tally of the number of correct and incorrect decisions, ignores the costs and benefits resulting from those decisions.

Oxytocin has been investigated as a pharmacological intervention in a variety of mental illnesses, including social anxiety disorder (Guastella et al., 2009), autism spectrum disorders (Guastella et al., 2010), and schizophrenia (Feifel et al., 2010); and disrupted oxytocin signaling has been implicated in post-partum depression (Feldman, 2012). Our results imply that oxytocin as an intervention may only be helpful to the extent that patients exhibit an overly-liberal threat detection bias, such as characterizes child abuse victims (Pollak and Kistler, 2002) and adults with social anxiety disorder (Gilboa-Schechtman et al., 2008), and in men only (at the dose administered here). Oxytocin might mitigate an overly-liberal threat detection bias by reducing estimates of the base rate of threat or reducing estimates of the magnitude of aversive feedback (costs), over-estimates of which could contribute to excessive social withdrawal or reduced social approach behaviors. However, if oxytocin’s effect is on the salience of aversive feedback but the patient’s impairment is better characterized as a base rate misperception, then treatment might show success (i.e., make an overly-liberal bias more neutral) for the wrong reason – modulation of perceived costs – which could potentially be problematic in the long-term.

In rodents, studies documenting oxytocin’s anxiolytic effects show its influence on behavioral decisions in non-social domains (e.g., Ring et al., 2006; Knobloch et al., 2012). If oxytocin also influences human decisions in non-social realms (e.g., Kirsch et al., 2005; Mikolajczak et al., 2010) then our results suggest that oxytocin pharmacotherapy could have unintended consequences, whatever its effects on emotion perception. For example, by inducing a devaluation of costs, oxytocin treatment could promote poor economic decisions or risk-prone behavior while nonetheless normalizing pathological social avoidance or mistrust.

A limitation of this study that must be addressed by future research is the difference in stress and anxiety ratings between the oxytocin and placebo groups (Table 1). It seems unlikely that the higher stress reported by oxytocin-participants was caused by the drug treatment; prior studies have reported no effects of oxytocin on self-reported mood, including anxiety and calmness (e.g., Kirsch et al., 2005; Domes et al., 2007a, 2007b; Baumgartner et al., 2008; Guastella et al., 2008; Di Simplicio et al., 2009; Bartz et al., 2010; Domes et al., 2010; Fischer-Shofty et al., 2010; Marsh et al., 2010). We controlled for the between-group difference statistically; nonetheless, a within-subjects design should be used in the future. With respect to the gender difference we report, a central limitation of this study is sample size. Power to further investigate the gender difference reported here would be enhanced by increased sample size.

Future directions for investigating the effects of oxytocin on the utility of emotion perception include studying facial expressions other than anger, and studying judgments that separate “threat” as part of the stimulus’ emotional meaning acquired prior to the experiment (e.g., an angry or fearful expression as a cue of potential threat) from the threat of making an incorrect decision (i.e., the punishment incurred by false alarms and missed detections). Further, based on prior studies of trust and aversive conditioning, we speculate that oxytocin may have reduced the salience of missed detection costs specifically. Systematic manipulations of all three signal detection parameters (similarity, pay-offs, and base rate) could test this hypothesis.

Acknowledgments

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Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2014.04.031.

References


Supplementary Material

Gender differences in oxytocin-associated disruption of decision bias during emotion perception.

* These authors contributed equally to the study.

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Supplementary Methods

The experiment described here was exploratory, opportunistically inserted into a larger study of the influence of oxytocin on affective processes. As such, we operated under several constraints due to limited time allotted to this experiment. These constraints included a between-subjects design for drug vs. placebo administration, a relatively long duration between drug administration and task completion, and, due to time, the use of a single facial expression.

Participants were recruited to the Center for Anxiety and Traumatic Stress Disorders (CATSD) at Massachusetts General Hospital through local hospital and media advertising. Exclusion criteria included: affective, anxiety, substance abuse or dependence, or lifetime psychotic Axis I DSM-IV diagnosis; severe unstable medical illness; history of seizure disorder; known hypersensitivity to oxytocin or to any of the excipients of Syntocinon® nasal spray; known hyponatremia or concurrent use of diuretics; pregnancy; lactation; or current use of psychiatric medications or hormones, such as estrogen. The psychiatric assessment was conducted by clinical interviewers trained in administering the Structured Clinical Interview for DSM-IV (First et al., 2002). Non-psychiatric medical conditions and medications were assessed by self-report. All participants gave informed consent in accordance with the policies of the Partners Institutional Review Board, which approved all procedures. Participants received $40 for completing the study. A urine toxicology test was performed for all participants, and a pregnancy test was performed for female participants prior to the administration of double blind oxytocin/placebo.

We chose a 30 UI dose of oxytocin because several recent studies used higher doses than the common 24 IU (Petrovic et al., 2008; Singer et al., 2008; Ditzen et al., 2009; Feifel et al., 2010; Mikolajczak et al., 2010) and because the original experiment that provided evidence that intranasally administered neuropeptides could enter the cerebrospinal fluid was done with doses higher than 24 IU (Born et al., 2002). Striepens et al. (2013) reported that the concentration of oxytocin in cerebrospinal fluid increased significantly from 60 to 75 minutes after intranasal administration of 24 IU oxytocin.

Following the 25 minute drug absorption period, participants completed tasks comprising parts of the larger research program prior to engaging in the emotion perception task described here (Supplementary Fig. S1). These other tasks investigated the biasing of perception by affective information. A continuous flash suppression (CFS) task used depictions of neutral, smiling, and scowling facial expressions (see Anderson et al., 2012). A "gossip" task used depictions of neutral facial expressions (see Anderson et al., 2011).

Face stimuli were converted from color to grey scale and placed on a black background. Viewed on an LCD computer monitor from 0.6 m distance, the faces subtended 7° horizontally x 11.5°
vertically. We used female #45 from the Interdisciplinary Affective Science Laboratory (IASLab) Face Set\(^1\). We used male #22 from the MacBrain Face Stimulus Set\(^2\). Scowling, "angry" facial depictions were used because our group runs other signal-detection based experiments in social anxiety disorder in which these stimuli have proven effective.

**Supplementary Fig. S1.** Timing and duration of study components. The emotion perception task described here was initiated approximately 50 minutes after drug administration and took approximately 15 minutes to complete.

**Supplementary Table S1.**
Age (years) of participants by group.

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\(^1\) Development of the IASLab Face Set was supported by the National Institutes of Health Director’s Pioneer Award (DP1OD003312) to Lisa Feldman Barrett. More information is available on-line at www.affective-science.org.

\(^2\) Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham (tott0006@tc.umn.edu) and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development.
**Supplementary Results**

Twenty oxytocin participants and 18 placebo participants assessed their double-blinded drug-administration condition. Participants answering the question, "Do you believe that the medication you have taken is an active drug?" with a rating on a scale from 0 (did not receive active drug) to 100 (received active drug) in 10-unit increments. There was no difference between oxytocin and placebo group ratings (p>0.5). The mean rating (M=38.9, SD=25.45) was significantly below 50 (p<0.02), indicating an overall bias for participants to believe they had not be given oxytocin.

**Supplementary Discussion**

**Supplementary Fig. S2.** In an unbiased perceptual environment, a perceiver can maximize his or her accuracy by exhibiting neutral response bias. Under uncertainty (when a perceiver cannot be certain of the correct category, i.e., "target" or "foil," to which a particular stimulus belongs) maximizing accuracy (the proportion of correct answers) is done by matching the proportion of answers to the base rate. Here, we used our mathematical model (Lynn et al., 2012) to create a neutral perceptual environment (base rate = 0.5; benefits of correct detection and correct rejection = +10 points each; costs of missed detection and false alarm = −10 points each). Overlapping target and foil signal distributions model perceptual uncertainty. A plot of the accuracy expected from criteria placed over all possible signal values (Scowl intensity) is maximal at neutral bias (c=0; dashed drop-line). Therefore, to the extent oxytocin neutralizes the idiosyncratic bias that perceivers bring to typical (i.e., unbiased) emotion perception studies, oxytocin should be associated with higher accuracy than placebo.
References for Supplementary Material