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Oxytocin's impact on social face processing is stronger in homosexual than heterosexual men☆

Matthias Thienel [a], Markus Heinrichs [b,c], Stefan Fischer [a], Volker Ott [d], Jan Born [a], Manfred Hallschmid [a,*]

[a] Department of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen 72076, Germany
[b] Department of Psychology, Laboratory for Biological and Personality Psychology, University of Freiburg, Freiburg 79104, Germany
[c] Freiburg Brain Imaging Center, University Medical Center, University of Freiburg, Freiburg 79106, Germany
[d] Department of Neuroendocrinology, University of Lübeck, Lübeck 23562, Germany

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Summary Oxytocin is an evolutionarily highly preserved neuropeptide that contributes to the regulation of social interactions including the processing of facial stimuli. We hypothesized that its improving effect on social approach behavior depends on perceived sexual features and, consequently, on sexual orientation. In 19 homosexual and 18 heterosexual healthy young men, we investigated the acute effect of intranasal oxytocin (24 IU) and placebo, respectively, on the processing of social stimuli as assessed by ratings of trustworthiness, attractiveness and approachability for male and female faces. Faces were each presented with a neutral, a happy, and an angry expression, respectively. In heterosexual subjects, the effect of oxytocin administration was restricted to a decrease in ratings of trustworthiness for angry female faces ($p < 0.02$). In contrast, in homosexual men oxytocin administration robustly increased ratings of attractiveness and approachability for male faces regardless of the facial expression (all $p \leq 0.05$), as well as ratings of approachability for happy female faces ($p < 0.01$). Results indicate that homosexual in comparison to heterosexual men display higher sensitivity to oxytocin's enhancing impact on social approach tendencies, suggesting that differences in sexual orientation imply differential oxytocinergic signaling.

* Corresponding author at: Department of Medical Psychology and Behavioral Neurobiology University of Tübingen, Otfried-Müller-Str. 25, Tübingen 72076, Germany. Tel.: +49 7071 2988925; fax: +49 7071 2925016.
E-mail address: manfred.hallschmid@uni-tuebingen.de (M. Hallschmid).

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1. Introduction

The hypothalamic oxytocin system, in addition to releasing the hormone into the system via the posterior pituitary, projects to widespread brain areas including hippocampus, amygdala, and nucleus accumbens (Ludwig and Leng, 2006). Findings in animals and humans consistently indicate a strong involvement of oxytocin in the regulation of affiliative and social approach behavior, including postpartum mother-infant bonding (e.g., Feldman et al., 2007), the processing of social stimuli (e.g., Guastella et al., 2009; Domes et al., 2012) and the induction of sexual arousal (for reviews see Carter, 1998; Heinrichs et al., 2009; Panksepp, 2009; Bartz et al., 2011; Meyer-Lindenberg et al., 2011). A promoting influence of intranasal oxytocin administration on trusting behavior was demonstrated in experiments assessing the participants' willingness to take social risks (Kosfeld et al., 2005; Baumgartner et al., 2008). In accordance, experimental studies of couple interactions have indicated an enhancing effect of oxytocin on behaviors maintaining social ties (Grewen et al., 2005; Ditzen et al., 2009; Taylor et al., 2010; Ditzen et al., 2012; Scheele et al., 2012).

The impact of oxytocin administration on the processing of facial stimuli as an essential feature of social interactions has been addressed in a number of previous studies. In imaging studies in male participants, intranasal oxytocin dampened the amygdala response to threatening social stimuli like negative facial expressions (Kirsch et al., 2005; Domes et al., 2007; Gamer et al., 2010) and attenuated the deterioration of ratings of likeability for male faces induced by aversive conditioning, likewise in parallel to a reduction in amygdala activation (Petrovic et al., 2008). In contrast, increased amygdala activation in response to fearful faces was found in female subjects (Domes et al., 2010). In a study focusing on the social appraisal of faces in subjects of both sexes (Theodoridou et al., 2009), intranasal oxytocin administration increased the perceived trustworthiness and attractiveness of facial stimuli independent of the respective sex of the participant and the presented face, suggesting that the impact of oxytocin treatment on face processing is not modulated by the sexual attitude toward a facial stimulus. However, this conclusion remains preliminary as the study did not control for possible influences of menstrual cycle phase and hormonal contraception.

Against this backdrop and considering the strong sexual component of oxytocin's role in human physiology, the present study aimed at clarifying to which extent sexual orientation modulates the effect of oxytocin administration on face processing. In order to exclude confounding influences of sex differences unrelated to sexual orientation, we compared oxytocin effects between male participants with either homosexual or heterosexual orientation, rather than between heterosexual men and women. In response to female faces, heterosexual men and homosexual women in comparison to heterosexual women and homosexual men exhibit stronger activation of reward-processing thalamic and orbitofrontal structures, and this pattern is reversed when male faces are presented (Kranz and Ishai, 2006). We therefore expected our approach to provide insight into interactions between oxytocin effects and sexual orientation toward men or women in general. Moreover, the ongoing discussion on the relationship between neuroendocrine factors and sexual orientation up to now has largely ignored the potential role of oxytocin (for review see Balthazart, 2011). In detail, we hypothesized that oxytocin administration generally enhances the approach-related appraisal of faces, yet depending on sexual orientation, i.e., that heterosexual men rate female faces higher for attractiveness and approachability after oxytocin administration, whereas in homosexual men this effect is observed for male faces. In contrast, the effect of oxytocin on ratings of trustworthiness was expected to be independent of the face's sex and the rater's sexual orientation, assuming that oxytocin modulates facial processing subject to the sexual component involved.

2. Methods

2.1. Participants

Thirty-seven healthy young male volunteers were recruited on site (i.e., via the university's mailing list and word-of-mouth advertising), online (part-time job websites), and via gay media outlets. Participants were assigned to two experimental groups according to their sexual orientation as indicated by their mean scores across the dimensions 'sexual attraction', 'sexual behavior', 'sexual fantasies', and 'self-identification' of the Klein Sexual Orientation Grid (KSOG; Klein et al., 1985) that categorizes sexual orientation from 1 (exclusively heterosexual) to 7 (exclusively homosexual). The homosexual and the heterosexual groups comprised 19 and 18 men, respectively. None of the subjects was on any medication and all relevant illness was excluded by clinical examination taking place within one week before the first experimental session. Groups were comparable regarding psychological and endocrine markers except for slightly increased serum testosterone concentrations in homo- as compared to heterosexual subjects (see Table 1 for group characteristics). Participants gave written informed consent to the study which conformed to the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Design and experimental procedure

According to a 2×2 experimental design, subjects of both groups participated in two conditions (oxytocin and placebo) that were spaced apart at least two weeks. The order of conditions was balanced across subjects and all experiments were performed in a double-blind fashion. Subjects were instructed not to eat or drink (except water) for 2 h before the experiment and not to ingest alcoholic or caffeinated drinks after 2000 h on the preceding day. Experimental sessions (Fig. 1) started around 1600 h with baseline assessments of the control parameters mood, vigilance, memory function, and anxiety. At 1630 h, subjects were intranasally administered 24 IU oxytocin (0.6 ml Syntocinon®, Novartis, Basel, Switzerland) and placebo (0.6 ml vehicle containing all Syntocinon ingredients except for the peptide), respectively, at 6 individual puffs (volume 0.1 ml; 3 per alternating nostril) with 30-s intervals in-between. After intranasal administration, neuropeptides like vasopressin, a nonapeptide with high structural similarity to oxytocin reach the central nervous

Table 1 Group characteristics.

Variable	Homosexual	Heterosexual	*p* Value
Relationship status (unattached/monogamous relationship/no response)	(5/11/3)	(7/9/2)	0.72
Age (years)	24.63 ± 0.95	25.28 ± 0.95	0.64
KSOG score	6.72 ± 0.09	1.14 ± 0.07	<0.001
SCL-90-R GSI, *T* score	48.95 ± 2.57	41.94 ± 2.77	0.07
SCL-90-R depression, *T* score	48.68 ± 2.53	44.89 ± 2.27	0.27
SCL-90-R interpersonal sensitivity, *T* score	49.16 ± 2.39	44.89 ± 2.09	0.19
STAI (trait) raw score	36.21 ± 2.33	31.58 ± 1.79	0.13
Subjective well-being on experimental days	4.18 ± 0.14	4.28 ± 0.12	0.62
Serum testosterone (μg/l)	6.54 ± 0.54	5.22 ± 0.29	0.04
Serum TSH (mIU/l)	1.89 ± 0.17	2.05 ± 0.20	0.57

All values (mean ± SEM except for relationship status) were obtained during enrollment taking place within one week before the first experimental session except otherwise indicated. KSOG, Klein Sexual Orientation Grid (Klein et al., 1985; scores of 1 and 7 denote exclusively heterosexual and homosexual orientation, respectively); SCL-90-R GSI, Global Severity Index according to the Symptom Checklist-90-Revised (Franke, 1995; score reflects the severity of reported psychological strain); STAI, State-Trait Anxiety Inventory X2 (Laux et al., 1981); TSH, thyroid-stimulating hormone. Subjective well-being was rated on a five-point scale at the start of each experiment and averaged across conditions. Serum concentrations of testosterone and TSH were determined by electrochemiluminescent immunoassay (ECLIA, China Medical Technologies, Beijing, China). *p* Values derived from unpaired *t* tests except for relationship status (Pearson's chi-squared test) and KSOG scores (Mann–Whitney *U*-test because of non-normal distribution).

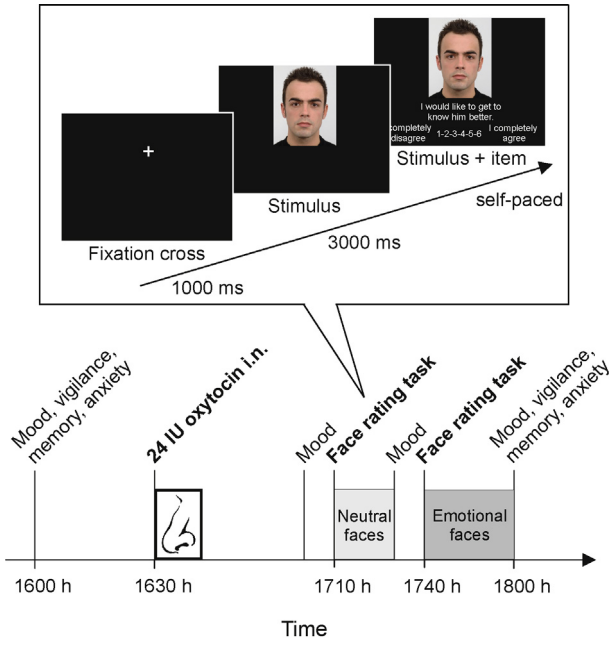

Figure 1 Experimental procedure. After baseline assessments of control parameters at 1600 h, healthy young homo- and heterosexual men were intranasally (i.n.) administered oxytocin (24 IU) and placebo, respectively, at 1630 h. Around 40 min later, the PC-based neutral face rating task started with the presentation of a fixation cross for 1000 ms, followed by the presentation of a male or female face for 3000 ms. Each face was subsequently rated on a six-point scale according to attractiveness, approachability, and trustworthiness, respectively, in response to 8 itemized judgments presented in randomized order below the face. Ratings were performed at self-paced speed. In the emotional part of the task that started around 1740 h, happy and angry versions of the neutral faces presented beforehand were rated. (See text for further details.) Throughout the session, mood was rated and the experiment ended at 1800 h with another assessment of mood and further control parameters.

compartment within 10–40 min (Born et al., 2002) and 24 IU oxytocin are known from previous studies to reliably elicit psychosocial effects (Heinrichs et al., 2003; Domes et al., 2007; Theodoridou et al., 2009). Forty minutes after substance administration and after a second round of mood ratings, subjects completed the PC-based face rating task and again rated their mood. The session ended with another assessment of the control parameters and the question which treatment the participants thought to have received.

2.3. Face rating task

The PC-based face-rating task comprised 20 faces (of 10 men and 10 women) with their gaze directed at the viewer, showing either a neutral expression (first part of the task, 20 facial stimuli) or happy and angry expressions (second part, 40 facial stimuli). All photographs were taken from the validated 'Radboud Faces Database' set (Langner et al., 2010) and had a resolution of 506 × 650 pixels. During presentation of each face, participants were asked to indicate their agreement or disagreement with 8 itemized judgments on a scale ranging from 1 (I completely disagree) to 6 (I completely agree). The 8 items belonged to 3 categories, i.e., attractiveness (He/she is sexy-looking; this person looks very attractive to me; I think he/she is good-looking; McCroskey and McCain, 1974), approachability (I would like to get to know him/her better), and trustworthiness (I think you can talk about everything with him/her; I think he/she is honest and genuine to others; I think you can build on him/her; I think he/she can keep a secret; Kassebaum, 2004). Items were presented successively below the target face in randomized order. Ratings were made using keyboard number keys in a self-paced fashion with the target face being displayed until the final response was made. The stimulus sequence in each part of the task was pseudo-randomized, i.e. both sex and affect were not repeated more than three times in a row. Parallel versions of the task were used for the two conditions in a counterbalanced order.

2.4. Measurement of mood, anxiety, vigilance and memory function

Self-reported mood was assessed on 5-point scales covering the categories good/bad mood, alertness/sleepiness and calmness/agitation (MDBF; Steyer et al., 1997) and on a checklist containing 123 adjectives assessing mood on 14 dimensions (EWL-K; Janke and Debus, 1978). In addition, subjects rated their current feelings of happiness, stress, anxiety, tiredness and concentration on visual analog scales (VAS) spanning 10 cm and anchored at "not at all" and "extreme." Self-perceived anxiety was also assessed with the 'state' section of the State-Trait-Anxiety Inventory (STAI-X1) containing 20 items (Laux et al., 1981). For the examination of vigilance, subjects repeatedly performed a simple 5-min PC-based task (Diekelmann et al., 2011). In this 5-min task, a red dot appeared at random intervals either on the left or the right side of the screen, and subjects were required to press the respective key as fast as possible, receiving immediate feedback in the form of the reaction time for correct responses or an error message. Mean reaction time was registered and adjusted for mistakes by adding the square root of the product of the mean reaction time and the number of mistakes. Short-term memory retention was assessed by means of the digit span task of the intelligence inventory HAWIE-R (Tewes, 1991). In this task, spoken lists of digits with a length of two up to 9 digits are to be immediately repeated by the subject in a forward (first block) or backward manner (second block).

2.5. Statistical analysis

Analyses relied on analyses of variance (ANOVA) for repeated measures with the between-subjects factor 'sexual orientation' and the within-subjects factors 'treatment' (oxytocin/placebo), 'judgment' (approachability/attractiveness/trustworthiness), 'sex of the facial stimulus' (male/female), 'affect of the facial stimulus' (happy/angry), and 'time' (for the control parameters) as appropriate. Significant interaction effects were specified by pairwise t tests. Supportive analyses of covariance (ANCOVA) included the covariates 'serum testosterone levels' and 'Global Severity Index scores of the Symptom Checklist-90-Revision' (SCL-90-R GSI; Franke, 1995; see Table 1) obtained at enrollment, corrected by the number of days between enrollment and the first experimental session. Data are presented as means ± SEM. A p-value <0.05 was considered significant.

3. Results

3.1. Face rating task — neutral faces

Overall statistical analyses revealed that oxytocin administration increased ratings for neutral faces exclusively in homosexual subjects ($F_{(1,35)} = 4.05$, $p = 0.05$ for sexual orientation × treatment), whereas across groups the effect of oxytocin treatment was not significant ($F_{(1,35)} = 1.41$, $p = 0.24$). Homosexual participants rated in particular male faces as more approachable ($t_{(18)} = 2.21$, $p = 0.04$) and attractive ($t_{(18)} = 2.08$, $p = 0.05$; $F_{(1,18)} = 5.27$, $p = 0.03$ for $\text{treatment}_{\text{homosexual}}$; Fig. 2A) after oxytocin administration, while the appraisal of neutral female faces appeared to be less affected (Fig. 2B; $t_{(18)} = 1.78$, $p = 0.09$ for approachability), although the sex of the presented faces did not significantly modulate the results ($F_{(1,18)} = 0.48$, $p = 0.50$ for $\text{treatment}_{\text{homosexual}} \times$ sex). Ratings of trustworthiness were not affected by oxytocin administration in the homosexual group (all $p > 0.40$; Table 2). In contrast to the pattern observed in the homosexual subjects, in the heterosexual subjects oxytocin treatment did not affect ratings of male and female neutral faces in any of the three categories (all $p > 0.26$; Fig. 2A/B and Table 2).

Independent of oxytocin treatment, ratings for neutral faces depended on the sexual orientation of the participants and the sex of the facial stimuli ($F_{(1,35)} = 6.86$, $p = 0.01$ for respective interaction), with heterosexual participants giving higher ratings for female than male faces ($F_{(1,17)} = 32.24$, $p < 0.001$ for $\text{sex}_{\text{heterosexual}}$). In the homosexual group, the sex of the facial stimuli was not relevant ($F_{(1,18)} = 1.42$, $p = 0.25$ for $\text{sex}_{\text{homosexual}}$).

3.2. Face rating task — emotional faces

In accordance with the pattern found for neutral faces, oxytocin effects on the appraisal of emotional faces again centered on the homosexual subjects ($F_{(1,35)} = 6.22$, $p = 0.017$ for sexual orientation × treatment; $F_{(1,35)} = 3.62$, $p = 0.066$ for treatment across groups), and were most pronounced for the approachability and attractiveness rating scales ($F_{(1,35)} = 4.24$, $p = 0.03$ for treatment × judgment). In the homosexual group, oxytocin administration increased ratings of attractiveness (all $p < 0.03$) and approachability ($p < 0.04$) for male faces independent of the affective valence (Fig. 2C and E), and moreover elevated ratings of approachability for happy female faces ($t_{(18)} = 3.03$, $p = 0.007$; $F_{(1,18)} = 8.68$, $p = 0.009$ for $\text{treatment}_{\text{homosexual}}$; $F_{(1,18)} = 0.57$, $p = 0.46$ for $\text{treatment}_{\text{homosexual}} \times$ affect; $F_{(1,18)} = 0.12$, $p = 0.73$ for $\text{treatment}_{\text{homosexual}} \times$ sex; Fig. 2D), without affecting ratings of trustworthiness (all $p > 0.09$; Table 2).

In contrast to homosexual subjects, heterosexual participants generally showed no effects of oxytocin administration ($p > 0.21$; Fig. 2C–F) with the exception of an oxytocin-induced decrease in ratings of trustworthiness for angry female faces ($t_{(17)} = -2.70$, $p = 0.015$; $F_{(1,17)} = 3.30$, $p = 0.087$, for $\text{treatment}_{\text{heterosexual}} \times$ sex × affect; Table 2). Exploratory analyses revealed that this effect was predominantly found in the singles of this group ($t_{(6)} = -2.95$, $p = 0.03$; $F_{(1,17)} = 7.71$, $p = 0.015$, for $\text{treatment}_{\text{heterosexual}} \times$ relationship status), whereas in the homosexual group, oxytocin effects generally did not differ between singles and subjects in a relationship ($F_{(1,18)} = 1.27$, $p = 0.28$; $F_{(1,35)} = 6.18$, $p = 0.019$ for treatment × sexual orientation × relationship status).

Across groups and experimental conditions, i.e., independent of oxytocin administration, happy faces generally received higher ratings than angry faces ($F_{(1,35)} = 67.73$, $p < 0.001$ for affect). Also, emotional female faces were generally rated higher than emotional male faces ($F_{(1,35)} = 31.83$, $p < 0.001$ for sex), with this pattern, as observed for neutral faces, particularly pronounced in heterosexual men ($F_{(1,17)} = 54.60$, $p < 0.001$ for $\text{sex}_{\text{heterosexual}}$; $F_{(1,35)} = 10.89$, $p = 0.002$ for sexual orientation × sex) and focusing on

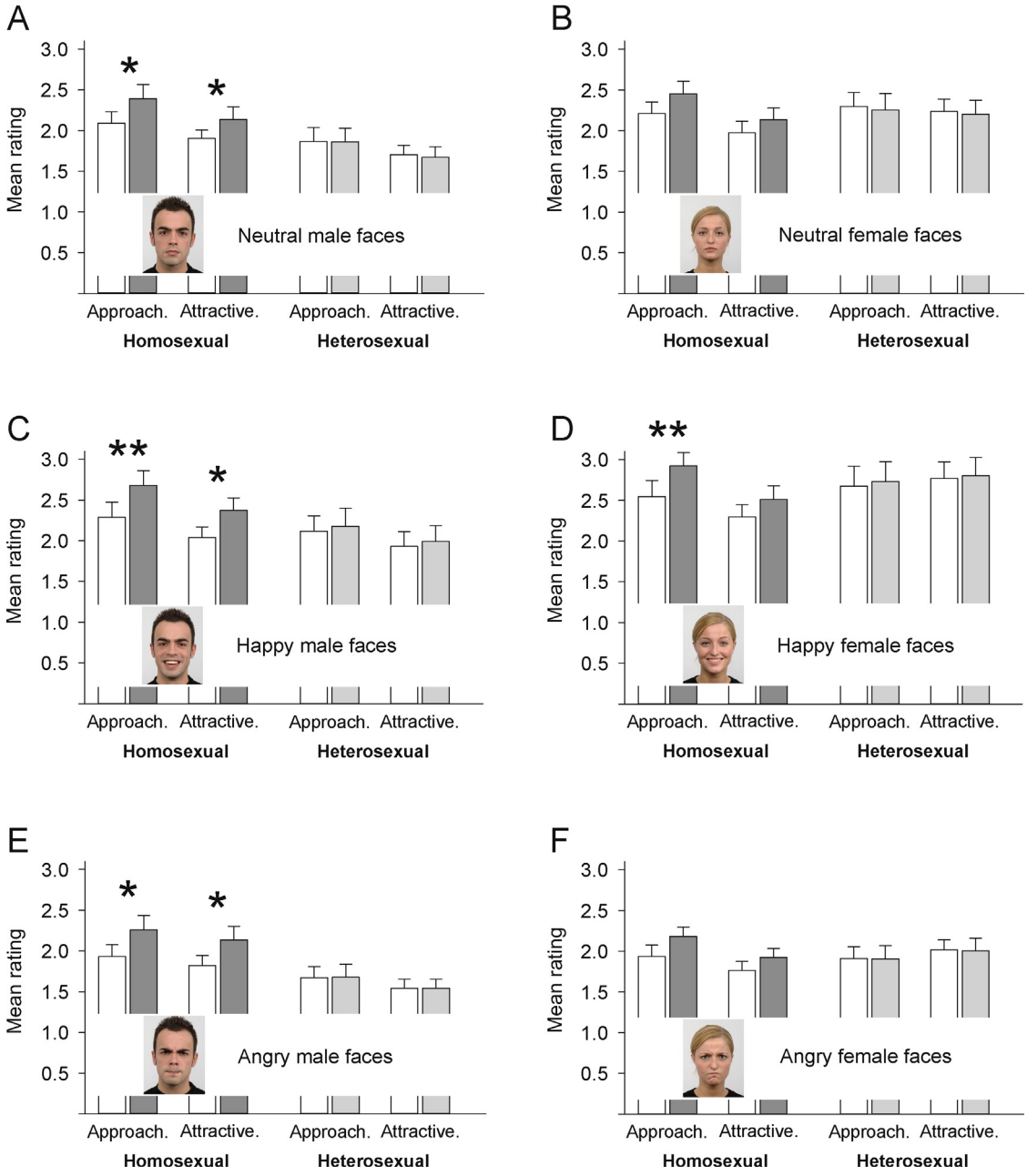

Figure 2 Mean (±SEM) ratings of approachability (Approach.) and attractiveness (Attractive.) for (A/B) neutral, (C/D) happy, and (E/F) angry male and female faces, given by homosexual ($n = 19$) and heterosexual men ($n = 18$) after intranasal administration of oxytocin (24 IU; gray bars) and placebo (vehicle; white bars), respectively. Ratings of approachability refer to one and ratings of attractiveness to three itemized judgments regarding the presented face (see text) anchored at 1 (I completely disagree) and 6 (I completely agree). *$p < 0.05$ and **$p < 0.01$ for comparisons between conditions (t-tests).

ratings of approachability and attractiveness ($F_{(1,17)} = 10.69$, $p = 0.001$), whereas the effect of the faces' sex was not significant in homosexual men ($F_{(1,18)} = 2.22$, $p = 0.15$). In both groups, ratings of approachability and attractiveness were highly correlated in both experimental conditions and regardless of the affective valence of the presented faces, reaching values between $r = 0.52$, $p = 0.001$ and $r = 0.84$, $p < 0.001$. The differential effects of oxytocin treatment in homo- vs. heterosexual subjects on ratings of approachability and attractiveness for neutral as well as emotional male and female faces are summarized in Fig. 3.

3.3. Independence of oxytocin's differential impact from group characteristics unrelated to sexual orientation

In ANCOVA models including the covariate 'testosterone', the observed pattern of oxytocin effects on the appraisal of neutral and emotional faces remained significant (neutral faces, $F_{(1,35)} = 4.14$, $p = 0.05$ for treatment × sexual orientation; emotional faces, $F_{(1,35)} = 7.51$, $p = 0.01$). The same held true for the inclusion of the SLC-90-R GSI score reflecting the severity of reported psychological strain ($F_{(1,35)} = 4.30$,

Table 2 Mean (±SEM) ratings of trustworthiness for facial stimuli given by homosexual (n = 19) and heterosexual men (n = 18) after intranasal administration of oxytocin (24 IU; oxytocin) and placebo (vehicle).

Stimulus	Group	Placebo	Oxytocin	p value
Neutral male faces	Homosexual	3.44 ± 0.15	3.54 ± 0.11	0.40
	Heterosexual	3.34 ± 0.13	3.21 ± 0.14	0.26
Neutral female faces	Homosexual	3.63 ± 0.14	3.68 ± 0.12	0.64
	Heterosexual	3.46 ± 0.13	3.43 ± 0.15	0.85
Happy male faces	Homosexual	3.81 ± 0.14	3.87 ± 0.11	0.62
	Heterosexual	3.68 ± 0.11	3.52 ± 0.15	0.21
Happy female faces	Homosexual	3.98 ± 0.16	4.19 ± 0.11	0.09
	Heterosexual	3.88 ± 0.12	3.85 ± 0.13	0.75
Angry male faces	Homosexual	3.07 ± 0.16	3.16 ± 0.17	0.48
	Heterosexual	2.90 ± 0.18	2.79 ± 0.15	0.32
Angry female faces	Homosexual	3.19 ± 0.17	3.31 ± 0.17	0.42
	Heterosexual	3.12 ± 0.15	2.84 ± 0.15	0.015

p = 0.046, and $F_{(1,35)}$ = 7.63, p = 0.009 for neutral and emotional faces, respectively). Also, analyses of oxytocin's effect on face processing that included the 4-level between-subjects factor 'recruitment' (mailing list, word-of-mouth, job websites, and gay media) ruled out a significant biasing effect of the individual recruitment strategy ($F_{(3,35)}$ = 1.94, $p > 0.15$ for recruitment; $F_{(3,35)}$ = 0.30, p = 0.82 for recruitment × treatment), while the differential treatment effect was still evident ($F_{(1,35)}$ = 6.06, p = 0.02 for sexual orientation × treatment).

3.4. Mood, anxiety, vigilance, memory, and treatment awareness

According to their VAS scores (Fig. 4), homo- and heterosexual subjects did not differ at baseline regarding happiness (all $p > 0.54$), stress ($p > 0.96$), and anxiety ($p > 0.52$; $p > 0.10$ for respective comparisons between conditions).

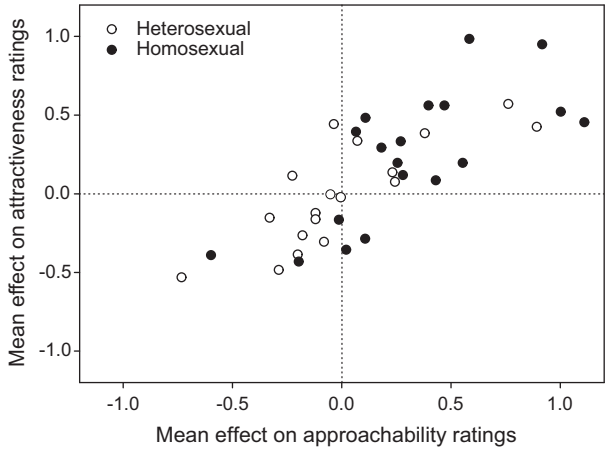

Figure 3 Averaged effects of oxytocin administration (expressed as differences between the oxytocin and the placebo condition) on ratings of attractiveness and approachability for neutral as well as emotional male and female faces in the individual heterosexual (white dots) and homosexual participants (black dots). Positive values indicate increased and negative values decreased rating scores, respectively.

Oxytocin administration had no effect on these measures (all $p > 0.44$ for treatment × time), and there were no group-specific changes in these parameters over time (all $p > 0.34$ for group × time). VAS scores of concentration and tiredness neither indicated differences between groups and treatment conditions (all $p > 0.13$). In accordance with the VAS, the MDBF and the EWL-K mood inventories indicated comparable values between groups during baseline (all $p > 0.46$ and $p > 0.09$, respectively) and post-treatment ($p > 0.22$ and $p > 0.50$) and no signs of oxytocin effects ($p > 0.54$ and $p > 0.86$, respectively). The 'state' scale of the STAI questionnaire corroborated the results of the anxiety VAS, indicating no differences between groups throughout the experiment ($p > 0.77$) and no effects of oxytocin administration ($p > 0.52$). Reaction times in the vigilance task ($p > 0.66$) and working memory performance ($p > 0.36$) were likewise unaffected by oxytocin treatment. Merely 13 of the 37 participants (35%) correctly guessed their respective treatment conditions ($\chi^2_{(2;N=37)}$ = 0.51, p = 0.89), indicating that the participants gained no treatment awareness.

4. Discussion

We investigated the effect of oxytocin administration on social perception in homo- and heterosexual men, assuming that sexual orientation modulates oxytocin's impact on approach tendencies toward facial stimuli, i.e., that the hormone increases the social appeal of male faces to a greater extent in homo- than heterosexual participants, and vice versa. This hypothesis was confirmed in part, with oxytocin increasing ratings of attractiveness and approachability for male, but to a lesser extent also for female faces, in the homosexual participants. In contrast, no effect of oxytocin treatment on approach tendencies was observed in heterosexual subjects. Contrary to expectations, ratings of trustworthiness that were expected to be generally improved by oxytocin administration were decreased after oxytocin treatment with regard to angry female faces in heterosexual subjects, but otherwise remained unaffected. These results indicate a generally greater sensitivity to the effect of oxytocin in homosexual than heterosexual men. They add to the ongoing discussion on oxytocin's role in dyadic social interactions.

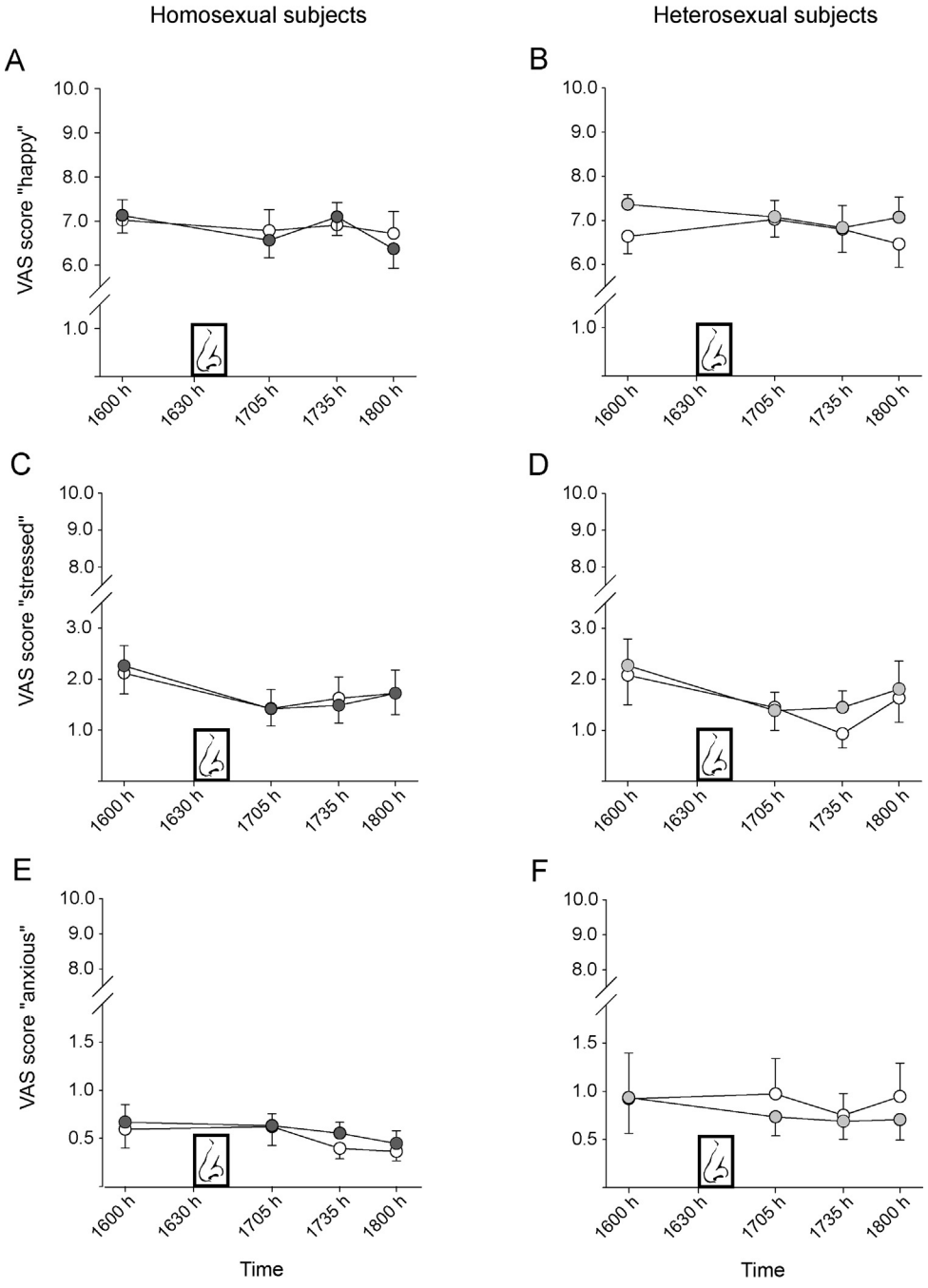

Figure 4 Visual analog scale scores on the dimensions "happy" (A/B), "stressed" (C/D), and "anxious" (E/F) obtained in homosexual (n = 19; left column) and heterosexual men (n = 18; right column) before and after intranasal administration of oxytocin (24 IU; gray dots) and placebo (vehicle; white dots) at 1630 h (nose symbol), respectively. Scales spanned 10 cm and were anchored at "not at all" (0) and "extremely" (10). Values are means ± SEM.

Our finding that oxytocin treatment did not increase ratings of trustworthiness at first glance is at odds with previous observations of an improving oxytocin effect on trustful behavior (Kosfeld et al., 2005), that, however, emerged in trust games involving monetary stakes and played in groups of participants without direct face-to-face interaction. To our knowledge, enhancing effects of oxytocin administration on ratings of trustworthiness for male and female facial stimuli as assessed in our set-up were only obtained in one further study in men and women, whose sexual orientation was not reported (Theodoridou et al., 2009). Our results do not support this finding, neither in male heterosexual nor homosexual raters. Rather, oxytocin treatment decreased rated trustworthiness of angry female faces in heterosexual men. According to laboratory experiments in heterosexual couples, plasma oxytocin concentrations are related to positive communication, affiliation, and emotional support between partners (Grewen et al., 2005). Also, oxytocin appears to generally increase positive behavior during a couple conflict (e.g., eye contact and

self-disclosure) in both men and women (Ditzen et al., 2009) and furthermore increases salivary alpha-amylase as a marker of sympathetic activity as well as emotional arousal in men (Ditzen et al., 2012). Thus, rather than indiscriminately enhancing trustworthiness, oxytocin's influence here is essentially dependent on the context. Noteworthy, the effects of oxytocin administration on couple interactions were observed in long-standing monogamous couples, and recent research indicates that the effects of the hormone in men might depend on their relationship status: oxytocin administration to heterosexual pair-bonded but not single male subjects increased their respective tendency to avoid physical closeness to female strangers (Scheele et al., 2012), suggesting that the hormone contributes to the maintenance of established relationships by promoting fidelity. In the present study, exploratory analyses indicated that after oxytocin administration, single rather than pair-bonded heterosexual males perceived angry (but not neutral or happy) female faces as less trustworthy. This pattern suggests that oxytocin might strengthen withdrawal tendencies particularly in single males confronted with unknown females expressing negative emotions because the avoidance of aversive social signals has greater relevance in potentially relationship-seeking than in pair-bonded men.

In line with our initial assumption, hetero- and homosexual subjects generally exhibited a differential response pattern, with heterosexual subjects giving higher ratings for female than male faces, whereas homosexual subjects rated faces of both sexes in a comparable fashion. The former finding is in accordance with neuroimaging studies indicating that reward-processing brain structures are more responsive to female than male faces in hetero- as compared to homosexual men (Kranz and Ishai, 2006). In marked contrast to our findings in heterosexual subjects, in homosexual participants oxytocin administration enhanced approach tendencies toward facial stimuli independent of their affective expression. This increase in social approach tendencies was most prominent for male faces, although happy female faces likewise received significantly higher ratings of approachability in the oxytocin condition, which suggests that sexual aspects did not strongly affect oxytocin's improving impact on social approach tendencies in homosexual men. This conclusion is further supported by the strong correlation between ratings of attractiveness and approachability, indicating that both rating scales jointly assessed the social rather than sexual appeal of the presented faces. Also, in the homosexual subjects, no differential treatment effects were found for pair-bonded and single men. In accordance with previous findings (e.g., Kosfeld et al., 2005; Petrovic et al., 2008; Theodoridou et al., 2009), mood and cognitive function were not modulated by oxytocin treatment, indicating that the hormone specifically acted on the processing of social stimuli.

The observed difference in oxytocin sensitivity between homo- and heterosexual men is a new finding that extends the literature on endocrine factors in sexual orientation (Balthazart, 2011). While animal studies suggest that the intrauterine sex steroid milieu contributes to later-life partner preference (Phoenix et al., 1959; Bakker et al., 1993), evidence for a sexual orientation-dependent regulation of the oxytocin system has not yet been found in animals or humans. Neuroimaging experiments have indicated increased responses to supposed human pheromones in the medial preoptic area of the hypothalamus of homo- in comparison to heterosexual men (Savic et al., 2005; Balthazart, 2011), a brain region expressing moderate to high densities of oxytocin receptors (Gimpl and Fahrenholz, 2001). In related studies, homosexual men (and heterosexual women) showed more widespread connections from the left amygdala than heterosexual men (and homosexual women), who displayed greater connectivity from the right amygdala (Savic and Lindström, 2008; Savic et al., 2010). Considering that oxytocin administration has been observed to modulate amygdala responses to facial stimuli in a sex-dependent manner (Domes et al., 2007,2010), it might be speculated that differential oxytocin action on these brain structures mediates a more pronounced behavioral effect of the hormone in homosexual men, with increased social approach due to dampened amygdala-driven social avoidance.

In accordance with some studies (Brodie et al., 1974; Neave et al., 1999) but contrasting with others (Loraine et al., 1971; Savic et al., 2005), homo- in comparison to heterosexual subjects displayed increased serum testosterone concentrations at enrollment. While interactions between testosterone and oxytocin in the regulation of social bonds are likely (van Anders et al., 2011), it is assumed that androgen effects on social recognition are conveyed via vasopressin rather than oxytocin signaling (Bluthe et al., 1990; for review see Gabor et al., 2012). Furthermore, our statistical control analyses do not support the notion that the effect of oxytocin treatment was modulated by factors such as testosterone and current psychiatric symptoms. The latter as well as self-reported mood, subjective well-being and perceived stress did not differ between experimental groups. Nevertheless, we cannot completely rule out that potential neurobiological group differences arising from earlier psychosocial experiences contributed to the differential response to oxytocin, especially when considering that 50% of gay men in Germany still report discrimination and victimization (European Union Agency for Fundamental Rights (FRA), 2013). From an evolutionary point of view, homosexual behavior has been suggested to contribute to survival by reinforcing same-sex alliances and thereby favoring reciprocal altruism and resource exchange (Kirkpatrick et al., 2000). Enhanced sensitivity to oxytocin in homosexual individuals as observed here might be one neuroendocrine mechanism underlying such a behavioral strategy.

In sum, our finding that homo- in comparison to heterosexual men are more sensitive to the beneficial impact of oxytocin administration on self-rated approach tendencies toward facial stimuli indicates that sexual orientation is a critical modulator of oxytocin's regulatory role in social interactions. The conclusion that sexual orientation might imply specific differences in oxytocinergic signaling pathways should be further explored and also remains to be tested in women.

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Conflicts of interest statement

The authors declare that they have no conflicts of interest.

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References

Bakker, J., Brand, T., van Ophemert, J., Slob, A.K., 1993. Hormonal regulation of adult partner preference behavior in neonatally ATD-treated male rats. Behav. Neurosci. 107, 480—487.

Balthazart, J., 2011. Minireview: hormones and human sexual orientation. Endocrinology 152, 2937—2947.

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. 15, 301—309.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., Fehr, E., 2008. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 58, 639—650.

Bluthe, R.M., Schoenen, J., Dantzer, R., 1990. Androgen-dependent vasopressinergic neurons are involved in social recognition in rats. Brain Res. 519, 150—157.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5, 514—516.

Brodie, H.K., Gartrell, N., Doering, C., Rhue, T., 1974. Plasma testosterone levels in heterosexual and homosexual men. Am. J. Psychiatry 131, 82—83.

Carter, C.S., 1998. Neuroendocrine perspectives on social attachment and love. Psychoneuroendocrinology 23, 779—818.

Diekelmann, S., Büchel, C., Born, J., Rasch, B., 2011. Labile or stable: opposing consequences for memory when reactivated during waking and sleep. Nat. Neurosci. 14, 381—386.

Ditzen, B., Nater, U.M., Schaer, M., La Marca, R., Bodenmann, G., Ehlert, U., Heinrichs, M., 2012. Sex-specific effects of intranasal oxytocin on autonomic nervous system and emotional responses to couple conflict. Soc. Cogn. Affect. Neurosci., http://dx.doi.org/10.1093/scan/nss083.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatry 65, 728—731.

Domes, G., Heinrichs, M., Glascher, J., Büchel, C., Braus, D.F., Herpertz, S.C., 2007. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol. Psychiatry 62, 1187—1190.

Domes, G., Lischke, A., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., Herpertz, S.C., 2010. Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology 35, 83—93.

Domes, G., Sibold, M., Schulze, L., Lischke, A., Herpertz, S.C., Heinrichs, M., 2012. Intranasal oxytocin increases covert attention to positive social cues. Psychol. Med. 1—7.

European Union Agency for Fundamental Rights (FRA), 2013. EU LGBT survey — European Union lesbian, gay, bisexual and transgender survey. Results at a glance. Publications Office of the European Union, Luxembourg.

Feldman, R., Weller, A., Zagoory-Sharon, O., Levine, A., 2007. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. Psychol. Sci. 18, 965—970.

Franke, G.H., 1995. SCL-90-R. Die Symptom-Checkliste von Derogatis — Deutsche Version. Beltz Test, Göttingen.

Gabor, C.S., Phan, A., Clipperton-Allen, A.E., Kavaliers, M., Choleris, E., 2012. Interplay of oxytocin, vasopressin, and sex hormones in the regulation of social recognition. Behav. Neurosci. 126, 97—109.

Gamer, M., Zurowski, B., Buchel, C., 2010. Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. Proc. Natl. Acad. Sci. U.S.A. 107, 9400—9405.

Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. 81, 629—683.

Grewen, K.M., Girdler, S.S., Amico, J., Light, K.C., 2005. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom. Med. 67, 531—538.

Guastella, A.J., Carson, D.S., Dadds, M.R., Mitchell, P.B., Cox, R.E., 2009. Does oxytocin influence the early detection of angry and happy faces? Psychoneuroendocrinology 34, 220—225.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54, 1389—1398.

Heinrichs, M., von Dawans, B., Domes, G., 2009. Oxytocin, vasopressin, and human social behavior. Front. Neuroendocrinol. 30, 548—557.

Janke, W., Debus, G., 1978. Die Eigenschaftswörterliste (EWL). Hogrefe, Göttingen.

Kassebaum, U., 2004. Interpersonelles Vertrauen. Entwicklung eines Inventars zur Erfassung spezifischer Aspekte des Konstrukts. (doctoral dissertation)University of Hamburg, Hamburg.

Kirkpatrick, R.C., Plato, Lévi-Strauss, C., 2000. The evolution of human homosexual behavior. Curr. Anthropol. 41, 385—413.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V.S., Gallhofer, B., Meyer-Lindenberg, A., 2005. Oxytocin modulates neural circuitry for social cognition and fear in humans. J. Neurosci. 25, 11489—11493.

Klein, F., Sepekoff, B., Wolf, T.J., 1985. Sexual orientation: a multivariable dynamic process. J. Homosex. 11, 35—49.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435, 673—676.

Kranz, F., Ishai, A., 2006. Face perception is modulated by sexual preference. Curr. Biol. 16, 63—68.

Langner, O., Dotsch, R., Bijlstra, G., Wigboldus, D.H.J., Hawk, S.T., van Knippenberg, A., 2010. Presentation and validation of the Radboud Faces Database. Cogn. Emot. 24, 1377—1388.

Laux, L., Glanzmann, P., Schaffner, P., Spielberger, C., 1981. Das State-Trait-Angstinventar. Theoretische Grundlagen und Handanweisung. Beltz Test GmbH, Weinheim.

Loraine, J.A., Adamopoulos, D.A., Kirkham, K.E., Ismail, A.A., Dove, G.A., 1971. Patterns of hormone excretion in male and female homosexuals. Nature 234, 552—555.

Ludwig, M., Leng, G., 2006. Dendritic peptide release and peptide-dependent behaviours. Nat. Rev. Neurosci. 7, 126—136.

McCroskey, J., McCain, T., 1974. The measurement of interpersonal attraction. Speech Monogr. 41, 261—266.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci. 12, 524—538.

Neave, N., Menaged, M., Weightman, D.R., 1999. Sex differences in cognition: the role of testosterone and sexual orientation. Brain Cogn. 41, 245—262.

Panksepp, J., 2009. Primary process affects and brain oxytocin. Biol. Psychiatry 65, 725—727.

Petrovic, P., Kalisch, R., Singer, T., Dolan, R.J., 2008. Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. J. Neurosci. 28, 6607—6615.

Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C., 1959. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65, 369—382.

Savic, I., Berglund, H., Lindström, P., 2005. Brain response to putative pheromones in homosexual men. Proc. Natl. Acad. Sci. U. S. A. 102, 7356—7361.

Savic, I., Garcia-Falgueras, A., Swaab, D.F., 2010. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. Prog. Brain Res. 186, 41—62.

Savic, I., Lindström, P., 2008. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. Proc. Natl. Acad. Sci. U.S.A. 105, 9403—9408.

Scheele, D., Striepens, N., Güntürkün, O., Deutschländer, S., Maier, W., Kendrick, K.M., Hurlemann, R., 2012. Oxytocin modulates social distance between males and females. J. Neurosci. 32, 16074—16079.

Steyer, R., Schwenkmezger, P., Notz, P., Eid, M., 1997. Der mehrdimensionale Befindlichkeitsfragebogen (MDBF). Handanweisung. Hogrefe, Göttingen.

Taylor, S.E., Saphire-Bernstein, S., Seeman, T.E., 2010. Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships? Psychol. Sci. 21, 3—7.

Tewes, U., 1991. Hamburg-Wechsler-Intelligenztest für Erwachsene — Revision 1991 (HAWIE-R)Huber, Bern, Stuttgart, Toronto.

Theodoridou, A., Rowe, A.C., Penton-Voak, I.S., Rogers, P.J., 2009. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm. Behav. 56, 128—132.

van Anders, S.M., Goldey, K.L., Kuo, P.X., 2011. The Steroid/Peptide Theory of Social Bonds: integrating testosterone and peptide responses for classifying social behavioral contexts. Psychoneuroendocrinology 36, 1265—1275.