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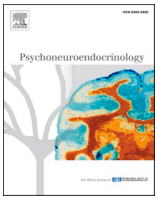

Oxytocin has sex-specific effects on trust and underlying neurophysiological processes

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ABSTRACT

The neuropeptide oxytocin (OT) regulates mammalian social approach behavior across sexes. Yet most OT studies in humans exclusively investigated men. Here, we studied sex differences in OT's effects on human trust behavior in 144 heterosexual participants (73 women, 71 men). Participants received 24 international units of intranasal OT or placebo treatment and played a trust game in the role of the investor while undergoing electroencephalography. Trustees were represented by photos of the other sex gradually varying in their pre-rated intensities of facial features signaling attractiveness and threat. On a behavioral level, we observed that OT increased trust in men and reduced it in women when trustees showed weak signals of attractiveness and threat. Correspondingly, on the neurophysiological level, we noted that OT intensified the P100 in male participants, but dampened it in female ones. Our findings demonstrate OT's sex- and context-specific effects on social approach behavior and an underlying early visual attention-related brain process. This evidence demonstrates the need to consider psychobiological mechanisms of sexual dimorphism in human OT research.

1. Introduction

In order to approach suitable conspecifics for establishing functional social affiliations, humans have evolved neuroendocrinological communication systems that orchestrate a set of brain systems (Carter, 2022; Jurek and Neumann, 2018). Specifically, the neuropeptide oxytocin (OT) has been identified as a facilitator of social approach in studies using placebo-controlled intranasal administration to manipulate its availability in the central nervous system (Bartz et al., 2011; Meyer-Lindenberg et al., 2011). However, research in humans using this method has mostly focused on male participants, although species- and brain region-specific sex differences in the OT system have been known from animal research (e.g., Caldwell, 2018). Through the present research we aimed to unravel unknown sex-specific, downstream consequences of OT on social approach behavior in humans. For that purpose, we recruited one of the largest mixed-sex samples within the field of human OT research (n = 169) while controlling for female participants' menstrual cycle by assessing them during their luteal phase (to ensure comparability with the literature, such as Lieberz et al., 2020). Social approach behavior was operationalized by means of resource-sharing decisions in a trust game (Berg et al., 1995; Lieberz et al., 2021). Moreover, by recording participants' electrophysiological

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brain activity, we aimed to illuminate the temporal dynamics of neurophysiological processes underlying OT's sex-specific effects. Indeed, functional magnetic resonance imaging (fMRI) studies have suggested that OT affects approach-related neural processing in several domains in a sex-dependent manner. Regarding the processing of threatening information, experimentally increasing central OT availability by means of intranasal administration (Spengler et al., 2017) is known to reduce activity in a brain network encompassing the amygdala, fusiform gyrus, and anterior cingulate cortex in men, while an increase of this network's activity has been found in women (Tully et al., 2018). Interestingly, similar sex-specific effects have been reported in studies using intracerebroventricular OT application in rats (Dumais et al., 2017; Lukas and Neumann, 2014). Sex differences in OT effects on neural processing, albeit in a less clear direction, have also been documented regarding the processing of rewarding information in a brain network encompassing the striatum and ventral tegmental area (VTA; Borland et al., 2019). OT seems to increase this network's activation in response to positive social interactions in men, but decrease its activation in women (e.g., Scheele et al., 2013). However, these findings do not generalize to pleasant facial expressions and to being touched by the romantic partner (e.g., Lieberz et al., 2020). Findings from research on rodents involving direct OT injections, OT receptor agonists, and OT receptor antagonists into the VTA, however, again support the assumption that OT strengthens behavior associated with socially rewarding experiences in males, but weakens such behavior in females (Borland et al., 2019). In sum, evidence from both animal and human research suggests that OT increases reward and decreases threat processing in males, but does the opposite in females. However, few of these studies have compared OT's sex-specific effects during the same study and investigated whether sex-specific neural signatures of social stimulus evaluation also impact on actual behavior.

While there is important information on OT's sex-specific effects on neural processing in the spatial domain, its effects on neural processing in the temporal domain are poorly illuminated. The high temporal resolution of electroencephalography (EEG) could provide a window into rapidly unfolding neurophysiological processes (e.g., Schiller et al., 2020a). Thereby, one could infer the dynamics of neuropsychological processes underlying sex differences in OT's social actions. For example, a recent review of the few studies combining OT administration with event-related potential (ERP) analyses showed that OT modulates neurophysiological processes associated with the dynamics of (social) perception and cognition that indicate the sequence of different processing stages (attention, selection, evaluation; Pehlivanoglu et al., 2020). These modulations were observed across time periods approximately ranging from 100 to 500 ms. By analyzing OT's effects on the temporal dynamics of neurophysiological processing associated with social approach behavior, one could thus understand whether the neuropeptide's sex-specific effects are driven by early or late occurring processes, and link them to differential neuropsychological processing.

In the present study, we investigated potential sex differences in OT's effects on actual social approach behavior. This behavior was measured by resource-sharing decisions in a trust game performed while participants' neurophysiological brain activity was being recorded via EEG. On the basis of OT's cross-species role in reproductive behavior (Burri et al., 2008), we aimed to study behavior within an evolutionarily relevant mating context. For that purpose, we created a "socially enriched" version of the trust game in which participants interacted with individuals of the other sex represented by photos. Given OT's sex-specific effects on neural activity in the approach- and avoidance-related domains of reward and threat processing, we used a previously validated set of facial stimuli (Brustkern et al., 2021) that was developed a priori to show either low- or high-intensity facial features signaling attractiveness and threat, respectively (i.e., resulting in four facial phenotypes: unattractive- & threatening-looking; attractive- & unthreatening-looking; unattractive- & unthreatening-looking; attractive- & threatening-looking; see Methods). On the basis of previous evidence demonstrating that OT increases reward and decreases threat processing in males, but does the opposite in females (Borland et al., 2019; Dumais et al., 2017; Lukas and Neumann, 2014; Scheele et al., 2013; Tully et al., 2018), we hypothesized that OT would increase trust in men, but decrease it in women. Regarding neurophysiological mechanisms, we expected that OT's sex-specific social effects would manifest in differences regarding early occurring attention-related processes, given that OT's effects even occur in response to very briefly presented social stimuli (Schulze et al., 2011) and are linked to changes in subcortical brain regions associated with rapid evaluations of the environment (Guex et al., 2020) that elicit approach or avoidance behavior of paramount importance for an individual's survival.

2. Methods

2.1. Sample

An a priori power analysis using an effect-size of Cohen's $d = 0.28$ from a study that re-analyzed data from three meta-analyses on intranasal OT effects in humans (Walum et al., 2016) yielded a required sample size of 156 participants (ANOVA: Repeated measures, within-between interactions, alpha = 0.05 and 1-beta = 0.95, G-Power© 3.1; Faul et al., 2009). To account for dropouts, we recruited 169 subjects (85 female, 84 male) between 18 and 35 ($M = 23.49$ years, $SD = 3.59$) years with romantic interest in the other sex (rated five or higher on a 7-point Likert scale from "not at all" [1] to "absolutely" [7]). Participants had to be healthy (no current or previous history of mental disorders and a total score below 14 in the Mini-Symptom-Checklist; Franke, 2017), single (i.e., not in a romantic relationship), right-handed, and have a body mass index between 17 and 30. Exclusion criteria were nicotine, cannabis, alcohol, or drug abuse, intake of medication that affects the central nervous system, studying psychology or economics, and insufficient fluency in the German language. Furthermore, nasal spray allergies or a current illness affecting the function of the nasal mucosa were exclusion criteria due to the intranasal OT administration. To control for hormonal fluctuations in the menstrual cycle (Lieberz et al., 2020) we also excluded women who were pregnant or using hormonal contraceptives.

We had to exclude 10 participants (seven females) because of technical issues during the experiment, and seven participants (one female) due to incomplete or deficient EEG data. We also excluded eight participants (four females) who were outliers in their reaction times. Three of these participants (one female) had reaction times of under 450 ms indicating random decision-making without considering the photos. Five of these participants (three females) had reactions times of around 3 s indicating that they had not complied with our instruction to decide spontaneously in under 3 s (see also 2.3). Our final sample entailed 144 participants (73 females).

2.2. Procedure

The experiment consisted of two appointments. The first group laboratory appointment took place with 4–11 participants simultaneously (90 min; note that the number of participants tested simultaneously did not differ between treatment groups: $p = .264$). Participants first provided written informed consent in line with the criteria of the Declaration of Helsinki, and the study was approved by the ethics committees of the University of Freiburg and University of Basel. To investigate whether participants' different traits might affect OT effects, we collected various questionnaires (see supplementary material). While participants answered these questionnaires, one of two research assistants asked them one by one into a separate room to have a portrait photograph taken. We told participants that the photos would be used in the trust game during the second appointment in order to make sure that participants believed that they were interacting with real participants. All participants wore a black T-Shirt, removed all accessories (e.g.,

jewelry, glasses) and were instructed to look into the camera with a neutral facial expression, in order to keep the images similar to those used from the Basel Face Database (Walker et al., 2018). After finishing the questionnaires, the head circumference of each participant was taken for the EEG-recording during the main experiment (second appointment). We arranged this experimental appointment for male participants at the end of the first appointment. Female participants were given ovulation test strips (AIDE OneStep urine test strips, sensitivity 20mIU/ml) to determine their menstrual cycle's luteal phase, during which the experiment took place (Lieberz et al., 2020). We asked participants to inform us immediately via e-mail when their test was positive, which indicated that ovulation would occur within the subsequent 24–36 h. To ensure that the experiment would not take place during the ovulatory phase or menstruation, we scheduled it between four and 11 days after the positive test. In addition, we asked participants to inform us and reschedule if they had already started menstruating before the scheduled appointment.

The experimental appointment was conducted with each participant individually in an EEG-laboratory (120 min). To minimize confounding other-sex influences in association with OT effects, both a female and male instructor led the experiment, with the interacting instructor being of the same sex as the participant. To ensure that female participants were not pregnant, they first conducted an early-detection pregnancy test (Clearblue®). Participants then self-administered 24 international units (IU) of OT or placebo intranasally (following standard procedures, for details, see supplementary material). Afterwards, we placed four electrodes around participants' eyes to measure their eye movement, and three electrodes on their upper body to measure participants' heart rate. Then, we seated participants 67 cm from a 73 cm x 54 cm screen on which the paradigms were projected in an electrically shielded room. We applied electrolyte gel between the 128 electrodes and scalp to achieve a good impedance level of less than 20 kΩ. Meanwhile, participants read the trust game's instructions including information on the payoff structure (for details, see 2.3) and filled out questions checking their comprehension of the task. Depending on how long the EEG took, participants started with the trust game while the EEG was being recorded from at least 40 min to at most 50 min after the spray administration, thereby guaranteeing that the tasks were conducted during the effective time window of OT ranging from 45 to 70 min (Spengler et al., 2017). Afterwards, two control tasks were conducted: Participants had to state anonymously how much of their compensation they wanted to donate to a charity organization of their choice (a list of eight organizations was presented), and how much money they wanted to invest in a lottery (participants could bet up to 5 Euros on an even or odd outcome when rolling a die; if the bet was correct, the amount was doubled, if the bet was incorrect, the amount was lost). Finally, participants received their compensation of 55 Euros (male participants) or 60 Euros (female participants; compensating for their greater efforts needed to determine their menstrual cycle's phase), plus 9.50–25 Euros depending on their decisions during the lottery and donation task, and depending on their and the other participants' decisions during the trust game ($M = 16.34$, $SD = 3.43$, range: 9.50–22.17; for details on the trust game's payoff structure, see Section 2.3).

2.3. Measuring trust

Participants played a dichotomized version of the trust game as investors, where they could either keep (= no trust) or transfer (= trust) their complete endowment to a trustee in each round. Other-sex trustees were represented by facial photos that varied on the dimensions of perceived attractiveness and perceived threat. These stimuli were created by using a data-driven computational approach which captures the variance in facial features that signal specific social attributions (Walker and Vetter, 2016). Briefly, "attractiveness" and "threat" vectors that were created based on previously collected (other-sex) ratings were applied to photos of neutral faces not displaying any emotional states (Todorov et al., 2013); these newly-generated stimuli were then rated again to ensure that the attractiveness and threat manipulations worked and that they were equivalent across sexes (Brustkern et al., 2021). Faces had features signaling either low or high intensities of attractiveness and threat, respectively (e.g., "high attractiveness & low threat"), resulting in four different phenotypes. After participants saw the photo of the trustee, they had to decide whether they wanted to keep their endowment (14 monetary units [MUs] for the participant and trustee, and the trial ended) or transfer it to the trustee. In the latter case the endowment was multiplied, and the trustee could either keep everything (60 MU for trustee) or transfer half of the amount back (30 MU for both participant and trustee). We used this payoff structure, as it led to a transfer rate of approximately 50% in a previous study without face stimuli and OT administration (von Dawans et al., 2012), hence preventing ceiling or bottom effects caused by OT or the attractiveness and threat manipulation of the facial stimuli. We told participants that the trustees on the photos had already made their decision; however, we had determined payments based on previously collected data (Baumgartner et al., 2008). Participants only learned about the proportion of back transfers at the end of the study in order to avoid sequence effects. 100 MUs were converted into 0.50 Euros at the end of the study.

Before the practice trials, we instructed participants about the buttons and showed a remark: "Please decide spontaneously whether you want to keep or transfer this amount. This usually happens in under 3 s. To get an impression of how long 3 s last, note this illustration." Then, a countdown of 3 s was presented. This remark was shown to stimulate more intuitive decision-making and to restrict reaction times as necessary for ERP analysis. After eight practice trials, participants were reminded of their decisions' real financial consequences for themselves, and the trustees, and could begin the actual experiment.

Participants interacted with 22 stimuli per phenotype, resulting in 88 trials in total (= 4 phenotypes x 22 stimuli), to ensure that a critical number of trials necessary for ERP analysis was reached. In each trial, participants first saw a blank screen presented with a jittered duration of 400–600 ms, followed by a fixation cross (jittered between 1000 and 1500 ms). Then, participants saw a picture of their interaction partner until they made their trust decision. Their decision was shown with a jittered duration of 1000–1250 ms, and the next trial started. We programmed the trust game using Presentation software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA). Fig. 1 illustrates an example trial and the experimental design.

2.4. EEG analysis

EEG was recorded and pre-processed following standard procedures (see, e.g., Schiller et al., 2020b, 2019). As OT had no sex-specific effects on response times, we focused our following analysis on a process's peak intensity, in line with classical ERP waveform analysis (review on OT ERP research in humans: Pehlivanoglu et al., 2020). Artefact-free trials were averaged to compute individual ERPs for each of the four phenotypes (low attractiveness & low threat: mean ± standard deviation = 20.57 ± 1.83; low attractiveness & high threat: mean ± standard deviation = 20.59 ± 1.89; high attractiveness & low threat: mean ± standard deviation = 20.40 ± 1.98; high attractiveness & high threat: mean ± standard deviation = 20.38 ± 2.00). For averaging, we used a time window from 0 to 1400 ms after stimulus onset during which participants made their trust decisions. To identify the time boarders of all neurophysiological processes occurring during trust decisions, we relied on spatio-temporal ERP microstates analysis (Lehmann and Skrandies, 1980). Microstates analysis is a data-driven approach that does not rely on an a priori selection of relevant processes and analyzed time points or electrodes. Rather, it segments electrical activity recorded during an event into time periods of stable neural network configurations, thereby identifying the brain's functional microstates, each of which represents distinct neurophysiological processes (Lehmann and Skrandies, 1980). For that purpose, the individual ERPs were imported

A

Within subject factors

attractiveness	threat
low	low
high	high

Between subject factors

sex	drug
female	placebo
male	oxytocin

B

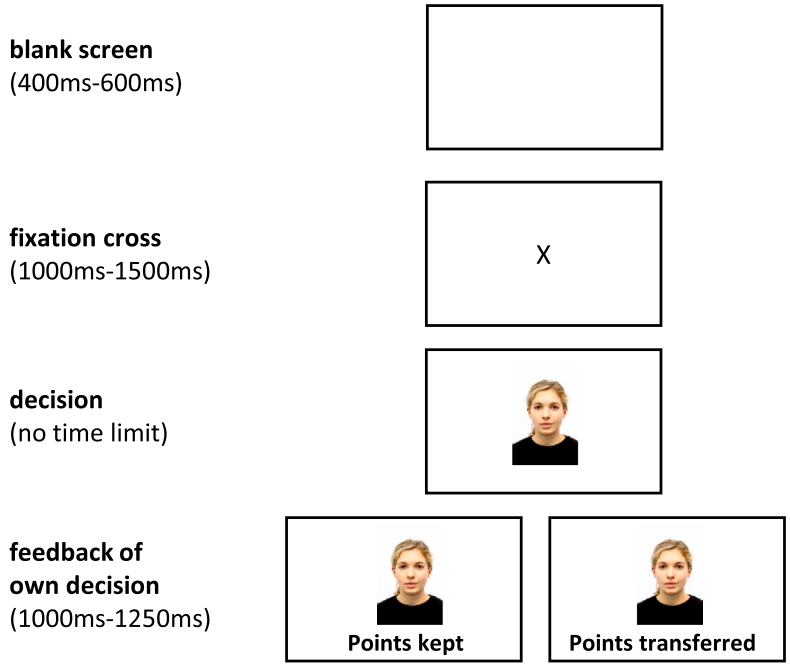

Fig. 1. Example trial and experimental design. A: Experimental design showing within and between subject factors and their levels. B: Sequence of presented screens and durations, as taken from Brustkern et al. (2021). Trial durations are shown in milliseconds (ms). Participants first saw a blank screen with a jittered duration of 400–600 ms, then a fixation cross for 1000–1500 ms, then saw a picture of the trustee until they made their decision, and then saw their own decision presented for 1000–1250 ms.

into the software Ragu (Version compiled on 24 November 2020; Koenig et al., 2011). Employing this software, we took the spatial K-means clustering approach (Koenig and Melie-García, 2010) to identify the most dominant topographies (i.e., clusters) in the four phenotypes' grand-mean ERP map series. Relying on the visual criterion provided by Ragu (showing the amount of explained variance explained by a given cluster solution), we identified the optimal number of clusters (Habermann et al., 2018). By means of a topographic fitting procedure (Michel et al., 1999) we then identified the resulting microstates – equaling the temporal boarders of the distinct neurophysiological processes underlying trust behavior - in each of the four phenotypes' grand-mean ERP map series (applying the constraint that each cluster must be present for at least 20 ms in the grand-mean ERP). Next, we used the peak detection module provided by the software Brain Vision Analyzer (Version 2.1.0.327, Brain Products) as well as manual correction (based on congruency of individual electrical field maps with the maps identified via ERP microstates analysis) in order to detect the time points of local intensity maxima of global field power (GFP) values (equaling the standard deviation of all electrodes at a given time, for more details see Murray et al., 2008) within the identified on- and offset times of each process (*peak intensity*). GFP equals the spatial standard deviation of the instantaneous voltages at all electrodes of a given potential field map (Skrandies, 1990). We used GFP values to reduce the noise of a single electrode and to get a reference-independent, whole-scalp measure of a process's strength of the electrical potential (Lehmann and Skrandies, 1980). At these time points (see Table S1 in the supplementary material), we extracted GFP values (for additional analyses of GFP values averaged across all time frames of each process, i.e., *mean intensity*, and analyses of single electrodes, see supplementary material).

2.5. Statistical analyses

2.5.1. Behavioral data

We first calculated *mean trust decisions* for each phenotype by dividing the number of participants' decisions to trust by the total number of decisions, i.e., 22, for each phenotype. We supplementary materialperformed a repeated measures ANOVA with *mean trust decisions* as the dependent variable, and with the between subject factors *participants' sex* (women vs. men) to investigate sex differences in OT effects, and *drug* (OT vs. placebo) to determine the influence of OT. *Facial attractiveness* and *threat* were included as within subject factors with two levels (i.e., low vs. high). We followed up on significant interactions by performing ANOVAs as post hoc tests. To investigate whether different traits of participants (e.g., levels of interpersonal trust, see Methods) might affect OT effects, we also included trait variables as covariates in the ANOVA to check whether it would alter the results.

We furthermore investigated the influence of several control variables like non-social risk taking and altruistic donations by including these variables as dependent variable in a repeated measures ANOVA, with the between subject factors *participants' sex* (women vs. men) and *drug* (OT vs. placebo). Regarding all statistical comparisons, *p*-values smaller than 0.05 were considered significant (two-tailed).

2.5.2. EEG data

For the EEG data, we analyzed the peak intensity (i.e., GFP) of each of the six microstates, by using the extracted value for each participant as the dependent variable in a repeated-measures ANOVA, and *participants' sex* (women/men) and *drug* (OT/placebo) as between subject factors. Facial *attractiveness* and *threat* were included as within subject factors with two levels (i.e., low and high). We repeated these analyses using mean intensity as dependent variable (for details, see supplemental material).

3. Results

3.1. Sex differences in oxytocin's effects on trust behavior

To investigate whether OT compared to placebo exerted sex-specific effects, we conducted a repeated measures ANOVA with *mean trust decisions* for each of the four phenotypes as dependent variables, and *participants' sex* and *drug* as between subject factors. We identified a significant main effect of *participants' sex*, $F(1,140) = 11.123$, $p = .001$, $\eta_p^2 = .074$, indicating that male participants trusted more often than female participants did. There was no main effect of *drug*, $F(1,140) = 0.431$, $p = .513$, $\eta_p^2 = .003$. However, there was a significant interaction between *participants' sex* and *drug*, $F(1,140) = 4.021$, $p = .047$, $\eta_p^2 = 0.028$. Following up on the interaction, we found that OT's effects on trust decisions were significant neither in men ($F(1,69) = 3.100$, $p = .083$, $\eta_p^2 = 0.043$), nor in women ($F(1,71) = 1.052$, $p = .308$, $\eta_p^2 = .015$). Descriptively, trust in males was higher when they received OT ($M = 0.67$ & $SD = 0.23$) than when given a placebo ($M = 0.57$ & $SD = 0.21$), while trust in females was lower when they received OT ($M = 0.48$ & $SD = 0.23$) than when given a placebo ($M = 0.53$ & $SD = 0.16$; see Fig. 2).

3.2. Effects of sex and oxytocin with attractiveness and threat on trust behavior

Next, we examined whether OT's effect compared to placebo on trust differed between women and men with regard to facial features of the trustee. We observed a significant interaction between *participants' sex* and *drug* and *attractiveness*, $F(1,140) = 6.029$, $p = .015$, $\eta_p^2 = .041$. Separate ANOVAs for phenotypes of low and high attractiveness showed

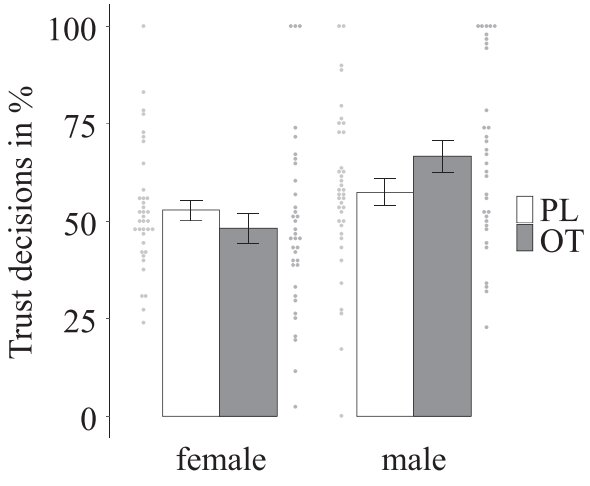

Fig. 2. Effects of participants' sex and oxytocin on trust.
N = 144. Bar-plot showing trust decisions in percent averaged over all phenotypes for female and male participants in the placebo (PL; white) and oxytocin (OT; grey) group. While OT's effects on trust decisions were significant neither in men (p = .083,), nor in women (p = .308), there was a significant interaction between participants' sex and drug (p = .047). Bars indicate ± 1 standard error. Dots represent the mean trust decision in percent for each participant.

that there was a significant interaction of *participants' sex x drug* in the *low attractiveness* condition, $F(1,140) = 6.292$, $p = .013$, $\eta_p^2 = .043$, but not in the *high attractiveness* condition, $F(1,140) = 1.410$, $p = .237$, $\eta_p^2 = .010$ (see Fig. 3). Following up on the significant *participants' sex x drug* interaction for trustees of *low attractiveness*, we found that OT increased trust decisions in men, $F(1,69) = 3.998$, $p = .049$, $\eta_p^2 = .055$, but had no significant effects in women, $F(1,71) = 2.281$, $p = .135$, $\eta_p^2 = .031$ (for further effects unrelated to OT, see supplementary material). Thus, OT, compared to placebo, exhibited sex-specific effects in women and men when they were interacting with unattractive trustees.

We then tested whether the OT effect compared to placebo on trust towards threatening vs. unthreatening trustees differed between women and men, and found a significant interaction of *participants' sex x drug x threat*, $F(1,140) = 4.740$, $p = .031$, $\eta_p^2 = .033$. Separate ANOVAs for phenotypes of low and high threat revealed a significant *participants' sex x drug* interaction for phenotypes of *low threat*, $F(1,140) = 8.579$, $p = .004$, $\eta_p^2 = .058$, but not for phenotypes of *high threat*, $F(1,140) = 0.966$, $p = .327$, $\eta_p^2 = .007$ (see Fig. 4). Further investigating the *participants' sex x drug* interaction in the *low threat* condition, we found that OT, compared to placebo, significantly increased trust in men, $F(1,69) = 4.105$, $p = .047$, $\eta_p^2 = .056$, and significantly reduced it in women, $F(1,71) = 4.488$, $p = .038$, $\eta_p^2 = .059$. Hence, OT, compared to placebo, revealed opposite effects on trust in women and men when they were interacting with unthreatening trustees.

In sum, we identified sex differences in OT especially when participants were interacting with trustees presenting low intensities of attractiveness and threat, respectively. This is also demonstrated by the non-significant interaction of *participants' sex x drug x attractiveness x threat*, $F(1,140) = 1.982$, $p = .161$, $\eta_p^2 = .014$, showing that OT's sex-specific effect primarily emerged from interactions with unattractive and/or unthreatening-looking other-sex individuals. Our findings were specific for trust decisions, as we detected no significant drug or sex effects on a non-social risk task or on charity donations ($ps > 0.106$; see supplementary material). Furthermore, there were no significant differences between treatment groups in age or trait variables, or how happy participants were with being single, which could confound treatment effects ($ps > 0.072$). When we controlled for these variables, the sex-specific OT effects on trust behavior remained significant (*drug x participants' sex*: $F(1, 140) = 5.319$, $p = .023$, $\eta_p^2 = .043$; *drug x participants' sex x attractiveness*: $F(1,140) = 8.299$, $p = .005$, $\eta_p^2 = .065$; *drug x participants' sex x threat*: $F(1,140) = 4.537$, $p = .035$, $\eta_p^2 = .037$). Finally, we identified no significant sex-specific OT effects on response times (*drug x participants' sex*: $F(1, 140) = 0.256$, $p = .641$, $\eta_p^2 = .002$; *drug x participants' sex x attractiveness*: $F(1,140) = 1.753$, $p = .188$, $\eta_p^2 = .012$; *drug x participants' sex x threat*: $F(1,140) = 0.415$, $p = .520$, $\eta_p^2 = .003$).

3.3. Neurophysiological effects of oxytocin and sex

Via microstates analysis, we identified an optimal number of six cluster maps in the time window from stimulus onset to 1400 ms, which is when participants on average made their trust decisions. These maps explained 95.52% of the variance in our EEG data. The repeated-measures ANOVA showed that there were no *drug* main effects or interaction effects with *drug* and *participants' sex* on the peak intensity of microstates 2–6 (as well as on the mean intensity of microstates 1–6, all $ps >= 0.080$; for more information, see supplementary material). However, there was a highly specific effect on the first microstate occurring between 0 and 144 ms (i.e., the P100, an ERP reflecting reflexive capture of visual attention by an external stimulus, Hopfinger and Mangun, 1998). The repeated-measures ANOVA with *peak intensity* of the GFP as dependent variable showed a significant main effect of *participants' sex*, $F(1,140) = 4.647$, $p = .033$, $\eta_p^2 = 0.032$, which was modified by an interaction between *participants' sex* and *drug*, $F(1,140) = 4.074$, $p = .045$, $\eta_p^2 = 0.028$ (see Fig. 5 A for the plot of the GFP for the ERPs for the OT and placebo group for women and men, respectively, and Fig. 5 B for the peak intensity). Following up on the interaction, we

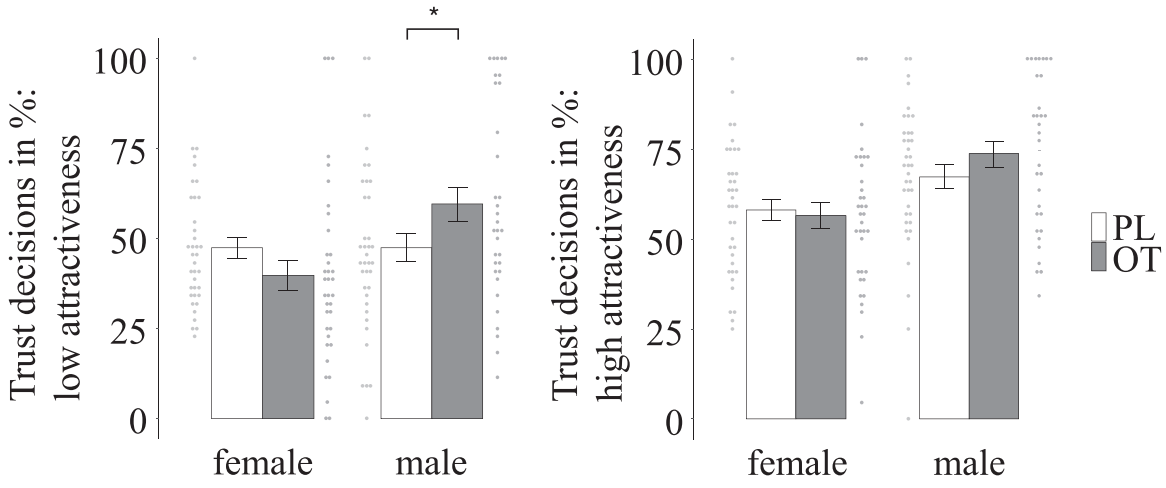

Fig. 3. Effects of participants' sex and oxytocin on trust towards trustees with low and high intensities of attractiveness.
N = 144. Bar-plot showing trust decisions in percent for the phenotype "low attractiveness" (left) and "high attractiveness" (right) for female and male participants in the placebo (PL; white) and oxytocin (OT; grey) group. We detected a significant participants' sex x drug x attractiveness interaction (p = .015), revealing that there was no significant OT effect in females (p = .135), and that OT significantly increased trust in males (p = .049, see asterisk) for trustees of low attractiveness, while there were no (sex-specific) OT effects in trustees of high attractiveness (all ps ≥ 0.200). Bars indicate ± 1 standard error. Asterisk indicates a statistically significant difference (p < .05). Dots represent the mean trust decision in percent for each participant and each phenotype.

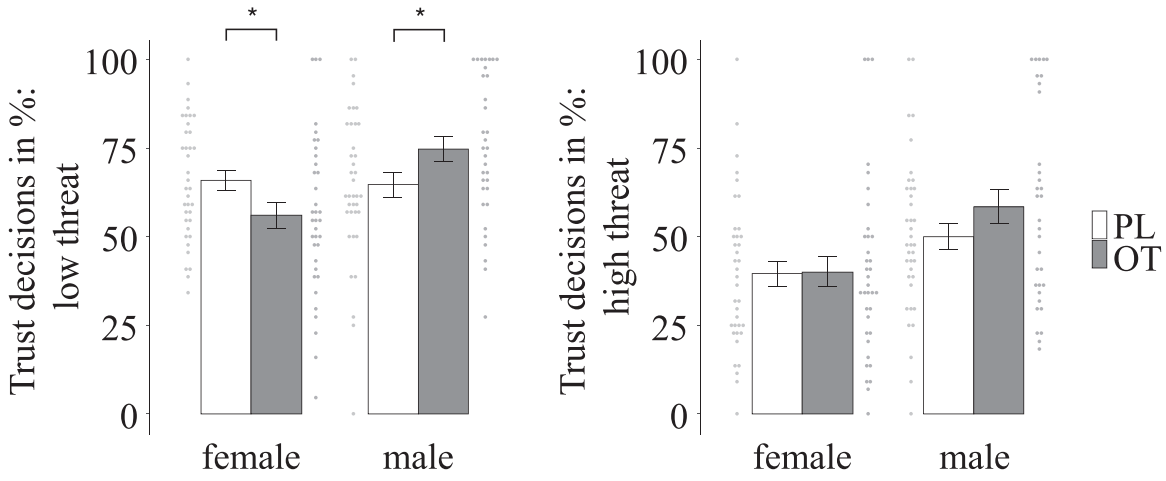

Fig. 4. Effects of participants' sex and oxytocin on trust towards trustees with low and high threat intensities.
N = 144. Bar-plot showing trust decisions in percent for the phenotype "low threat" (left) and "high threat" (right) for female and male participants in the placebo (PL; white) and oxytocin (OT; grey) group. There was a significant interaction of participants' sex x drug x threat (p = .031), revealing that OT, compared to placebo, significantly decreased trust in females (p = .038) and significantly increased it in males (p = .047) for trustees of low but not of high threat (all ps ≥ 0.162). Bars indicate ± 1 standard error. Asterisks indicate statistically significant differences (p < .05). Dots represent the mean trust decision in percent for each participant and each phenotype.

found that, descriptively, in women, OT reduced the intensity ($M = 2.83$, $SD = 1.32$), compared to placebo ($M = 3.45$, $SD = 1.64$), $F(1,140) = 3.584$, $p = .060$, $\eta_p^2 = 0.025$), and increased the intensity in men (PL: $M = 2.47$, $SD = 1.64$; OT: $M = 2.89$, $SD = 1.52$; $F(1,140) = 0.939$, $p = .334$, $\eta_p^2 = 0.007$). We observed similar effects performing single electrode analyses of the amplitude recorded at the O1 electrode, which is an electrode usually analyzed for the P100 (Bigelow et al., 2021, see supplementary materials for details). None of the other interactions, or the drug main effect were statistically significant, see supplementary material. Hence, resembling our behavioral results, OT, compared to placebo, revealed sex-specific effects in women and men on the P100 intensity in response to the trustees' faces.

3.4. Neurophysiological effects of participants' sex and oxytocin with attractiveness and threat

To follow up on the behavioral effects, we investigated whether OT exerted a sex-specific effect on P100 intensity in response to trustees of low attractiveness and low threat, respectively. The ANOVA analyzing P100 intensity in response to trustees with low attractiveness showed that there was a significant interaction of *participants' sex x drug*, $F(1,140) = 5.507$, $p = .020$, $\eta_p^2 = 0.038$ (see Fig. 6, left). Post hoc tests showed that for women, OT, compared to placebo, significantly reduced P100 intensity in response to unattractive trustees, $F(1,140) = 4.388$, $p = .038$, $\eta_p^2 = 0.030$, while there was no significant effect in men, $F(1,140) = 1.516$, $p = .220$, $\eta_p^2 = 0.011$.

Similarly, the ANOVA analyzing P100 intensity in response to trustees of low threat showed that there was a significant interaction of *participants' sex x drug*, $F(1, 140) = 4.209$, $p = .042$, $\eta_p^2 = 0.029$ (see

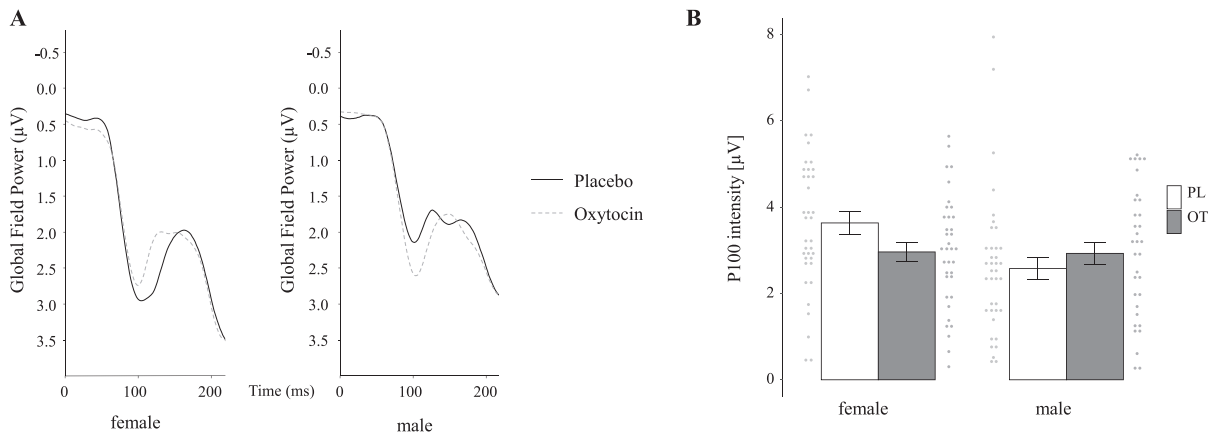

Fig. 5. Neurophysiological effects of oxytocin and sex on the P100. A: Plot of the Global Field Power (GFP) for the ERPs in response to the trustees' faces for female (left) and male (right) participants in the OT (grey, dashed line) and placebo (black, solid line) group. B: Bar-plots showing the P100 peak intensity (i.e., GFP) for female (left) and male (right) participants in the placebo (PL; white) and oxytocin (OT; grey) group. There was a significant interaction of *participants' sex x drug* ($p = .045$), revealing that OT, compared to placebo, reduced the P100 intensity in females on a trend level ($p = .060$), while there was no significant effect in males ($p = .334$). Bars indicate ± 1 standard error. Dots represent each participant's P100 peak intensity.

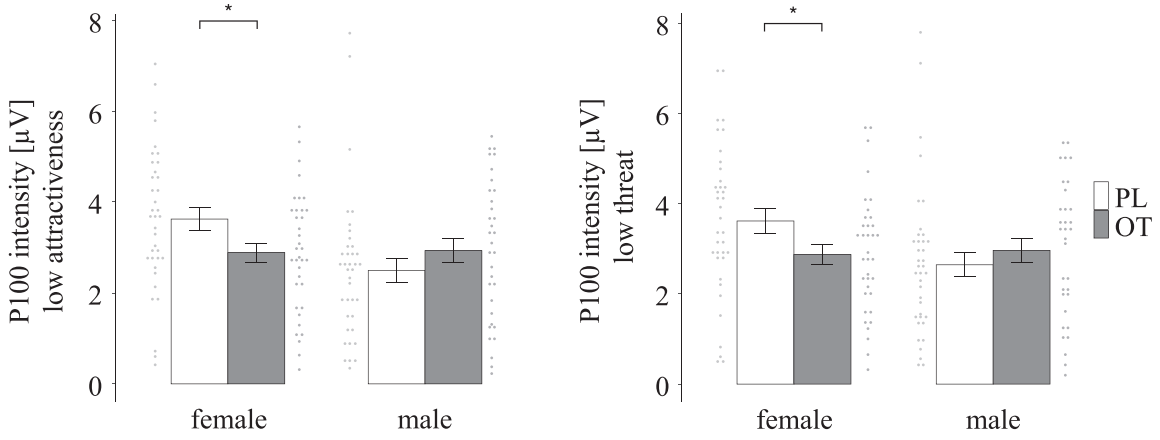

Fig. 6. Effects of participants' sex and oxytocin on P100 peak intensity (i.e., GFP) in response to trustees with a low intensity of either attractiveness (left) or threat (right).
N = 144. Bar-plot showing P100 peak intensity for the phenotype "low attractiveness" (left) and "low threat" (right) for female and male participants in the placebo (PL; white) and oxytocin (OT; grey) group. There was a significant interaction of participants' sex x drug both in response to unattractive trustees ($p = .020$) and unthreatening trustees ($p = .042$), revealing that OT, compared to placebo, significantly decreased P100 intensity in females ($p = .038$), while there was no significant effect in males (all ps ≥ 0.220) in response to phenotypes of low attractiveness or low threat. Bars indicate ± 1 standard error. Asterisks indicate a statistically significant difference ($p < .05$). Dots represent each participant's P100 intensity.

Fig. 6, right). Post hoc tests showed that OT, compared to placebo, significantly reduced P100 intensity in response to unthreatening trustees in women, $F(1,140) = 4.240$, $p = .041$, $\eta_p^2 = .029$, while there was no significant effect in men, $F(1,140) = 0.726$, $p = .396$, $\eta_p^2 = .005$. Hence, the neurophysiological effects of OT are similar to the behavioral results in that they show that OT compared to placebo exerted sex-specific effects on P100 intensity in response to the trustees of both low attractiveness and low threat in women and men. For results regarding the P100 intensity in response to trustees of high attractiveness and high threat, respectively, see supplementary material.

4. Discussion

Sex differences in neuroendocrinological systems regulating social approach behavior are evident in animal research and have been documented in human research regarding neural circuitries associated with rapid evaluations of the social environment. The present study systematically investigated OT's effects on human social approach on the behavioral and neurophysiological level in both women and men. Approach behavior was measured via a participant's resource-sharing decisions in an incentivized trust game played within an evolutionarily-relevant mating context in which heterosexual participants interacted with other-sex individuals whose facial features varied in their intensity (i.e., signaling distinct levels of attractiveness and threat). OT exerted sex-specific effects of modest effect size on both trust behavior and an early occurring, visual attention-related neurophysiological process (i.e., P100) in that OT increased trust and intensified P100 in men, while it reduced trust and dampened P100 in women. This sex difference emerged during interactions with other-sex individuals who were neither attractive nor threatening, thus not capturing visual attention by their intrinsic motivational relevance.

By demonstrating OT's sex-specific effects on trust, our study expands upon findings providing controversial evidence on whether OT modulates trust in males (Baumgartner et al., 2008; Declerck et al., 2020; Kosfeld et al., 2005). More specifically, we demonstrated that OT increases males' trust in other-sex interactions with trustees revealing weak signals of attractiveness and threat. As in previous research demonstrating OT's sex-specific roles in both animal and human social

interactions (Bolea-Alamanac et al., 2018; Lieberz et al., 2020), we further demonstrate that OT does not increase trust in unattractive interaction partners, and that it even dampens trust in unthreatening interaction partners in women as assessed during their menstrual cycle's luteal phase. On a behavioral level, this finding differs from another study's which demonstrated that OT reduced the social distance that female participants maintained towards an attractive, male experimenter (Preckel et al., 2014). However, their analyzed sample differed from the present study's by including women taking oral contraceptives and in a stable romantic relationship, two factors that strongly affect trust behavior in a mating context (Kleinert et al., 2020). In sum, our findings demonstrate that OT's effects are more context- and person-dependent (Bartz et al., 2011) and of more modest effect size than initially assumed, calling for evolutionary informed investigations of OT's behavioral effects in distinct, naturalistic social settings in large mixed-sex samples.

There are several biologically driven explanations for the sex difference we observed in OT's role in human approach behavior. First, there are reports of higher endogenous levels of OT in women than men, which are detected in both central (i.e., cerebrospinal fluid) as well as in methodologically less valid (Valstad et al., 2017) peripheral (i.e., blood, urine) measures (Engel et al., 2019). Second, gonadal hormones (e.g., estradiol, progesterone, and testosterone) differing naturally in their endogenous levels across sexes (Bolea-Alamanac et al., 2018) are known to interact with OT signaling in animals (Frankiensztajn et al., 2018) and humans (Coenjaerts et al., 2022). Third, OT synthesis in the human brain may differ across sexes, although evidence pointing in this direction is scarce so far (Dumais and Veenema, 2016). Fourth, from an evolutionary perspective, endogenously elevated OT levels in women – as experimentally induced by means of intranasal OT administration - are typically found during pregnancy, labor and breast-feeding (Gimpl and Fahrenholz, 2001). In light of the high parental investment costs in women due to gestation and lactation (Trivers, 1996), it might be more beneficial for women in this condition to save resources, bond with their offspring's father and protect their offspring instead of approaching unknown men.

Beyond demonstrating OT's sex-specific effects on social approach behavior, our study also suggests potential psychobiological mechanisms driving these differences. Corresponding with our behavioral findings, OT modulated the intensity of an early-occurring neurophysiological process, i.e., the P100, reflecting the reflexive capture of visual attention by an external stimulus (Hopfinger and Mangun, 1998). Specifically, OT increased this process's intensity in men, while it decreased its intensity in women during interactions with unattractive and unthreatening trustees. The P100 is thought to be associated with the earliest stage of visual, attention-related information processing, being source localized to extrastriate areas within the ventral visual pathway (e.g., Schiller et al., 2016), and being modulated by facial features (e.g., Pourtois et al., 2005). Translational research in monkeys has identified a potential neural pathway of OT's effects on the P100, revealing feedback-like projections by which amygdala activity, which is strongly modulated by OT administration (Meyer-Lindenberg et al., 2011), may modulate activity of the visual processing system (Freese and Amaral, 2005). One could thus hypothesize that OT enables increased trust towards the other sex in men by intensifying early amygdala-gated, visual attention-related processing of social stimuli particularly when their salience is low. In contrast, it might hinder trust in women by dampening such early attention-related processing when the social partner is not motivationally relevant enough.

In sum, the present study illuminates personal (sex) and contextual (salience of facial features) factors that moderate OT's regulation of social approach behavior in humans. Furthermore, our results provide novel evidence on specific psychobiological mechanisms underlying OT's role in approach behavior by demonstrating that OT modulates the intensity of early occurring, attention-related neurophysiological processing. Addressing these fundamental knowledge gaps in OT research is highly relevant in light of the idea of applying intranasal OT as an augmentative strategy for treating disorders characterized by social dysfunction. Yet, as a limitation note that this study's design does not permit us to disentangle participants' and face stimulus's sex effects, because OT's observed sex-specific effects could also be produced by the fact that male and female faces are evaluated differently (Oh et al., 2020; see also Brustkern et al., 2021). It is also conceivable that OT did not modulate trust towards certain phenotypes (e.g., attractive female trustees) due to ceiling effects or because their facial features already increased endogenous OT activity. In light of findings suggesting that OT might facilitate empathic responding in males (e.g., Bartz et al., 2019; Schiller et al., 2020a), one may also speculate that OT strengthened trust towards unattractive and unthreatening trustees by increasing empathy. Hopefully, our results will inspire future research that may determine (a) the impact of different OT administration dosages in samples containing both sexes, (b) the interactive effects of OT and gonadal hormones that fluctuate during distinct menstrual cycle phases, and (c) whether the observed sex-specific and antagonistic effects on OT on social approach generalize to other, non-mating contexts and to social interactions occurring outside the laboratory. Such research might help us better understand the psychobiological mechanisms of the OT signaling system regulating human social approach behavior.

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Conflict of interest statement

We declare we have no conflicting interests.

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Author contributions

B.S., J.B., M.W., A.H., and M.H. conceived and designed the study. B. S. and J.B. collected data. B.S., J.B., M.W., A.H., and M.H. analyzed the data and wrote the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106076.

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