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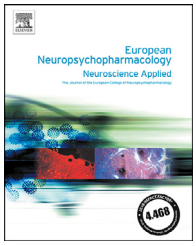

Oxytocin changes behavior and spatio-temporal brain dynamics underlying inter-group conflict in humans

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ABSTRACT
Inter-group conflicts drive human discrimination, mass migration, and violence, but their psychobiological mechanisms remain largely unknown. Here, we investigated whether the neuropeptide oxytocin modulates behavior and spatio-temporal brain dynamics in naturalistic inter-group conflict. Eighty-six male members of natural rival social groups received either oxytocin or placebo intranasally. In a decision-making paradigm involving real monetary stakes, participants could sacrifice their own resources to modulate the monetary gains and losses of in- and out-group members. Oxytocin eliminated the reduction in out-group gains – particularly in individuals with low emotional empathy, whereas those given placebo exhibited this negative social behavior. Our spatio-temporal analysis of event-related potentials elicited by outcome valuation revealed that oxytocin replaced a neurophysiological process associated with the negative valuation of out-group gains via a process associated with positive valuation between 200-500ms after outcome presentation. Oxytocin thus seems to modulate inter-group behavior in humans via a specific alteration of valuation-related brain dynamics.

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1. Introduction

Inter-group conflicts between members of rival social groups (e.g., ethnic populations, opposing political parties, religious groups) are a leading cause of discrimination, violence, and mass migration in both ancient and contemporary human societies (Bernhard et al., 2006; Choi and Bowles, 2007; Esteban et al., 2012). Wars and genocide accounted for an estimated 200 million deaths in the 20th century, and although the numbers are declining, have already accounted for millions of deaths in the 21th century (Rummel, 1994; World Health Organization, 2016). In the past decades, interest has grown across the social, evolutionary, psychological, and biological sciences in studying the psychobiological mechanisms underlying inter-group conflict (Cikara and van Bavel, 2014). Such an interdisciplinary approach builds on the assumption that one can best understand this elementary human phenomenon by combining methods that encompass many levels of analyses (Cacioppo and Cacioppo, 2013). Ultimately, this research area may generate knowledge about how to design targeted interventions for alleviating inter-group conflicts and achieving peaceful co-existence among diverse social groups (Tropp, 2012). Previous research has identified a pronounced absence of empathy towards rival out-group members as a potential psychological mechanism driving negative social behavior in inter-group conflicts (Cikara et al., 2011b; Gutsell and Inzlicht, 2012). Here, we investigated whether oxytocin, a key neuropeptide in vertebrate social behavior (Israel et al., 2012; Meyer-Lindenberg et al., 2011; Scheele et al., 2015) and a potential neurohormonal mediator of empathy (Bartz et al., 2019; Gonzalez-Liencres et al., 2013), modulates behavior and spatio-temporal brain dynamics underlying naturalistic inter-group conflict.

Most placebo-controlled intranasal administration studies have suggested that oxytocin facilitates prosocial behavior, for example by reducing social stress (Heinrichs et al., 2003) and by increasing interpersonal trust (Kosfeld et al., 2005), social cognition abilities (Domes et al., 2007), and empathy-related responses (Bartz et al., 2019; Geng et al., 2018; Hurlemann et al., 2010). Recent research has also acknowledged that oxytocin's effects can vary across individuals and situations (Bartz et al., 2011) yielding heterogeneous findings regarding its role in modulating social behavior in the domain of inter-group interactions (e.g., increasing in-group cooperation and defensive aggression against threatening out-groups, De Dreu and Kret, 2016; increasing contributions to inter-group contests, Zhang et al., 2019; reducing out-group rejection, Marsh et al., 2017; increasing empathic responses to out-group members in pain, Shamay-Tsoory et al., 2013). Given the marked persistence of the hormonal mechanisms regulating social behavior across diverse species (Donaldson and Young, 2008), it seems essential that we study the effects of oxytocin administration on inter-group interactions in an ecologically valid situation. We therefore investigated interactions between members of rival social groups in natural-inter-group conflict (e.g., members from rival soccer clubs; Schiller et al. 2014a, 2019a). To evoke strong emotions and immersion, we studied behavior in response to both positive and negative outcomes affecting in- and out-group members (e.g., Cikara et al., 2011a). We hypothesized that increased brain oxytocin levels would promote more positive and empathic responses to positive outcomes affecting out-group members, whereas oxytocin's effects on empathy for negative outcomes might be masked by its simultaneous dampening effects on overall reactivity to negative outcomes (e.g., Heinrichs et al., 2003; Singer et al., 2008).

Our study addressed this research question by means of a multi-method psychoneuroendocrinological approach combining placebo-controlled intranasal oxytocin administration, a third-party decision-making paradigm with real financial consequences and interactions in naturalistic inter-group conflict, and a spatio-temporal analysis of event-related potentials (ERP; Brandeis et al., 1995; Michel et al., 2009). More specifically, we studied the effects of oxytocin on participants' willingness to sacrifice their own resources in order to modulate the outcomes of in- and out-group members (see Figure 1A). As participants' resources are completely independent from the behavior of their interaction partners, their behavior is free from strategic considerations such as reciprocity or reputation (Fehr and Fischbacher, 2004). Hence, our paradigm allows us to study oxytocin's effects on participants' self-interest-free, natural tendency for displaying positive or negative social behavior towards group members. To collect evidence favoring the possible mechanistic interpretation that oxytocin increases empathic responding, we investigated whether oxytocin's effects on negative social behavior towards out-group member were pronounced in individuals with a low self-reported overall ability to demonstrate emotional empathy (for details, see Experimental procedures). Finally, using a spatio-temporal ERP microstates analysis (for recent examples, see Cacioppo et al., 2015; Schiller et al., 2016), we identified the so far unknown neurophysiological subprocesses underlying the valuation of in- and out-group members in inter-group conflict modulated by oxytocin administration at high temporal resolution. This data-driven approach requires no a priori selection of relevant processes, time points or electrodes. Briefly, 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 neuropsychological processes (Lehmann, 1987; Lehmann and Skrandies, 1980; Michel et al., 2009). Capitalizing on this analysis, we could test the tentative hypothesis that oxytocin administration reduces negative social behavior towards out-group members by altering the asymmetric valuation of in- and out-group members (Cikara et al., 2011a; Hein et al., 2010; Ruff and Fehr, 2014). Specifically, we analyzed whether oxytocin might replace those processes associated with negative valuations of out-group members by processes associated with positive valuations during a time period previously associated with valuation-related processing (i.e., from 0 to 500ms after stimulus presentation; Pedroni et al., 2011).

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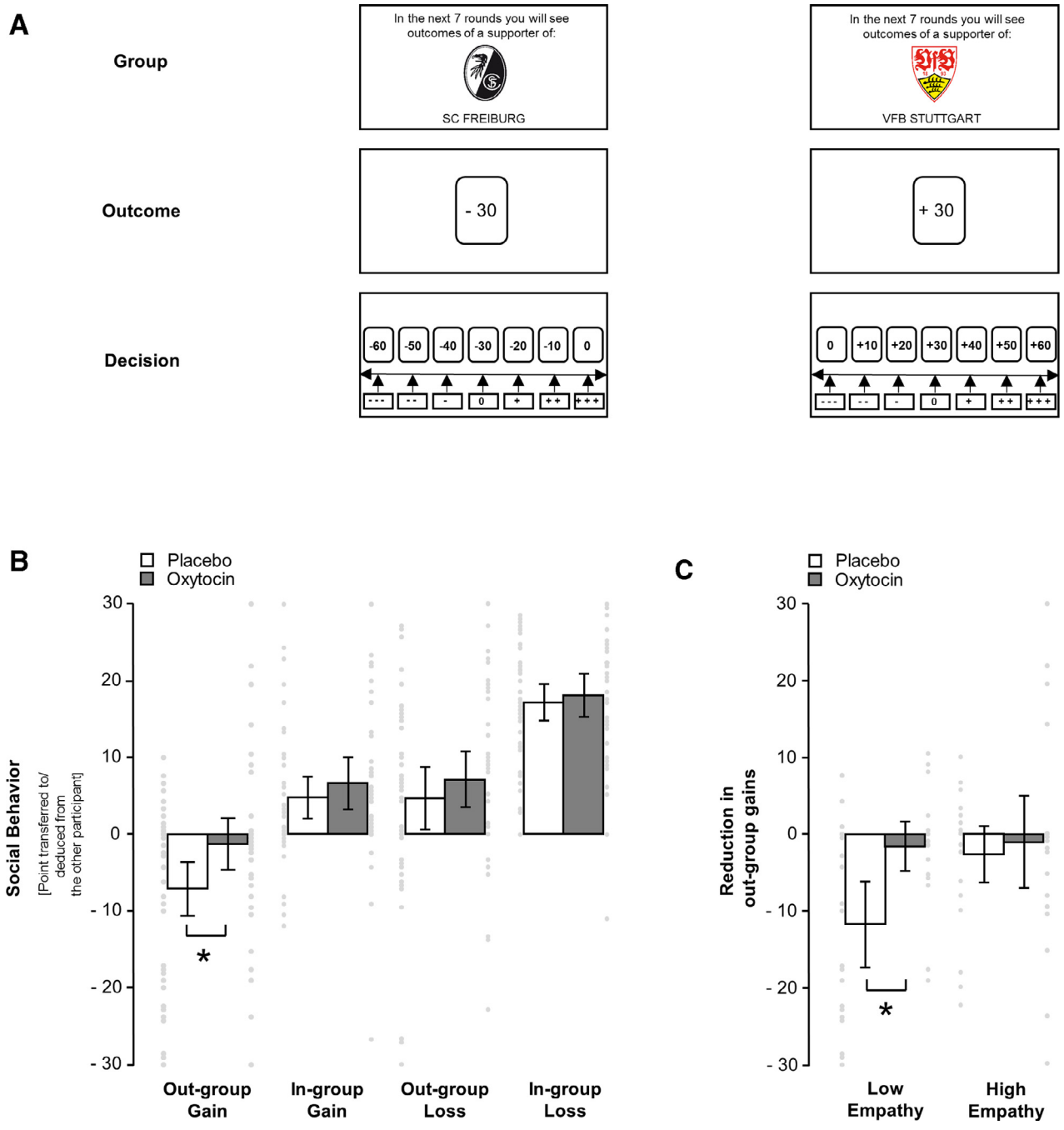

Fig. 1 Third-party decision-making paradigm and mean transfer amount (in points) in individuals receiving oxytocin or placebo. **A**: Participants first saw an emblem of their favored or a rival soccer team/political party indicating that, in the next 7 rounds, they would see outcomes of an in- or an out-group member (Block: in-group vs. out-group). Next, the outcome of the game-of-chance was shown (Outcome: losses vs. gains). Participants then had to make their decisions by selecting one of seven options from the decision screen (Decision). In each trial, participants received ten points which they could either keep for themselves or sacrifice in order to modulate outcomes. For each point spent, they could either in- or decrease another participant's outcome by three points. Thus, the possible modulation of outcomes ranged from decreasing the outcome by 30 points to increasing the outcome by 30 points. **B**: Error bars represent 95% confidence intervals. Asterisks indicate a statistically significant difference ($p < 0.05$, two-sided). Small gray dots represent individual data points. The y-axes show social behavior, i.e., mean points transferred to or deducted from in- and out-group members for the placebo (white; $n = 43$) and oxytocin condition (gray; $n = 43$). Notably, oxytocin eliminated the reduction in out-group gains. **C**: Error bars represent 95% confidence intervals. Asterisks indicate a statistically significant difference ($p < 0.05$, two-sided). Small gray dots represent individual data points. Mean reduction in out-group gains for participants with low (left) and high (right) empathy in the placebo (white) and oxytocin (gray) condition. Oxytocin eliminated the reduction in out-group gains in participants with low self-reported ability for emotional empathy (see Experimental Procedures).

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2. Experimental procedures

2.1. Participants

To test whether our results are generalizable beyond a specific social group (Schiller et al., 2014a), we recruited ninety-one male participants who were fans of rival soccer clubs or supporters of opposing political parties. Five participants had to be excluded from further analysis because of excessive artifacts in their EEG recordings (<50% of data were available after automatic and manual artifact corrections; including those five participants did not change our behavioral findings' significance), leaving a sample of 86 participants for analysis (oxytocin condition: n = 43; placebo condition: n = 43). Mean age was 23.7 ± 4.59 years (range: 18-39). We measured each participant's identification strength with his favored soccer club or political party using a modified version of the Sport Spectator Identification Scale (5-point Likert scale; Wann and Branscombe, 1993) and individually selected the fitting rival out-group accordingly. We found that, on average, participants exhibited medium to strong identification with their group (Mean ± Standard deviation = 3.16 ± 0.66; soccer fans: n = 38, Mean ± Standard deviation = 3.39 ± 0.77; political supporters: n = 48, Mean ± Standard deviation = 2.98 ± 0.49; soccer fans vs. political supporters: $F[1, 84] = 9.50$, $p = 0.003$; to control for potential differences in identification between soccer fans and political supporters, we included the factor "group type" in all analyses). The Ethics Committee of the University of Freiburg approved this study, which was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Participant recruitment and sample size

We solicited contact information of students in lecture halls and contacted them by e-mail to ask for their personal interests in several domains (e.g., arts, music, politics, soccer). Finally, we recruited participants with no current or previous history of neurological and psychiatric disorders, alcohol or drug abuse, and who had, on a scale from 1 (very weak) to 5 (very strong), at least medium (= 3) self-reported interest in soccer or in politics (Baumgartner et al., 2014, 2013). Based on an estimated average small-to-medium effect size of oxytocin's social effects (Cohen's $d = 0.28$; Walum et al., 2016), between 72 ($\alpha = 0.05$, $\beta = 0.80$, number of groups = 2, number of measurements = 4, correlation among repeated measures = 0.5, nonsphericity correction = 1) and 92 participants ($\alpha = 0.05$, $\beta = 0.90$, number of groups = 2, number of measurements = 4, correlation among repeated measures = 0.5, nonsphericity correction = 1) are needed to detect a significant effect (ANOVA: repeated measures, within-between interaction, G-Power©; Faul et al., 2009). Ninety-one healthy male participants took part in the experiment.

2.3. Experimental procedure

There were two appointments: the first was conducted in our group laboratory permitting the simultaneous measurement of 16 participants. After having signed the informed consent form, participants played a game-of-chance involving real monetary consequences and completed the Balanced Emotional Empathy Scale (Mehrabian, 1997). To statistically control for potential random differences between treatment groups in trait variables relevant for inter-group behavior, we collected several additional questionnaires (Moral Foundations Questionnaire, Graham et al., 2011; Self-Control Scale, Tangney et al., 2004; Sensitivity to Punishment and Sensitivity to Reward Questionnaire, Torrubia et al., 2001; Social Dominance Orientation, Jost and Thompson, 2000; Social Value Orientation, Murphy et al., 2011, note that we adapted this task: participants first distributed resources between themselves and a randomly-determined in-group member, then distributed resources between themselves and a randomly-determined out-group member). The second appointment took place in the EEG laboratory. In a randomized, placebo-controlled, double-blind between-group design, participants received either 24 International Units (IU) of OT (n = 43) or placebo (n = 43) via intranasal administration (Guastella et al., 2013; Heinrichs et al., 2003). Then participants were guided to an electrically shielded cabin in which 64-channel EEG measurements were taken. Participants read the instructions and answered control questions on the third-party decision-making paradigm, followed by a five minutes resting EEG recording (for details, see Schiller et al., 2019b). Forty-five minutes after intranasal administration (Spengler et al., 2017), participants started the decision-making paradigm in which they could sacrifice their resources to modulate the game-of-chance outcomes of other in- and outgroup members. Participants were aware that the other in- and out-group members had played the game-of-chance knowing that their outcomes would later be modulated by other participants. Using 7-point Likert scales, we also collected several subjective ratings (pre/post mood ratings, quality of interaction, current financial situation, socio-economic status, and experience of substance effects).

2.4. Game of chance

In the game of chance, participants drew cards (90 trials) from piles on a PC screen with randomly distributed gains (+30, +20, +10) and losses (-30, -20, -10). They started with a deposit of 1000 points and each outcome was added to or subtracted from their income (exchange rate: 100 points = 1 Euro). In fact, the majority of outcomes (84 out of 90 trials) was pre-determined to keep diverse experiences in the game-of-chance from influencing decision-making during the second appointment, and to guarantee that each participant in the decision-making paradigm would see the same distribution of outcomes.

2.5. Third-party decision-making paradigm

In the third-party decision-making paradigm, participants saw the game-of-chance outcomes that affected randomly-determined in- and out-group members and that had no effects on their own resources. Participants knew that all decisions would remain anonymous and that participants whose outcome they could modulate in the game-of-chance would have no opportunity to reciprocate behavior. During the paradigm (Fig. 1A), participants first saw a fixation cross, followed by the information stating whether they could influence the outcomes of an in-group or an out-group member. For that purpose, a group symbol was shown, displaying the emblem of a soccer club or a political party. To increase statistical power (Friston et al., 1999), we used a block-design such that seven outcomes in a row concerned the same participant from a specific social group. After the group symbol, participants saw an outcome of the game-of-chance, displayed by a numbered card with gains or losses. Next, participants saw the decision screen. They received ten points per trial each of which they could use to either increase or decrease the in-group or out-group member's outcome by three points (exchange rate: 100 points = 1 Euro). Thus, if they spent the maximum amount of 10 points, they could either increase or decrease the outcome by 30 points. Via button press, participants had to select one of seven decision options (modulation of outcome: +30, +20, +10, 0, -10, -20, -30). Participants were instructed that they had to select one of the options within ten seconds, otherwise they would lose their points during that trial. In total,

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participants could modulate 84 outcomes (42 of each social group). Participants needed twelve minutes on average to complete the paradigm.

2.6. EEG recording

Scalp impedance was kept below 10 kΩ. FCz served as the reference electrode, AFz as the ground electrode. Horizontal and vertical electrooculographic signals were recorded with two additional electrodes at the left and right outer canthi and one electrode at the left infraorbital. The EEG was online band-pass filtered between 0.1 and 100 Hz, and the data digitized with a sampling rate of 500 Hz.

2.7. EEG preprocessing

EEG data were preprocessed by using Brain Vision Analyzer (Version 2.0.1.327; Brain Products Gmbh, Munich). Ocular correction was conducted via a semi-automatic Independent Component Analysis (ICA)-based correction process. EEG signals with excessive noise were replaced by using a linear interpolation of adjacent electrodes. Heavily corrupted channels were interpolated before the ICA procedure to optimize the statistical identification of eye movement-related ICA components. After removing these components, we screened the channels again and, if necessary, interpolated additional channels. After an automatic artifact rejection (maximum voltage step: 50 μV; maximum amplitude difference in intervals of 150 ms length: 150 μV; maximum amplitude: ± 100 μV), data were visually examined by two independent raters to eliminate residual artifacts. Data were then band-pass filtered (no additional high-pass, low-pass 30 Hz) and re-derived to average reference.

2.8. EEG analysis

To analyze electrophysiological activity elicited by outcome valuation, we analyzed a time window from outcome presentation to 500ms thereafter. We selected this time window because previous research on the temporal dynamics of outcome evaluation has revealed that differences in the processing of outcomes with distinct valences occur during this time window (Pedroni et al., 2011; Wu and Zhou, 2009). No baseline correction was conducted. Artifact-free trials were averaged to compute individual ERPs, for each of the four outcome conditions (out-group gain: Mean ± Standard deviation = 19.08 ± 2.43; in-group gain: Mean ± Standard deviation = 19.19 ± 2.21; in-group loss: Mean ± Standard deviation = 18.91 ± 2.64; out-group loss: Mean ± Standard deviation = 19.28 ± 2.24). Then, the individual ERPs were averaged into four grand-mean ERPs, one for each outcome condition. We took the spatial K-means clustering approach to identify sequences of time periods with quasi-stable scalp map topographies (functional microstates; Lehmann, 1987; Lehmann and Skrandies, 1980). This approach uses global map dissimilarity (Lehmann and Skrandies, 1980) as a measure of topographical difference between any two maps. The spatial cluster analysis revealed the most dominant topographies (i.e., clusters) in the grand-mean ERP map series of the four experimental conditions. We chose the optimal number of clusters by analyzing silhouette plots (Rousseeuw, 1987). We chose the four cluster solution because the five cluster one led to one cluster with no structure. A topographic fitting procedure helped us identify the resulting microstates in each condition (Michel et al., 1999). In the second step, we fit back the clusters (as identified in the four grand-mean ERP map series) to the individual ERPs in each condition. Each time point was labeled with the cluster it correlated best with (in terms of global map dissimilarity), yielding a measure of cluster presence (in milliseconds) for each individual ERP in the four outcome conditions, separately.

2.9. Source localization analysis

The sLORETA (Pascual-Marqui, 2002) solution space, which has been used in many EEG studies (Nash et al., 2013; Pizzagalli et al., 2001; Schiller et al., 2014b), consists of 6,239 voxels (voxel size: $5 \times 5 \times 5$ mm) and is restricted to cortical gray matter and hippocampi, as defined by the digitized Montreal Neurological Institute probability atlas. The sLORETA functional images represent the electrical activity at each voxel as squared magnitude (i.e., power) of computed current density (unit: amperes per square meter, A/m^2). sLORETA computes the electrical neuronal activity without assuming a predefined number of sources. Our aim was to identify the intracerebral sources underlying valuations-related microstates. On the basis of findings from our data-driven ERP microstates analysis, we assumed that valuations-related processing occurs during microstates C and D. As both microstates occurred during a similar time period, but differed in the processed outcome's valence (microstate C: losses; microstate D: gains), we tested whether contrasting the sources of both microstates to each other would reveal more strongly activated areas associated with negative valuations during microstate C, and those associated with positive valuations during microstate D. For each subject, we first averaged all scalp maps within microstate C (in response to losses) and microstate D (in response to gains) and then estimated the individual sLORETA functional images for each microstate. To reveal the characteristic neural sources of microstate C in comparison to microstate D, we statistically contrasted the individual sLORETA functional images of microstate C to the individual sLORETA functional images of microstate D during the time window these microstates occurred. We assessed the localization of the intracerebral sources by whole-brain voxel-by-voxel *t*-tests of the sLORETA images of the log-transformed computed current density power between microstates C and D. In the resulting statistical 3D images, we identified voxels as statistically different through a nonparametric approach using a randomization strategy (Nichols and Holmes, 2002) that determined the critical probability threshold values for the observed t-values with correction for multiple testing. In the second step, we repeated this analysis contrasting the intracerebral sources of microstate C and D during the processing of out-group gains in participants with low empathy in the oxytocin and the placebo conditions.

2.10. Statistical analysis

For the behavioral analysis, we calculated the effect of a third-party's decisions on the outcomes of other participants separately for the four outcome conditions (out-group gains, in-group gains, out-group losses, in-group losses). We first conducted an overall ANOVA with the within-subjects factors "social group" (in-group versus out-group) and "valence" (gains versus losses) and the between-subjects factors "treatment" (oxytocin versus placebo), and "group type" (soccer versus politics). To reveal the nature of significant interaction effects involving the "treatment" factor, we calculated ANOVAs using the between-subjects factors "treatment" and "group type", separately for the four outcome conditions. We also calculated one-sample *t*-tests testing for significant differences in a certain behavior from zero, separately for the two treatment conditions. To see whether oxytocin's effects differed between participants with high and low empathy, we included "empathy" (high versus low, classified according to a median

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split) as an additional between-subjects factor. With regard to the spatio-temporal ERP analysis, we used randomizing statistics (Koenig et al., 2011; Koenig and Melie-Garcia, 2010) to test for significant differences in the temporal occurrence of microstates involving the factors "treatment" (oxytocin versus placebo), "valence" (gains versus losses), and "social group" (in-group vs. out-group) and conducted correlation and moderated mediation analyses to relate the temporal occurrence of those microstates to individual behavior (Hayes, 2013). Regarding all statistical comparisons, P-values smaller than 0.05 were considered significant (two-tailed).

3. Results

3.1. Effects of oxytocin on behavior

The overall ANOVA exhibited a significant interaction effect "social group X valence X treatment" ($F[1, 82] = 4.79$, $p = 0.031$, $\eta^2 = 0.06$; for details see Supplemental Results). Subsequent ANOVAs calculated separately for the four outcome conditions revealed that the behavioral effects of oxytocin administration were highly specific for out-group gains, as there were no effects on behavior in the response to in-group gains, out-group losses, or in-group losses (all $p > 0.20$; Fig. 1B). Individuals in the placebo condition sacrificed their own resources to significantly reduce out-group gains (Mean ± Standard deviation = -7.14 ± 11.38, t[42] = -4.12, $p < 0.001$). As predicted, individuals in the oxytocin condition reduced out-group gains less than those in the placebo condition ($F[1, 82] = 5.44$, $p = 0.022$, $\eta^2 = 0.06$; Fig. 1B). Notably, in contrast to the placebo condition, individuals in the oxytocin condition did not reduce out-group gains significantly (Mean ± Standard deviation = -1.33 ± 10.87, t[42] < 1, $p > 0.20$). Thus, oxytocin administration did not only reduce, it actually eliminated negative social behavior against out-group members. We detected no differences in demographic and trait variables, subjective ratings during the experiment, or the general willingness to sacrifice resources between treatment groups, which could confound this effect (all $p > 0.076$). Additionally, when we control for all these variables, the behavioral effect of oxytocin administration remains significant ($F[1, 60] = 7.76$, $p = 0.007$, $\eta^2 = 0.12$). We did not find any oxytocin effects on response times (all $p > 0.20$, see Figure S1).

3.2. Oxytocin's effects on behavior in individuals with high versus low empathy

To see whether oxytocin eliminates negative social behavior towards out-group members by increasing empathic responses to out-group gains, we analyzed the effects of oxytocin on modulating out-group gains in individuals with high and low empathy. We observed a significant difference ($F[1, 78] = 4.12$, $p = 0.046$, $\eta^2 = 0.05$), with individuals with *high empathy* revealing no significant reduction in out-group gains irrespective of substance administration (placebo condition: Mean ± Standard deviation = -2.66 ± 8.40, $t[21] = -1.49$, $p = 0.15$; oxytocin condition: Mean ± Standard deviation = -1.04 ± 13.71, t[21] < 1, $p > 0.20$; oxytocin vs. placebo: $F[1, 40] < 1$, $p > 0.20$). In contrast, individuals with *low empathy* significantly reduced out-group gains in the placebo condition (mean ± SD = -11.84 ± 12.35, t[20] = -4.39, $p < 0.001$). Notably, intranasal oxytocin reduced such negative social behavior in low-empathy individuals down to the level of high-empathy individuals (Mean ± Standard deviation = -1.63 ± 7.11, t[20] = -1.05, $p > 0.20$; oxytocin vs. placebo: $F[1, 38] = 10.88$, $p = 0.002$, $\eta^2 = 0.22$; Fig. 1C; note that we also identified a significant interaction effect of "treatment X empathy" in an ANOVA using the continuous empathy score; for details, see Supplemental Results). Again, these findings were highly specific, as empathy did not moderate oxytocin effects on behavior in the other three outcome conditions (all $p > 0.20$) and did not influence behavior in low- or high-empathy individuals in the other three outcome conditions (all $p > 0.19$; see Figure S2).

3.3. Oxytocin's effects on neurophysiological processes

Our general aim was to identify changes in valuation-related processing due to oxytocin administration using a data-driven spatio-temporal ERP analysis. We identified four cluster maps (A-D) that explained 91% of the variance observed in ERPs elicited by outcome valuations within a time window from outcome presentation to 500ms thereafter. Map A displays left-lateralized, frontal positivity and right-lateralized temporal negativity. Map B showed the characteristic P100 distribution with a bilateral positivity over occipital electrodes. Maps C and D both showed a P300-like posterior positivity, which was less pronounced, less anterior, and more left-lateralized during map D (Fig. 2A).

3.3.1. Identification of neurophysiological processes associated with valuation-related processing

In the *first step*, we searched for microstates, i.e. processes associated with positive and/or negative valuations. For that purpose, we fit the four identified cluster maps to the grand-mean ERPs of the four outcome conditions and analyzed the effects of "valence" on their temporal occurrences. Importantly, we identified two microstates, i.e., microstates C and D which occurred depending on the valence of the processed information (for details, see Figure S4). Whereas microstate C occurred when participants were confronted with losses (*gains:* 0ms, *losses:* 314ms, $p = 0.002$), microstate D occurred when participants were confronted with gains (*gains:* 300ms, *losses:* 0ms, $p < 0.001$; see Fig. 2C). These findings suggest that during a time period previously associated with valuation-related processing (~200-500ms after outcome presentation), negative valuations take place during microstate C, whereas positive valuations take place during microstate D. Corroborating this assumption, comparing the intracerebral sources of these two microstates (microstate C during losses vs. microstate D during gains) revealed relatively stronger activation in areas associated with negative valuations during microstate C (e.g., left insula, Liu et al., 2007; Fig. 2C), and relatively

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stronger activation in areas associated with positive valuations during microstate D (e.g., medial orbitofrontal cortex, Kringelbach, 2005; Fig. 2C; $p < 0.05$, whole-brain corrected; for details see Supplemental Results and Table S1).

3.3.2. Modulation of neurophysiological processes associated with valuation-related processing by oxytocin

In the *second step*, we analyzed whether oxytocin may eliminate the reduction in out-group gains in participants with low empathy by modulating the temporal occurrence

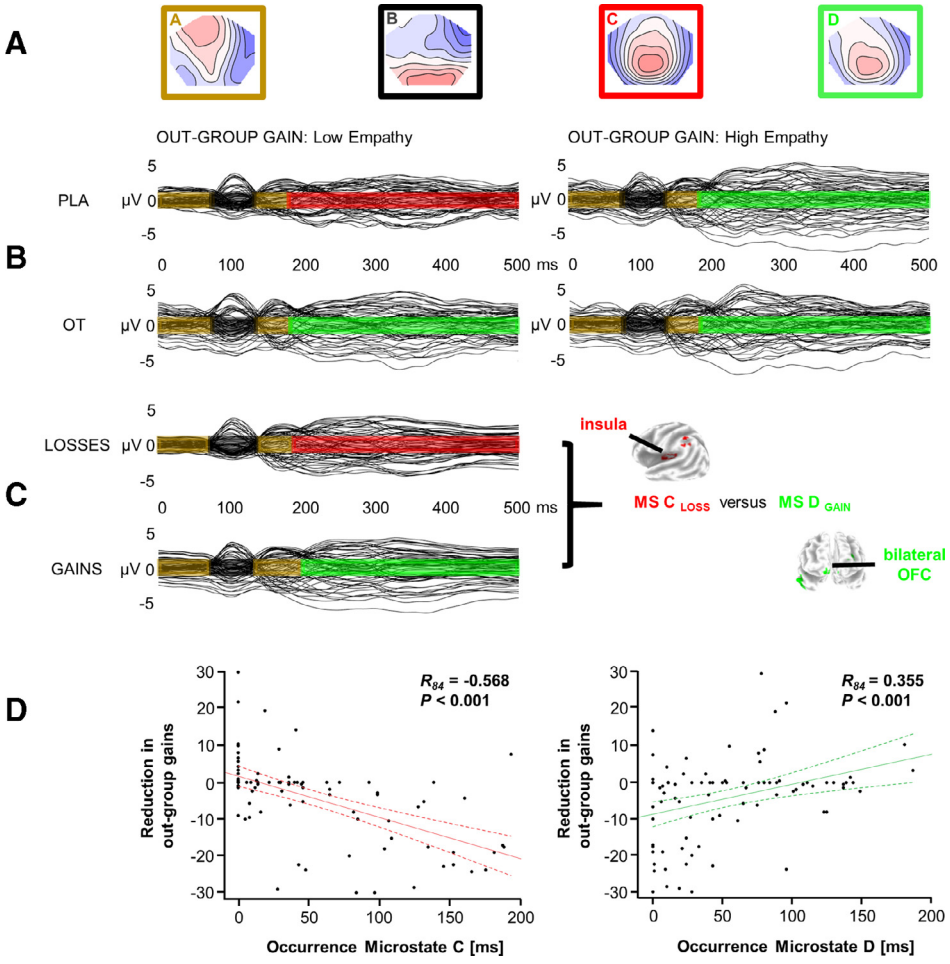

Fig. 2 Effects of oxytocin on neurophysiological processes revealed from a spatio-temporal ERP microstates analysis (for recent application of this approach, see Schiller et al. 2016; for a detailed methodological description, see Michel et al. 2009). Briefly, segmenting electrical activity elicited by outcome valuation into time periods of stable neural network configurations (= stable EEG scalp map topographies) via a clustering approach (Brandeis et al., 1995; Michel and Murray, 2012) identifies functional microstates in the brain that represent specific, valuation-related processes. Here, we investigated whether oxytocin would replace neurophysiological processes associated with negative valuations of out-group gains by processes associated with more empathic, positive valuations and whether these changes would provide a mechanistic explanation for oxytocin's effects on behavior. **A**: Optimal cluster solution with four distinct topographies (maps A-D). Head seen from above. Red indicates positive values, blue negative values, referred to average reference. The colored background corresponds to the assignment shown in B-D. **B**: Microstates (MS) across time (ms) for out-group gains in people with low (left) and high (right) empathy in the placebo (PLA; top) and oxytocin condition (OT; bottom). Microstates are marked in color on the superimposed grand mean ERP waveforms. **C**: *Left*: Microstates across time (ms) in response to losses (top) or gains (bottom), averaged across outcomes affecting in-group and out-group members. *Right*: Statistically comparing the intracortical sources between the microstates C and D (significant voxels are colored red [microstate C > microstate D] and green [microstate D > microstate C]). **D**: Predicting an individual's reduction in out-group gains by that individual's temporal occurrence of microstate C (left) and microstate D (right), including regression lines and confidence intervals (95%). **E**: Predicting differences in the individual temporal occurrence of microstate C compared to microstate D by that individual's self-reported ability for emotional empathy (see Experimental procedures) for participants in the placebo condition (left panel) and oxytocin condition (right panel). **F**: Path diagram (including regression coefficients, s.e.m.- and p-values) of the moderated mediation analysis, demonstrating that oxytocin eliminates the reduction in out-group gains, moderated by empathy, via modulating the temporal occurrences of microstates C and D in response to out-group gains.

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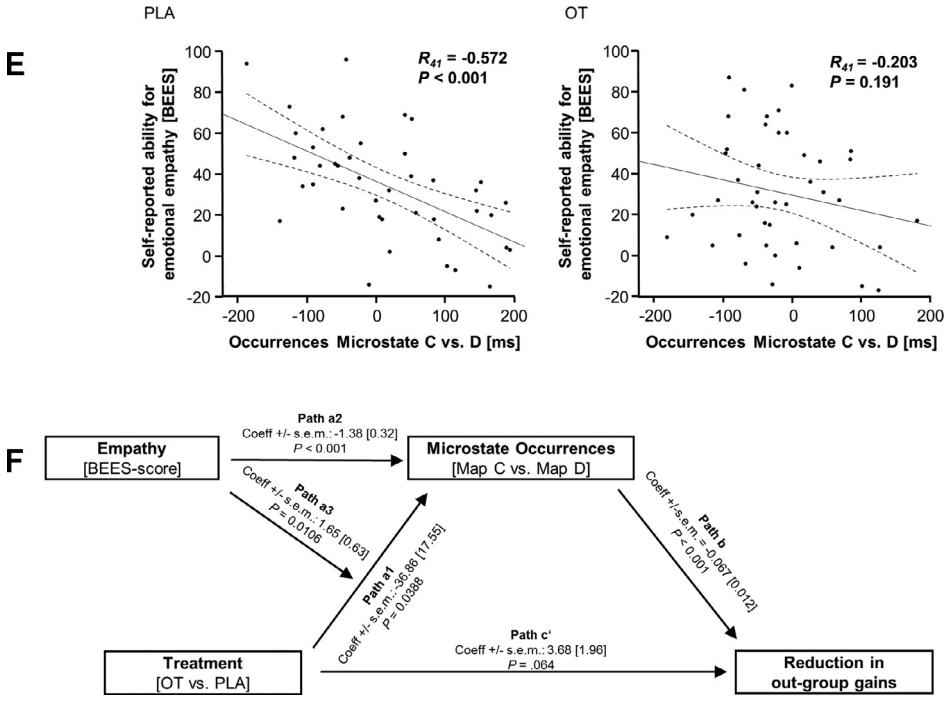

Fig. 2 Continued

of microstates, i.e., valuation-related processes. We fit the four cluster maps to the grand mean ERPs of out-group gains, separately for participants in the oxytocin and placebo conditions and those with low and high empathy. Indeed, we identified significant differences between the oxytocin and placebo conditions in the temporal occurrence of the two valuation-related microstates occurring between 200 and 500 ms after the presentation of out-group gains (like our behavioral findings, these findings were highly specific, as there were no "treatment" effects in the other three outcome conditions, all $p > 0.11$). Whereas in participants with low empathy, negative valuations-related microstate C occurred in the placebo but not in the oxytocin condition (*placebo:* 300 ms, *oxytocin*: 0 ms, $p = 0.005$; Fig. 2B), positive valuations-related microstate D occurred in the oxytocin but not placebo condition (*placebo*: 0ms; *oxytocin*: 302ms, $p = 0.003$; Fig. 2B). Interestingly, only microstate D occurred in both the placebo and the oxytocin conditions in participants with *high empathy* (*placebo*: 308 ms, *oxytocin*: 300 ms, $p > 0.20$); microstate C did not occur at all (*placebo*: 0ms, *oxytocin*: 0ms, $p > 0.20$). Thus, microstate C only occurred in participants who significantly reduced out-group gains (participants with low empathy in the placebo condition). In contrast, microstate D occurred in participants exhibiting no reduction in out-group gains. Contrasting the intracerebral sources of microstates C and D during the processing of out-group gains in participants with low empathy between the oxytocin and the placebo conditions again demonstrated relatively stronger activation in negative valuations-related areas during microstate C, and relatively stronger activation in positive valuations-related areas during microstate D ($p < 0.01$; uncorrected; for details, see Supplemental Results and Table S2). In sum, these findings suggest that oxytocin reduces negative social behavior in response to out-group gains by replacing a negative valuations-related process by a positive valuations-related one.

3.3.3. Oxytocin's effects on neurophysiological processes and behavior

Finally, we analyzed whether individual temporal occurrences of valuation-related microstates would predict individual behavior. Thereby we wanted to test whether oxytocin eliminated the reduction in out-group gains by modulating valuation-related neurophysiological processes, moderated by an individual's self-reported ability for emotional empathy. Indeed, we observed that the occurrence of the negative valuations-related microstate C correlated positively with the reduction in out-group gains ($r[84] = 0.57$, $p < 0.001$; Fig. 2D), whereas the occurrence of positive valuations-related microstate D correlated negatively ($r[84] = -0.36$, $p < 0.001$). We also found that an individual's self-reported ability for emotional empathy did predict the relative individual temporal occurrences of valuation-related microstates in the placebo ($r[41] = -0.572$, $p < 0.001$), but not in the oxytocin condition ($r[41] = -0.203$, $p = 0.191$; placebo vs. oxytocin: $Z = -1.947$, $p = 0.026$; Fig. 2E). Moreover, we found evidence of moderated mediation, indicating that oxytocin eliminated the reduction in out-group gains in participants with medium and low empathy by replacing a neurophysiological process associated with negative valuations of out-group gains by a process associated with positive valuations ($p < 0.05$; Fig. 2F). More specifically, oxytocin decreased the occurrence of negative valuations-related microstate C in comparison to positive valuations-related microstate D (Path a1; Fig. 2F). This effect was moderated by empathy (Path a3), which

also had direct effects on the microstate occurrences (Path a2). Bootstrapping statistics revealed that oxytocin did not reduce the relative occurrence of microstate C compared to microstate D in participants with high empathy (mean + 1SD; $p < 0.05$), but that it did so in participants with medium empathy (mean; $p < 0.05$), and those with high empathy (mean + 1SD; $p < 0.05$), which in turn reduced negative social behavior towards out-group members (Path b). Moreover, oxytocin's direct effect on reducing out-group gains (Path c', controlling for the indirect effect of oxytocin on behavior via the temporal occurrences of microstates) was not significant and it was significantly smaller than the indirect effect via the occurrences of microstate C vs. microstate D ($p < 0.05$). Changes in the occurrence of valuation-related microstates C and D thus fully mediated the effects of oxytocin on the reduction in out-group gains, in particular in participants with low and medium empathy.

4. Discussion

This study is the first to have investigated whether oxytocin modulates behavior and its underlying neurophysiological processes in naturalistic inter-group conflict. As a mediator regulating social cognition and behavior (Heinrichs et al., 2009; Meyer-Lindenberg et al., 2011), does oxytocin also replace unempathic, negative responses to out-group members by more empathic, positive responses? We provide evidence that intranasal oxytocin administration not only reduced, it in fact eliminated negative social behavior towards out-group members. These effects were specifically evident in individuals with low dispositional empathy (Bartz et al., 2011). Moreover, our neurophysiological results suggest a potential explanation for oxytocin's effects: the reducing of out-group gains could be predicted by the temporal occurrences of two neurophysiological processes elicited by the valuation of out-group gains: whereas the longer occurrence of a negative valuations-related process (microstate C) was associated with a stronger reduction in out-group gains, the longer occurrence of a positive valuations-related process (microstate D) was associated with a weaker reduction thereof. Notably, oxytocin replaced the negative-valuations related process occurring in participants with low empathy in the placebo condition by the positive valuations-related process. Thus, oxytocin seemed to enable individuals to positively value out-group gains, whereas in the placebo condition, out-group gains were valued as personal losses. Hence, oxytocin administration may eliminate negative social behavior towards disliked out-group rivals via more empathic, positive valuations.

If oxytocin enabled more empathic, positive valuations of out-group gains, one might wonder why it did not affect behavior in response to in-group losses, in-group gains, or out-group losses. Several studies have reported increased empathy for both positive and negative outcomes concerning in-group members (Cikara et al., 2011a). One could thus speculate that being empathic towards in-group members represents the default response that does not require strong empathic ability. This speculation is supported by our finding that, in participants of the placebo condition, self-reported empathic ability did affect behavior in response to out-group gains ($r[41] = 0.40$, $p = 0.009$), but not in response to in-group gains ($r[41] = -0.11$, $p > 0.20$), in-group losses ($r[41] = -0.25$, $p = 0.10$), or out-group losses ($r[41] = 0.27$, $p = 0.077$). In other words, reacting empathically to in-group gains, in-group losses, and out-group losses (which most people do, as revealed in our averaged behavioral data) does not seem to require strong empathic ability, yet granting out-group members their gains does, thus explaining why oxytocin affects behavior only in this condition. In sum, our findings suggest that oxytocin might act as a neuroendocrine mediator of empathic responses that "buffers" negative social behavior. Future studies should also include a direct subjective measure of empathic responses to solidify the assumption that the observed reduction in out-group gains is due to oxytocin increasing empathy or due to modulating other processes possibly also correlated with dispositional empathy (e.g., increasing inequity aversion, reducing envy). These findings might also be relevant for the treatment of clinical populations suffering from empathy deficits, pointing to the potential use of oxytocin in combination with psychotherapy for disorders entailing social impairments (Meyer-Lindenberg et al., 2011).

Our results also provide new implications for clarifying oxytocin's controversially discussed role in inter-group behavior (Chen et al., 2011). Previous studies took a highly controlled laboratory approach by studying oxytocin's effects on behavior in interactions between members of experimentally created social groups ("minimal groups") and under conditions in which the participants could mutually affect their resources ("second-party"). Their bottom line is that oxytocin increases prosocial behavior towards minimal in-groups but has no effects on behavior towards minimal out-groups as long as those groups posed no threat (De Dreu and Kret, 2016). As minimal groups have no history of previous interactions and thus gain significance only during the experimental procedure, such research indicates that oxytocin promotes group-interested behavior within groups while they are forming and whose members' self-interests are mutually dependent. But do such findings transfer to third-party behavior, which is free of self-interests, in interaction between members of natural social groups with a history of previous intense and conflicting interactions? Existing evidence has suggested that oxytocin increases preferential cognitive processing of natural in-group members (Sheng et al., 2013), but differences in inter-group cognition do not necessarily transfer to differences in inter-group behavior (Amodio, 2014). Furthermore, a recent study indicated that oxytocin's effects on the inter-group behavior of third-parties differ from those on the behavior of second-parties (Daughters et al., 2017), but as that study used minimal groups, it remains unknown how oxytocin affects third-party behavior in naturalistic inter-group conflicts. Our data fills this crucial knowledge gap by demonstrating that oxytocin eliminates third-parties' negative social behavior toward natural out-group members, but does not increase prosocial behavior towards natural in-group members whose affiliative bonds are already established and with whom they share no mutual interests.

From an evolutionary perspective, the ancient brain oxytocin system orchestrates a set of brain systems to ensure various species-preserving behaviors, including parturition, lactation, and parental behavior which might, if

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the offspring are threatened, also include maternal defense behavior (see De Jong & Neumann, 2018, for a critical discussion of the controversial findings on oxytocin's role in aggressive behavior). Under all these conditions, the avoidance of social conflicts and the ability to exhibit social approach behavior is highly relevant to ensuring survival of the young (Rilling and Young, 2014). An exogenous increase in brain oxytocin levels via intranasal administration might mimic an evolutionarily well-conserved neurophysiological response pattern. Our data suggest that increased brain oxytocin reduced negative social behavior in a social context. This interpretation is in line with recent behavioral findings showing that oxytocin administration increases prosocial donation behavior toward disadvantaged refugees (Marsh et al., 2017). As these refugees represent out-group members with low status and lacking any common history of conflict with the participants, one might speculate that they elicited empathic reactions in most participants that were reinforced by oxytocin (see also Influs et al., 2018), an interpretation corroborated by our study's neurophysiological evidence.

The last 15 years have witnessed enormous growth in the amount of research demonstrating oxytocin's key role in regulating human social behavior. Future research requires nuanced, evolutionarily informed investigations of oxytocin's effects on behavior in naturalistic social settings while considering the specific socio-cognitive processes mediating its behavioral effects. The spatio-temporal analysis of electrophysiological brain activity applied in this study provides a window into the socio-cognitive processes that brain oxytocin changes: oxytocin eliminated negative social behavior towards out-group members in naturalistic intergroup conflict by modulating valuation-related processing. This finding also illustrates how electrical neuroimaging can improve our understanding of how and when oxytocin changes the temporal dynamics of social cognition and behavior, a rather new research field with great potential to reveal the still not well understood neurophysiological mechanisms of oxytocin's effects in humans (Schiller et al., 2019b; Singh et al., 2016; Waller et al., 2015; Wynn et al., 2019). Our results may inspire fertile research employing multiple methodologies combining electrical and metabolic neuroimaging with the intranasal administration of neuropeptides in naturalistic social settings. Such research has great potential to deepen both our knowledge of hormonal effects on neural processing and our understanding of the neurobiological mechanisms of human social behavior.

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Author contributions

B.S., G.D., and M.H. conceived the project and planned experiments, interpreted data, and wrote the manuscript. B.S. performed experiments and analyzed data.

Declaration of Competing Interest

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.12.109.

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