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Running title

Oxytocin modulates human communication

Authors

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Highlights

- **Oxytocin is known to play a crucial role in affiliative and social behaviors in mammals.**
- **This study contributes to our understanding of the neuro-endocrinology of social cognition by showing that oxytocin influences how humans share knowledge.**
- **We show that oxytocin administration drives individuals to generate more effective communicative signals, and to rapidly adjust those signals to what the addressee understands.**
- **We suggest that those effects are two instances of a fundamental oxytocinergic role in regulating exploration of cognitive models of the (social) environment.**

Abstract

Oxytocin is a neuropeptide known to influence how humans share material resources. Here we explore whether oxytocin influences how we share knowledge. We focus on two distinguishing features of human communication, namely the ability to select communicative signals that disambiguate the many-to-many mappings that exist between a signal's form and meaning, and adjustments of those signals to the presumed cognitive characteristics of the addressee ("audience design"). Fifty-five males participated in a randomized, double-blind, placebo controlled experiment involving the intranasal administration of oxytocin. The participants produced novel non-verbal communicative signals towards two different addressees, an adult or a child, in an experimentally-controlled live interactive setting. We found that oxytocin administration drives participants to generate signals of higher referential quality, i.e. signals that disambiguate more communicative problems; and to rapidly adjust those communicative signals to what the addressee understands. The combined effects of oxytocin on referential quality and audience design fit with the notion that oxytocin administration leads participants to explore more pervasively behaviors that can convey their intention, and diverse models of the addressees. These findings suggest that, besides affecting prosocial drive and salience of social cues, oxytocin influences how we share knowledge by promoting cognitive exploration.

Keywords: oxytocin; human communication; exploratory behavior; audience design; social interaction

1. Introduction

Oxytocin is a neuromodulatory hormone involved in controlling the physiology of reproductive behavior across several species. In social mammals, oxytocin is involved in social and affiliative behaviors, reducing social anxiety and increasing sensitivity to social cues. In humans, administration of this hormone influences a number of cognitive processes involving other agents, enhancing mental-states recognition and material resource-sharing with familiar partners (Declerck, Boone, & Kiyonari, 2010; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Kosfield & Heinrich, 2005). Humans routinely share non-material resources such as knowledge, but in an evolutionarily unusual manner. This resource is not simply broadcasted, but shared by generating signals out of the manifold possibilities by which one can express meaning [“referential flexibility”; (Levinson, 2006; Tomasello, Carpenter, Call, Behne, & Moll, 2005)]. Those signals are also continuously adjusted to the presumed characteristics of an addressee ["audience design"; (Bell, 1984; Brand, Baldwin, & Ashburn, 2002; Campisi & Ozyürek, 2013; Clark & Carlson, 1982; Clark & Murphy, 1982; Levinson, 2006; Newman-Norlund et al., 2009; Snow & Ferguson, 1977; Tomasello, 2008)]. These two distinctive features of human knowledge-sharing have been extensively described (Brennan, Galati, & Kuhlen, 2010; Clark, 1996; Galantucci & Garrod, 2011), but mechanistic insights on their neurobiological implementation are lacking. Given oxytocin’s ability to influence motivational and cognitive processes involving material resource sharing with other agents, here we explore whether and how this neuropeptide modulates those two distinctive features of human knowledge-sharing. We focus on the generation of signals with new meanings that minimize referential ambiguity, in order to capture “referential quality”, i.e. how well people solve the referential flexibility problem. We also focus on the adjustment of those signals to the presumed characteristics of an addressee, in order to capture audience design.

We consider three non-mutually exclusive possibilities grounded on different models of oxytocin function. Those predictions are tested by quantifying the production of novel communicative

behaviors during live interactions with an adult and a child addressee. First, if oxytocin operates by unconditionally enhancing prosociality (Kosfield & Heinrich, 2005; Zak, Stanton, & Ahmadi, 2007), then oxytocin administration should have a directional effect on audience design, i.e. enhancing the spontaneous adjustments that adult communicators produce when directing their speech, gestures, and accompanying motions towards child addressees (Brand et al., 2002; Campisi & Ozyürek, 2013; Newman-Norlund et al., 2009; Stolk, Hunnius, Bekkering, & Toni, 2013). Second, if oxytocin increases sensitivity to social cues (Bartz, Zaki, Bolger, & Ochsner, 2011; Shamay-Tsoory & Abu-Akel, 2016), then oxytocin administration should have a different effect on audience design, i.e. leading interlocutors to make their communicative behavior as emphatic and precise as required by the cues reflecting the level of comprehension of the addressee (Grice, 1969; Newman-Norlund et al., 2009). Third, if the social anxiolytic effects of oxytocin promote social exploration (Bale, Davis, Auger, Dorsa, & McCarthy, 2001; Chang & Platt, 2014; Ring et al., 2006; Windle, Shanks, Lightman, & Ingram, 1997), then oxytocin administration should influence both referential quality and audience design. Namely, oxytocin could drive interlocutors to explore more pervasively possible behaviors for conveying their intention (De Dreu et al., 2013; Hare, Melis, Woods, Hastings, & Wrangham, 2007), leading them to generate signals that solve a larger portion of a communicative challenge. By the same token, oxytocin could also drive interlocutors to explore diverse models of the addressees, leading to rapid communicative adjustments to the level of comprehension of the addressee.

2. Materials and Methods

2.1. Participants

Fifty-eight right-handed healthy males (mean age = 22, SD = 3 years) participated in this study. A power analysis (power = 80%) based on the medium-large effect size (d=0.5 and d=0.7) of previous studies assessing the effects of oxytocin intervention on human social behavior (Kosfield & Heinrich, 2005; Zak et al., 2007) indicated that a sample size between N=26 and N=49 would be adequate to assess the presence of an effect of oxytocin. Although those studies were not addressing exactly the

same question studied in this report, those data were the best available estimate for performing a power analysis during the planning of this study, leading us to consider a sample size of N=40 for each of the two groups. However, recruitment rate prevented us from completing the full sample within the time available for this study. Participants gave written informed consent according to the institutional guidelines of the local ethics committee (Committee on Research Involving Human Subjects, Region Arnhem-Nijmegen, the Netherlands; study protocol registration number 37419.091.11) and were compensated by study credits or at a rate of €10 per hour of participation in the experiment, and €10 for taking the drug/placebo.

2.1.1. Participant recruitment and inclusion

Participants were recruited by means of leaflets on various places at Radboud University Nijmegen, via mailings to the participant pool of the Max Planck Institute for Psycholinguistics, as well as via a digital university-wide participant-recruitment system. The advertisement asked for participation in an MEG and fMRI experiment on the effect of a natural substance or a placebo on communication with others (imaging findings published in De Boer, 2017; Radke et al., 2017; Ye, Stolk, Toni, & Hagoort, 2016). Inclusion criteria mentioned in the advertisement were: sex (only males), age (18-35), dexterity (right-handed), no metal in the body, no claustrophobia, no use of medicine (except for normal use of paracetamol), no use of drugs or alcohol, no working at night (> 3 days per month) or intercontinental flights. Furthermore, they were asked to refrain from caffeine, alcohol or cigarettes 24 hours prior to research and from food or drink (except water) 2 hours prior to research. When males were interested in participation, they contacted the experimenters via e-mail, received additional information about the study and a pre-screen questionnaire. Additional inclusion criteria were that participants were native speakers of Dutch, had no psychiatric, endocrine, or neurological disorders, abused no alcohol or drug, smoked no more than five cigarettes per day and did not participate in other pharmacological studies and did not donate blood within the last two months. A total number of 89 participants were assessed for eligibility, of which 31 were excluded in the

enrolment phase (see also Fig. 1). In the analysis phase, three participants were excluded. One did not seem to understand the instructions of the task (<20% of trials correct), one did not believe our manipulation indexing communicative adjustment and for one participant data acquisition failed.

2.2. Pharmacological intervention

Upon arrival at the Donders Centre for Cognitive Neuroimaging (Nijmegen, The Netherlands) in the afternoon, participants self-administered a nasal spray (3 puffs per nostril each with a dose of 4IU) containing either 24IU of oxytocin (Syntocinon, Novartis, Basel, Switzerland; N = 28) or a saline solution (a placebo; N = 27). At the end of the experiment, participants were asked to make an attempt to identify the intervention and dosage of the substance they had received, using a 7-points Likert scale (substance: from -3 "I definitely received a placebo" to +3 "I definitely received a drug"; dosage: from -3 "I definitely received a low dose" to +3 "I definitely received a high dose"). Participants in the oxytocin and placebo group provided similar guesses on the identity or dosage of the substance received (substance: $t(53) = -0.22$, $p = 0.8$; dosage: $t(45) = 0.33$, $p = 0.7$).

2.3. Experimental design and procedure

This study was a double-blind, randomized, placebo-controlled between-group design. Given that this study is focused on the generation of *novel* communicative behaviours ~~("referential flexibility")~~, we explicitly chose to sample participants only once. This choice is meant to improve the specificity of the findings (e.g. avoiding confounds related to learning effects), at the cost of the lower statistical power afforded by a between-subjects design. We verified that the two groups consisted of participants matched along study-relevant dimensions by measuring a number of physiological and psychological indexes (e.g. cortisol, testosterone, social traits; see *"6. Supplementary information"*).

Following drug administration, participants were given written task instructions, and familiarized themselves with the mechanics of a game-controller by completing three practice trials. Execution of

the communicative task (see "*2.4. Communicative interactions")* started 45 minutes after drug administration, and lasted about 30 minutes. Immediately afterwards, participants filled out a questionnaire on the characteristics of the addressees [(Newman-Norlund et al., 2009); Fig. S1]. Data reported here were collected as part of a larger study on the effect of oxytocin on social behavior [see (De Boer, 2017; Radke et al., 2017; Ye et al., 2016)].

2.4. Communicative interactions

The communicative behavior of the participants was quantified with an experimentally controlled communicative task ["Tacit Communication Game"; (Newman-Norlund et al., 2009; Stolk, D'Imperio, Di Pellegrino, & Toni, 2015; Stolk, Hunnius, et al., 2013)]. On each trial, the joint goal of a Communicator-Addressee pair was to collect a target from a digital game board. Only the Communicator knew the target's location, and only the Addressee could collect the target, leading the Communicator to select behaviors that the Addressee could interpret for understanding where the object was located (Target-location; Fig. 2A). In this game, Communicators and Addressees converge on novel signals from an open-ended set of possibilities, such that different pairs use different signals to convey the same meaning (De Ruiter et al., 2010; Stolk et al., 2014; Stolk, Verhagen, et al., 2013). This variation in communicative signals makes it possible to test whether oxytocin administration influences the referential quality of the signals generated by the participants (see *"2.4.1. Referential quality";* Fig. 2A). The experimental circumstances also afford a stringent test on whether oxytocin administration influences prosocial behavior and how communicative behavior is adjusted to implied knowledge about the Addressee, other factors being kept equal. This was achieved by informing each participant that he would be playing the communicative game with two different Addressees, either an *Adult* or a *Child*, sitting in separate rooms with their own monitors to see the Communicator's token moving on the game board. In reality, a confederate blindly performed the role of both *Adult* and *Child* Addressee such that the two Addressees differed only in terms of the Communicator's expectations about their cognitive abilities. Previous work has repeatedly shown that

participants spontaneously generate communicatively specific adjustments towards a younger Addressee (Newman-Norlund et al., 2009; Stolk et al., 2015; Stolk, Hunnius, et al., 2013). This experiment exploits those communicative adjustments as a quantitative index of audience design (see *"2.4.2. Audience design";* Fig. 2B).

2.4.1. Referential quality

An experimenter familiar with this communicative task (MdB) performed trial-by-trial classification of the communicative signals used by the participants during the task (2750 trials), while remaining blind to which substance (*Oxytocin* or *Placebo*) was received by which participant. A communicative signal was defined as a sequence of movements with which a Communicator described the Target-field and/or the Target-location. Communicative behaviors (e.g. pausing on a field to indicate that it contains the Target-location) were distinguished from instrumental behaviors (e.g. moving back to the nest swiftly) by the degree from which they deviated from optimal behavior should the behavior have been executed to fulfill an instrumental goal (Sperber & Wilson, 1986). We considered two types of detours. The first was a deviation on the time spent on a field; a behavior functionally equivalent to the use of prosodic markers during verbal communication: e.g. spending a long time in a field serves no instrumental purpose in the game. The second detour was a deviation in the path towards a field: taking a detour to reach a field is suboptimal, hence the detour itself can be considered communicative. In some trials, it was unclear whether a movement or a pause was communicative or instrumental. Behavior was coded as communicative if it occurred consistently in more than two subsequent trials. To achieve a balance between identifying an interpretable (i.e. limited) number of signal types and capturing the considerable inter-trial and inter-subject variability, we considered five broad categories: *Field-Only*, *Target-Anchor*, *Nest-Anchor*, *Draw-On-Board* and a fifth category *Miscellaneous*. In order to assess inter-rater-reliability, a second independent rater (RL) categorized the communicative behavior of six random participants (three from each group), remaining blind to

the group status of each participant. This additional categorization covered >10% of the total number of trials coded by the first rater (MdB).

The five categories of communicative behaviors have different referential quality, meaning that they vary in how successfully different target locations can be indicated. For instance, moving the token bird to, and spending time on the field containing the target (i.e. the Target-field; indicated as one of the nine squares in Fig. 2A and represented by Roman numbers in Fig. 3A), is a signal adequate to indicate the Target-field to the Addressee, but insufficient to disambiguate between multiple potential locations within that field (i.e. Target-locations, represented with white circles in Fig. 2A and with Arabic numbers in Fig. 3A; *Field-Only* signal; see Video 1 for an example trial performed by one of the Communicator-Addressee pairs). Therefore, only 20% of the Target-locations (3 out of the 15 potential Target-locations) could be indicated with this signal. Accordingly, participants used systematic detours into their movement trajectories and pauses in their movements to suggest the precise Target-location within the Target-field. Those detours might appear intuitive and unequivocal. In fact, those signals need to be generated ex-novo, and understood by the Addressee. This generative element requires complex relational reasoning (Blokpoel, 2015), involving the search for an analogous overlap between the representational structures of the Target-location and of the movements (Gentner, 1983). The Target-location could be indicated by a detour consisting of a movement to the field adjacent to the target (*Target-Anchor* signal). With this signal 80% of the Target-locations could be indicated (Fig. 3A, Video 2). The *Nest-Anchor* signal suggested the relevant Target-location with a visit to a field adjacent to the central field (nest): The spatial relation between the visited field and the nest was isomorphic to the spatial relation between the Target-location and the center of the Target-field. With this signal *every* potential Target-location could be disambiguated (Fig. 3A; Video 3). *Draw-On-Board* signals were identified as such when a participant represented the configuration of the potential Target-locations in the Target-field with movements across the whole game board. With this signal *every* potential Target-location could be disambiguated (Fig. 3A; Video

4). *Miscellaneous* signals were signals that did not correspond to any of the categories mentioned above.

2.4.2. Audience Design

From previous experiments, we learned that *time on Target-field* can be used as an index of audience design behavior in this particular game. More precisely, *time on Target-Field* was defined as the time interval between entering the Target-field and the first button-press within that field. In case the Target-field was visited multiple times within a trial, we have chosen as in previous studies (Newman-Norlund et al., 2009; Stolk et al., 2015; Stolk, Hunnius, et al., 2013; Stolk, Verhagen, et al., 2013) the mean *time on Target-field* as a conservative measure of this index of audience design (see *"6.1.3. Additional behavioral data analyses"* for control analyses of the effect of DRUG and ADDRESSEE on *planning time*, *movement time*, number of fields visited during one signal (*number of moves*) and the *ratio of time on Target-field and time on Non-target-field*).

We considered the effect of two additional factors on the *time on Target-field* index: time-varying adjustments to the Addressees over the course of the experiment and adjustments following an error. First, we considered whether *Oxytocin* and *Placebo* would differentially influence adjustments to the presumed Addressee over the course of the experiment. Previous work has shown that participants reduced their *time on Target-field* as they experienced statistically matched behavior across the *Child* and *Adult* Addressees, that is, the adult confederate was blind to which of the two roles s/he was playing and therefore behaved in a similar way for both roles [see Table S2; (Newman-Norlund et al., 2009; Stolk et al., 2015; Stolk, Hunnius, et al., 2013)]. We tested whether the communicative behavior evoked in the first block (first five trials) spent with either one of the two Addressees differed from the performance evoked during the remaining trials (last twenty trials) according to the formula: *time on Target-field*$_{\text{Adjustment}}$ = [*time on Target-field*(*Child*$_j$) – *time on Target-field*(*Adult*$_j$)]/*time on Target-field*(*Adult*$_j$), with *j* = trials 1 to 5 or trials 6 to 25. Second, we considered whether *Oxytocin* and

Placebo would differentially influence trial-by-trial adjustments to a communicative error, according to the formula: *time on Target-field*$_{\text{Post-error}}$ = [*time on Target-field*(trial$_{i+1}$) – *time on Target-field*(trial$_i$)]/*time on Target-field*(trial$_i$), with *i* = an incorrect trial. This index did not include trials where the Target-field was not visited, the first trial of the experiment, trials where trial$_{i-1}$ involved a change in Addressee, or trials where trial $_{i+1}$ or trial$_{i-1}$ was also erroneous.

Each Communicator-Addressee pair completed fifty trials, subdivided in ten blocks of five trials (Fig. 1B; total testing time: ~30 min). The sequences of communicative problems and the order of presentation of the presumed Addressees (starting with either *Adult* or *Child*) were counter-balanced between participants. The experiment was programmed using Presentation® software (Neurobehavioral Systems, Albany, CA, USA) on a Windows XP personal computer, and performed in a magnetoencephalograph (CTF275, VSM MedTech Ltd, Coquitlam, BC, Canada) for measuring neural activity during the communicative game (neural data will be described in a separate report).

2.5. Statistical Analysis

2.5.1. *Referential quality*

The statistical model employed to test our index of referential flexibility consisted of the percentages of occurrence of the five types of communicative signals (*Field-Only*, *Target-Anchor*, *Nest-Anchor*, *Draw-Board* and *Miscellaneous*) for each participant. These numbers were entered as dependent variables in a multivariate ANOVA. As far as the authors are aware, it is technically impossible to perform a 2x2 MANOVA with a between-subject (DRUG: *Placebo, Oxytocin*) and within-subject factor (ADDRESSEE: *Adult, Child*), Therefore, two separate MANOVAs were performed with as dependent variables the percentages of occurrence of the five types of communicative signal: one with the factor DRUG and one with the factor ADDRESSEE. Several post-hoc tests were conducted: five with a between-subject factor DRUG for each of the communicative signal types and two with a within-subject factor ADDRESSEE for the *Oxytocin* and *Placebo* group.

2.5.2. *Audience Design*

The statistical model employed to test our index of audience design used trial level observations and assessed the effects of two experimental manipulations and their interaction on the *time on Target-field*. Again, we tested on the within-subject factor (ADDRESSEE) and the between subject factor (DRUG). To control for un-specific effects due to variation in movement speed over the course of the experiment, the analysis of *time on Target-field* considered the time participants spent moving around fields that did not include the target (*time on Non-target-field*) as a nuisance covariate. Trials during which participants did not visit a Non-target-field (such as when indicating $target_9$ on $field_{VI}$) were excluded, given that those trials prevented estimating the effect of general movement speed. Mixed linear regression models were estimated in R (www.R-project.org, Vienna, Austria; lmer function of the lme4 package, version 1.0-4). The repeated-measures nature of the data within participants was taken into account by considering participant as a random factor and ADDRESSEE as its random slope.

A test for time-varying adjustments on the parameter *time on Target-field* towards the Addressees was implemented as a Mixed linear model with factors DRUG (*Oxytocin*, *Placebo*) and BLOCK (*Early*, *Late*). Given the limited power of the sample, a post-hoc non-parametric One-Sample Wilcoxon-Signed Rank test was performed to test if participants in the *Oxytocin* group made communicative adjustments for the Addressee at the beginning of the experiment. There were only 314 trials suitable for analysis of trial-by-trial adjustments to a communicative error. Given the limited power afforded by this sample, we focused this analysis on testing whether the group median (*Oxytocin*, *Placebo*) of post-error adjustment was different from zero with a nonparametric One-Sample Wilcoxon-Signed Rank test.

3. Results

The first finding of this study pertains to oxytocin-related variations in the referential quality of the communicative behaviors generated by the participants (~~capturing referential flexibility~~; Fig. 3B; for statistics see Table S3A).

Communicators in the *Oxytocin* and *Placebo* group composed communicative signals with different referential quality (main effect of DRUG: $F(4,50) = 3.88$, $p = 0.008$, $\eta^2 = 0.237$) while producing communicative signals of comparable referential quality for the two presumed Addressees (main effect of ADDRESSEE: $F(4,50) = 1.07$, $p = 0.373$, $\eta^2 = 0.080$; Fig. 3B). Communicators receiving *Placebo* preferentially used the *Field-Only* and *Target-Anchor* signals (see Video 1 and 2; *Field-Only*: 36 ± 13% of all trials; main effect of DRUG; *Target-Anchor*: 37 ± 27% of all trials; main effect of DRUG; Fig. 3B and for statistics Table S3B). With these signals, respectively 20 and 80% of the Target-locations could be indicated unambiguously. Communicators receiving *Oxytocin* preferentially used the *Nest-Anchor* signal (25% ± 33% of all trials; main effect of DRUG; Fig. 3B and for statistics see Table S3B) with which all of the potential Target-locations could be indicated unambiguously. The majority of the participants employed these signals from the start of the experiment onwards, already before they encountered communicative problems that could not be disambiguated by signals with weaker referential quality (*Field-Only* and *Target-Anchor* signals). The preferential use of the *Nest-Anchor* signal was not influenced by which Addressee the signal was directed to (no main effect of ADDRESSEE for any of the signal types, see Table S3B). Neither did the preferential use of the *Nest-Anchor* signal alter the overall dynamics of the movements involved in the signals (*relative time on Target-field and Non-target-field*; no main effect of DRUG: for statistics see Table S5). The two raters (MdB and RL) coded 87.3% of the trials in the same manner (intraclass correlation: 0.83; Kappa: 79.50). Most of the coding differences pertain to uncertainties between the *Field-Only* strategy and the *Target-Anchor* strategy. The magnitude and content of those residual differences makes it unlikely

that this difference influences the main finding of the study. More precisely, there was limited if any inter-rater confusion between *Nest-Anchor* and *Target-Anchor* strategies, i.e. the two strategies affected by the *Oxytocin* intervention.

The second finding of this study pertains to the oxytocinergic modulation of the magnitude of systematic variations in movement time on the field containing the target object as a function of the presumed abilities of the Addressees, an index of audience design (Fig. 4). Namely, Communicators in the *Placebo* group spent longer time holding their token on the Target-field when they believed to be communicating with a *Child* than with an *Adult* Addressee. In contrast, Communicators in the *Oxytocin* group did not differentiate between the two presumed Addressees (DRUG by ADDRESSEE interaction on the *time on Target-field* parameter: Fig. 4A; main effect of ADDRESSEE for *Placebo*; *Child*: 1504 ± 977ms, *Adult*: 1417 ± 951ms; no main effect of ADDRESSEE for *Oxytocin*; *Child*: 1447 ± 997ms, *Adult*: 1436 ± 1006ms; see Table S4 for statistics).

Additional observations indicate that the lack of communicative adjustments induced by *Oxytocin* administration (Fig. 4A) was not due to negligence of the Addressees' presumed abilities. Namely, participants receiving *Oxytocin* attributed different ages and abilities to the two presumed Addressees, and their attributions did not differ from those made by the *Placebo* group (see Table S2). Participants receiving *Oxytocin* communicated as effectively as participants receiving *Placebo* (69% success, chance level: 7%; Fig. S2B), and displayed communicative adjustments to the presumed abilities of the Addressees in the first few trials of the experiment (Fig. 4B; One-Sample Wilcoxon Signed Rank Test of *time on Target-field*: $p = 0.005$). Furthermore, *Oxytocin* administration did not blunt participants' motivation to generate communicative adjustments when the performance of the Addressee required it. In trials that followed a communicative error, participants receiving *Oxytocin* made more emphatic communicative movements, spending more time on the Target-field than in trials following a successful communicative interaction (One-Sample Wilcoxon Signed Rank Test of

time on Target-field: p = 0.012; Fig. 4C). Participants receiving Placebo did not make these post-error adjustments (One-Sample Wilcoxon Signed Rank Test of *time on Target-field*: p = 0.662).

Given the raising concerns on limited statistical power and effect size inflation of oxytocin studies (Walum, Waldman, & Young, 2016), the statistical inferences of this study were verified by bootstrapping the parameter estimates of the relevant statistics, thus providing statistical inferences independent from an assumed reference distribution. Concerning the referential quality of the communicative signals, we have assessed the reliability of this statistical inference by resampling the statistical metric of the MANOVA (Pillai's trace), using the sample function of the R base package. By calculating the proportion of resampled Pillai's trace values greater than or equal to the observed Pillai's trace value, we could provide a statistical inference independent from an assumed reference distribution. This statistical analysis shows that 99.75% of the resampled Pillai's trace values had a value above the observed Pillai's value of 0.024, corresponding to a p-value of 0.0025. Concerning the communicative adjustments, we have assessed the reliability of this statistical inference by bootstrapping the parameter estimates of the mixed-linear models using the bootMer function of the lme4 R package. By calculating the proportion of bootstrapped parameter estimates greater than or equal to the observed parameter estimate, we could provide a statistical inference independent from an assumed reference distribution, using the PBmodcomp function of the pbkrtest package. This new statistical analysis confirms the presence of an interaction between DRUG and ADDRESSEE (p(PBtest) = 0.029), driven by the presence of an ADDRESSEE effect in the *Placebo* group (p(PBtest) = 0.013) and not in the *Oxytocin* group (p(PBtest) = 0.557).

4. Discussion

This study tests if and how oxytocin influences two distinctive features of human knowledge-sharing, the generation of novel signals able to disambiguate the many-to-many mappings that exist between a signal's form and meaning, and their adjustment to the presumed characteristics of an addressee (capturing "audience design"). The effects of oxytocin on those features have been quantified with an open-ended communication game, using nonverbal signals, over multiple live interactions with human interlocutors. There are two main findings. First, oxytocin drives participants to generate signals that provide an unambiguous solution for a larger portion of the problems afforded by the communicative challenge, as compared to the signals preferentially used by the placebo group. Second, oxytocin drives participants to rapidly adjust their communicative behavior to the actual level of understanding experienced in the addressees, and away from their expectations of the addressees' cognitive abilities. In the following section, we elaborate on how these findings relate to the three, non-mutually exclusive, models of this hormone's function described in the introduction, namely a prosocial-tendencies enhancing effect (Ditzen et al., 2009; Kosfield & Heinrich, 2005), a social-salience enhancing effect (Bartz et al., 2011; Lambert, Declerck, & Boone, 2014; Leknes et al., 2012; Shamay-Tsoory & Abu-Akel, 2016), or a social-exploration enhancing effect (Bale et al., 2001; Chang & Platt, 2014; Ring et al., 2006; Windle et al., 1997).

If oxytocin unconditionally enhance prosociality, then its administration should enhance the spontaneous adjustments that adult communicators produce when directing their behaviours towards child addressees. The current observations indicate that prosocial behaviours were not unconditionally enhanced, but tailored to the actual performance of the addressee. The rapid adaptation of the oxytocin group to the actual performance of the addressees could fit with the hypothesis that oxytocin enhances processing and saliency of social information (Bartz et al., 2011; Shamay-Tsoory & Abu-Akel, 2016). Namely, oxytocin could enhance processing of the communicative cues produced by the two putative addressees, driving the oxytocin group to rapidly adjust their

communicative behavior towards the statistically matched performance experienced in those addressees. However, both the hypotheses of enhanced prosociality and sensitivity to social cues might not parsimoniously explain the second oxytocinergic effect of this study, i.e. increased proficiency in generating a general-purpose solution of the possible communicative problems. Crucially, the oxytocin group generated signals able to disambiguate multiple communicative problems already before being confronted with communicative problems that could not be disambiguated by signals that were less general-purpose. All potential communicative problems were graphically available on the board to every participant, at every trial, from the onset of the experiment. Rather than reacting to a series of cues contingent to the current communicative problem and adjust their signals accordingly, the oxytocin group appeared to consider all potential possible communicative problems from the start.

We suggest that the two effects evoked by oxytocin in this study might be instances of an enhanced cognitive exploratory tendency induced by that neuropeptide. Namely, participants receiving oxytocin might be more inclined to explore alternative solutions to the communicative challenge, and rapidly re-evaluate the solution evoked by the current trial in the game. Similarly, participants receiving oxytocin might be more inclined to explore alternative models of the presumed characteristics of the addressees, and rapidly re-evaluate the model evoked by the photos of the addressees. In a similar way, it was found that oxytocin attenuated the N400 signal, a well-known electrophysiological marker of semantic integration, suggesting that oxytocin drives listeners to comprehend speech containing information that was incongruent with facts of the world, possibly by promoting the exploration of alternative world scenarios (Ye et al., 2016).

The notion of oxytocin promoting cognitive exploration in humans unifies a number of existing observations on the behavioral consequences and neurobiology of oxytocin administration. For instance, it has been shown that oxytocin promotes social exploration in other mammals, possibly by

boosting pre-existing social tendencies through a reduction in social anxiety (Chang & Platt, 2014; Radke, Roelofs, & De Bruijn, 2013). Reduced social anxiety can release the expression of cognitive competences that would be otherwise inhibited by competitive social dynamics (Burkart, Hrdy, & Van Schaik, 2009; Hare et al., 2007; Melis, Hare, & Tomasello, 2006), driving individuals to take more risky foraging decisions (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Kosfield & Heinrich, 2005; Lynn, Hoge, Fischer, Barrett, & Simon, 2014), an indication of enhanced exploratory tendencies. At the neurobiological level, several effects of oxytocin are mediated through the dopaminergic system (Rilling & Young, 2014; Skuse & Gallagher, 2009), a neuromodulator involved in controlling the exploration-exploitation trade-off (Humphries, Khamassi, & Gurney, 2012; Kayser, Mitchell, Weinstein, & Frank, 2015).

It remains to be seen whether the effects of enhanced cognitive exploration evoked by oxytocin in this study are specifically social. Although the live communicative interactions used in this study are prototypically social, it has been argued that solving referential communicative problems requires *domain-general* inferential capacities (Fodor, 1983, 2001; Sperber & Wilson, 1986), i.e. the ability to generate connections between different conceptual structures that make up potential solutions to the communicative problem (Blokpoel, 2015; Blokpoel et al., 2011; Stolk, Verhagen, et al., 2013; van Rooij et al., 2011). Furthermore, it has been argued that oxytocin might enhance risky economic decisions regardless of whether the risk has a social component (Lynn et al., 2014).

The communicative adjustments observed in this study can be interpreted in the light of a distinction that has been made in the field of experimental pragmatics, namely a distinction between “global” and “local” adaptations (Brennan et al., 2010). Global adaptations consist of responses to information about an interlocutor’s characteristics derived from prior personal experience, expectations, or stereotypes. Local adaptations consist of responses to cues that become available as the interaction unfolds. Given that those who received oxytocin first adjust to the expected abilities of the child

addressee at the onset of the game (global adaptation), and then adjust to the addressees' ongoing communicative behavior (local adaptations) more readily than those who received a placebo, one could infer that oxytocin preferentially influences local adaptations, without altering stereotyped knowledge (global adaptations).

4.1. Interpretational issues

A number of alternative interpretations are excluded by features of the experimental design and by empirical observations. First, the lack of communicative adjustments induced by oxytocin administration was not due to negligence of either the addressees' presumed abilities (Declerck et al., 2010), or the addressees' role. For instance, the oxytocin group might have considered the addressees as members of an out-group unworthy of investing "communicative resources" in (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011), or they might have solved the communicative problems as an individual puzzle (De Ruiter et al., 2010). In fact, the oxytocin group attributed different ages and cognitive abilities to the two presumed addressees, adjusted their communicative behavior to expectations about the cognitive abilities of the addressee in the first few trials of the experiment, and remained sensitive to the addressees' performance throughout the experiment, as indicated by their communicative adjustments following a communicative failure. Second, it might be argued that the current results cannot be generalized, since the task setting fails to capture the rapid multimodal nature of the interactions occurring during daily human communication. For instance, the roles of the communicator and addressee were fixed, and the communicator was allowed to respond only within a limited time window. Yet, even within the constraints of these experimental simplifications, it has been shown that this task captures communicatively relevant adjustments generated on the basis of on-going communicative behavior of an addressee and of the shared communicative history of a pair (De Ruiter et al., 2010; Stolk, Verhagen, et al., 2013). Furthermore, differently from several works focused on eliciting verbal reports when studying humans' ability to attribute mental states to other people (Aoki et al., 2014; Wade, Hoffmann, & Jenkins, 2015), this task

addresses this issue by considering participants' ability to influence the mental states of others through non-verbal behaviors, i.e. the referential quality of their spontaneously generated behaviours and communicative adjustment. This approach provides a sensitive index of communicative abilities, minimizing demands on cognitive control abilities collateral to the question at hand. However, the current experimental design does not allow for distinguishing between adaptations in audience design driven by better-than-expected performance of the presumed child addressee in comparison to the adult addressee, or by worse-than-expected performance of the presumed adult in comparison to the child addressee. Third, although the reported differences between the groups are likely to be related to the experimental manipulation, the possibility cannot be ruled out that non-treatment specific person-dependent factors contributed to the adopted communicative strategies. While no group differences were evident on the assessed physiological or psychological indices, the possibility cannot be ruled out that group differences in other factors, such as e.g. IQ, were related to the observed group differences in the adopted strategy.

The effect size reported in three independent studies that have already used the same task (Newman-Norlund et al., 2009; Stolk et al., 2015; Stolk, Hunnius, et al., 2013) indicate that the current study is adequately powered for detecting communicative adjustments in the placebo group (power (1-β) = 0.88). Given the lack of specific reports on oxytocin effects on metrics of human communication, the effects size found in this study can inform future replications or exploratory studies on this issue. Furthermore, given the raising concerns on limited statistical power and effect size inflation of oxytocin studies (Walum et al., 2016), the statistical inferences of this study were verified by bootstrapping the parameter estimates of the relevant statistics, thus providing statistical inferences independent from an assumed reference distribution.

Conclusion

This study provides evidence that oxytocin alters two distinguishing features of human knowledge sharing during live communicative interactions: namely the ability to provide solutions to the many-to-many mappings that exist between a signal's form and meaning ("referential quality"), and adjustments of those signals to the presumed cognitive characteristics of the addressee ("audience design"). Oxytocin enhances participants' ability to pro-actively consider possible communicative problems when generating a solution to a specific communicative challenge. Furthermore, oxytocin drives participants to rapidly adjust their behavior towards ongoing performance and away from prior expectations about those addressees. Taken together, these findings support the notion that besides affecting prosocial drive and salience of social cues, in humans, oxytocin might enhance exploratory tendencies of the potential communicative behaviors afforded by a (social) challenge.

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Figures

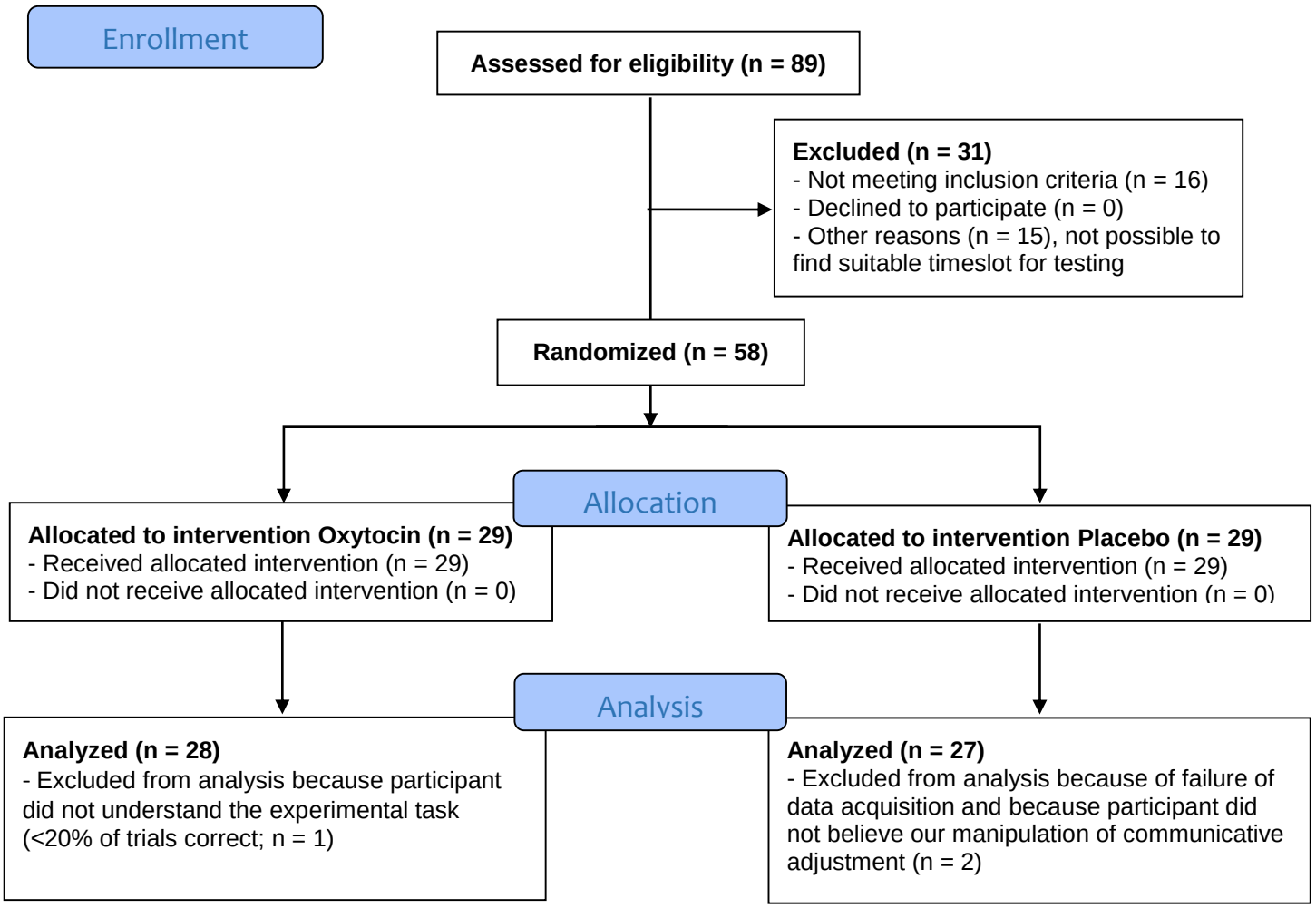

Figure 1. CONSORT flow diagram

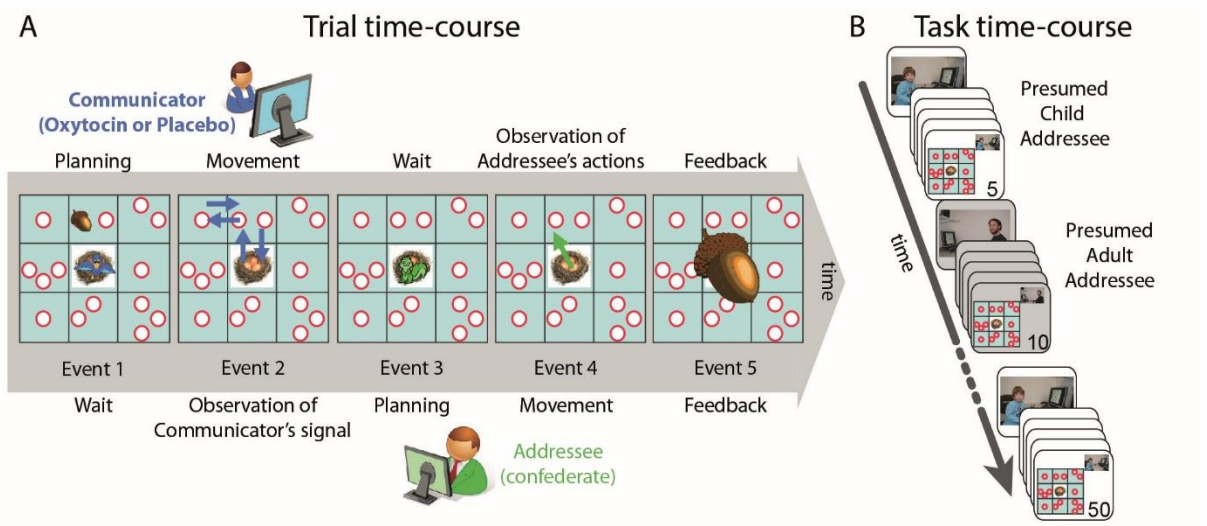

Figure 2. Participants communicated non-verbally with two different addressees, an adult or a child, in an experimentally-controlled live interactive setting. (A) Trial time-course. The task involved a Communicator (i.e. a participant receiving either an oxytocin or placebo nasal spray); and an Addressee (i.e. a confederate). The joint goal of the players was for the Communicator (in blue) to signal the location of the target (an acorn) and for the Addressee (in green) to retrieve the target on the basis of the signal generated by the Communicator. Communicator and Addressee could not see or hear one another, and thus could only communicate by movements of their tokens (a bird and a squirrel respectively). Their game-board consisted of 9 fields (3x3 squares in a grid lay-out) containing a total of 15 potential locations for the target (represented by the 15 white circles). Each trial consisted of 5 successive events. **Event 1**: The Communicator was provided with an unlimited amount of time to plan how to convey the acorn's location to the Addressee by movements on the board with the bird token. The acorn's location was visible only to the Communicator. **Event 2**: The Communicator moved his bird token across the board with a hand-held game controller (maximum movement time: 5 seconds). The movements of the bird token were visible to both Communicators and Addressees. Communicators could only make horizontal or vertical displacements over the center of each field and, as a consequence, the bird token could not be overlaid on some of the Target-locations. During the game, the Communicator had to generate novel signals to solve these spatial

disparities. Event 3: The Addressee planned on which of the 15 Target-locations he/she would move his/her squirrel token to retrieve the acorn. Event 4: The Addressee moved his or her squirrel token across the board. The Addressee's squirrel token was visible to both Communicator and Addressee and could be precisely overlaid on each Target-location. Event 5: Both players received feedback on their joint communicative success (correct or incorrect). (B) Task time-course. Communicators were made to believe they played with an *Adult* (represented by a photograph of a 25-year old male) or *Child* Addressee (represented by a photograph of a 5-year old boy), in alternation. In fact, an adult confederate performed both roles blindly, as s/he was not informed about the role s/he was currently playing, nor about the solutions of the communicative problems. This lead to statistically matched response times and performance on the task (Fig. S2), such that the Addressees only differed in terms of the Communicator's expectations about their cognitive abilities. Before the onset of each block of 5 trials, a digital photograph of the current presumed Addressee was presented on the screen. A smaller picture was shown in the top right corner during each trial to remind participants with whom they were playing [adapted from (Stolk, Hunnius, et al., 2013)].

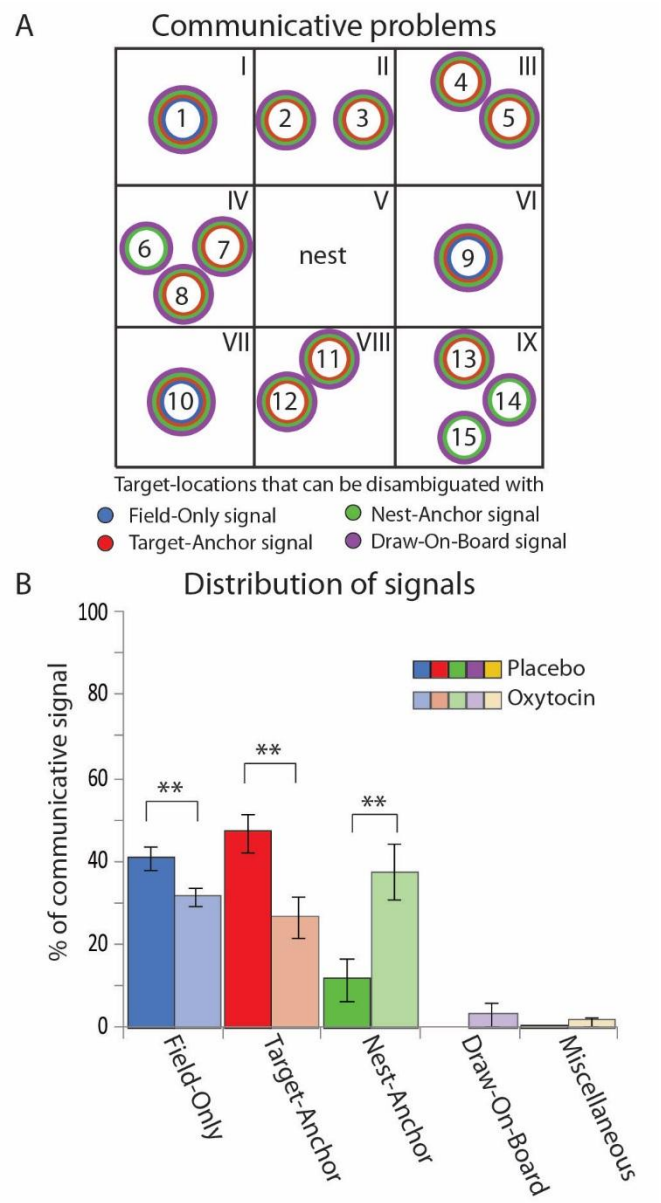

Figure 3. *Oxytocin* drives participants to generate communicative signals that disambiguate more communicative problems than the signals preferentially used by the *Placebo* group. (A) Communicative problems. Game board representing all 15 Target-locations (indicated with Arabic numbers) and the communicative signals by which their position could be disambiguated. With the *Field-Only* signal (in blue; see Video 1), the Communicator could not disambiguate between multiple Target-locations within one Target-field (the nine squares indicated with Roman numbers), as the bird token could only be overlaid in the center of a field but not on a specific Target-location. Thus, only 20% of Target-locations (3 out of 15 possible locations) could be disambiguated with the *Field-Only* signal. With the *Target-Anchor* signal (in red; see Video 2), the Target-location is indicated by making a detour in path

or time on the field adjacent to the Target-location. This approach cannot disambiguate Target-locations that had no *unique* adjacent field (Arabic numbers: 6, 14, and 15). Thus, only 80% of Target-locations could be disambiguated with the *Target-Anchor* signal. The *Nest-Anchor* signal (in green; see Video 3) and the *Draw-On-Board* signal (in purple; see Video 4) could unambiguously mark each of the 15 Target-locations. Communicators using these signals relied on an isomorphism between their movements from the nest and the spatial relation between the Target-location and the center of the Target-field. A fifth category ("*Miscellaneous*") included signals that could not be assigned to any of the previous categories. (B) Signal distribution. % of signals used across all 2750 trials (error bars represent ±1 SEM). Communicators in the *Placebo* group (darker colored histograms) preferentially used the *Field-Only* and *Target-Anchor* signal, whereas Communicators in the *Oxytocin* group (lighter colored histograms) preferentially used the *Nest-Anchor* signal (see Table S3 for statistical information).

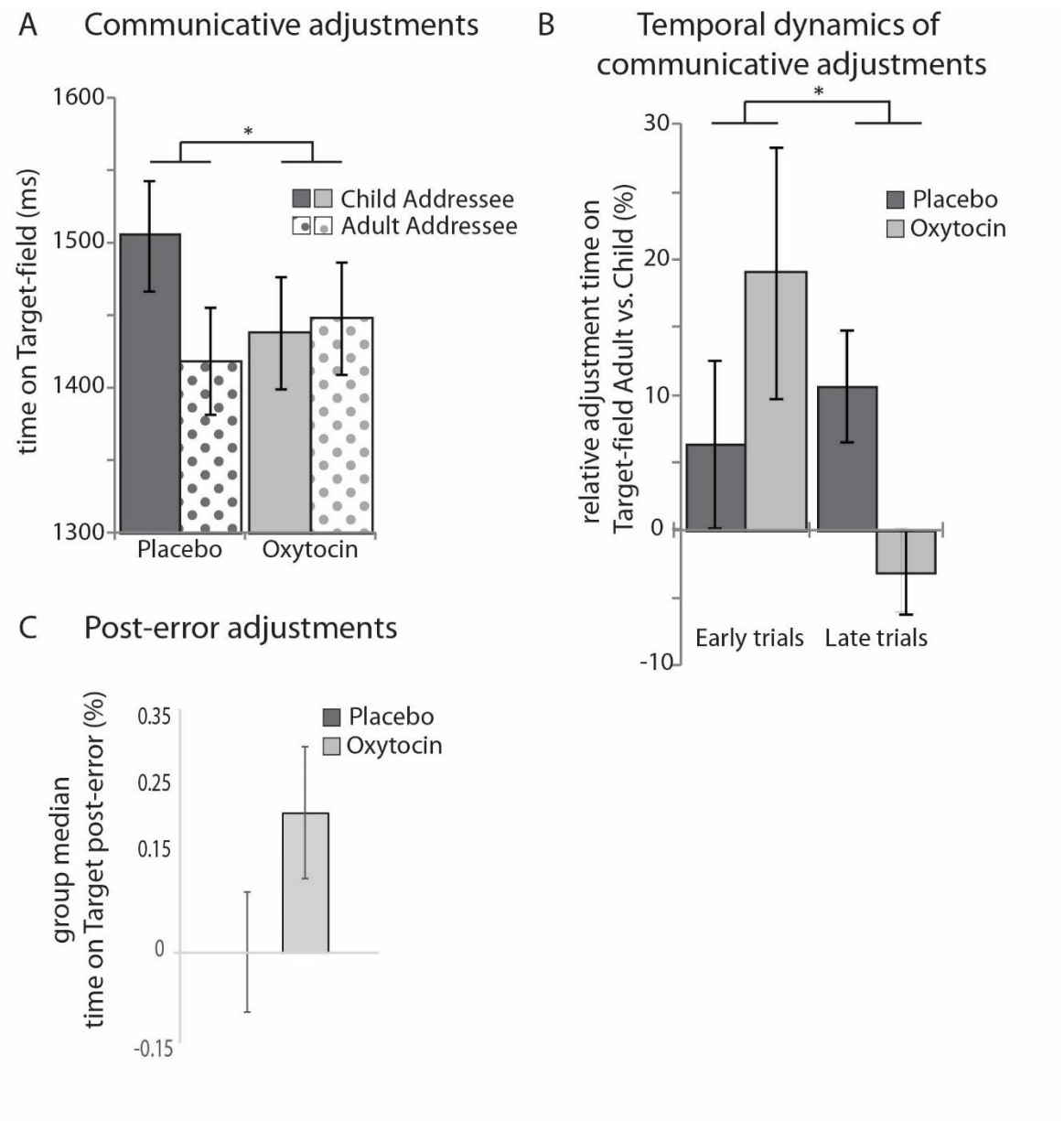

Figure 4. Oxytocin administration drives participants to rapidly adjust their communicative behavior to the actual level of understanding experienced in the Addressees and away from expectations about the cognitive abilities of the Addressee. (A) Communicative adjustments. Communicators who received a *Placebo* made communicative adjustments based on their expectations of the cognitive abilities of the Addressees, holding their token longer on the field where the target was located (*time on Target-Field*) when they believed to be communicating with a *Child* Addressee (filled histograms) than with an *Adult* Addressee (dotted histograms). Communicators who received *Oxytocin* held their token on the Target-field for time-intervals similar across Addressees (see Table S4 for statistical information;

error bars represent ±1 SEM). **(B) Temporal dynamics of communicative adjustments.** A post-hoc analysis revealed that participants who received *Oxytocin* (lighter histograms) made communicative adjustments based on expectations about the cognitive abilities of the Addressee in the first five trials, spending longer time on the Target-field when the Addressee was believed to be a *Child*. In the subsequent trials, this adjustment disappeared, and the communicative behavior of the *Oxytocin* group adapted to the statistically matched performance across Addressees (both the roles of the *Child* and *Adult* Addressee were performed by a confederate who was blind as to which of the two roles s/he was playing; DRUG by BLOCK interaction: no main effect of DRUG and BLOCK; see Table S4 for statistical information; error bars represent ±1 SEM). **(C). Post-error adjustments.** A post-hoc test revealed that participants who received oxytocin made adjustments after an error (Wilcoxon-Signed Rank test if the *Oxytocin* group median of the per-subject median of post-error adjustments is different from 0; $p = 0.012$), while those who received a placebo did not make these adjustments (Wilcoxon-Signed Rank test if the *Placebo* group median of the per-subject median of post-error adjustments is different from 0; $p = 0.662$; error bars represent ±1 SEM).