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Oxytocin Modulates Semantic Integration in Speech Comprehension

Zheng Ye[1,2], Arjen Stolk[1], Ivan Toni[1], and Peter Hagoort[1,3]

Abstract

■ Listeners interpret utterances by integrating information from multiple sources including word level semantics and world knowledge. When the semantics of an expression is inconsistent with their knowledge about the world, the listener may have to search through the conceptual space for alternative possible world scenarios that can make the expression more acceptable. Such cognitive exploration requires considerable computational resources and might depend on motivational factors. This study explores whether and how oxytocin, a neuropeptide known to influence social motivation by reducing social anxiety and enhancing affiliative tendencies, can modulate the integration of world knowledge and sentence meanings. The study used a between-participant double-blind randomized placebo-controlled design. Semantic integration, indexed with magnetoencephalography through the N400m marker, was quantified while 45 healthy male participants listened to sentences that were either congruent or incongruent with facts of the world, after receiving intranasally delivered oxytocin or placebo. Compared with congruent sentences, world knowledge incongruent sentences elicited a stronger N400m signal from the left inferior frontal and anterior temporal regions and medial pFC (the N400m effect) in the placebo group. Oxytocin administration significantly attenuated the N400m effect at both sensor and cortical source levels throughout the experiment, in a state-like manner. Additional electrophysiological markers suggest that the absence of the N400m effect in the oxytocin group is unlikely due to the lack of early sensory or semantic processing or a general downregulation of attention. These findings suggest that oxytocin drives listeners to resolve challenges of semantic integration, possibly by promoting the cognitive exploration of alternative possible world scenarios. ■

INTRODUCTION

Listeners use information from linguistic and extralinguistic sources to interpret utterances. In particular, the listener's knowledge about the world can be immediately retrieved from memory and integrated with word meanings during language comprehension (Hagoort & van Berkum, 2007; Jackendoff, 2002). When the semantics of an expression conflicts with his or her world knowledge, the listener may have to search through the conceptual space for alternative possible world scenarios that can make the expression more acceptable. Such cognitive exploration could be costly in terms of computational resources. The listener therefore would have to recruit mechanisms that determine how many resources to allocate for the search, that is, how deep and exhaustive the cognitive exploration should be. In this study, we investigated the motivational mechanisms that could modulate the integration of world knowledge and word meanings.

Oxytocin is a neuromodulatory hormone involved in the physiology of male and female reproductive behavior across species (Veening, de Jong, Waldinger, Korte, & Olivier, 2015). In mammals, oxytocin has also acquired a motivational role, promoting social exploration and interaction via reducing social anxiety (Ebitz, Watson, & Platt, 2013; Ring et al., 2006; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Bale, Davis, Auger, Dorsa, & McCarthy, 2001; Windle, Shanks, Lightman, & Ingram, 1997). In humans, the acute administration of this hormone enhances affiliative tendencies and financial cooperation (De Dreu & Kret, 2016; Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). Those effects have been linked to a role of oxytocin in enhancing the salience of social and affective cues and in facilitating the recognition of others' feelings (Hu et al., 2015; Aoki et al., 2014; Unkelbach, Guastella, & Forgas, 2008; Hollander et al., 2007). According to this cue enhancement account, oxytocin administration might emphasize the mismatch between expectations derived from word level semantics, world knowledge, and social cues of an utterance (Tesink et al., 2009, 2011). However, oxytocin has also been shown to reduce anxiety (Kumsta & Heinrichs, 2013). In this framework, oxytocin administration might enhance social tolerance and facilitate the listener in exploring the conceptual space of solutions to a social challenge, leading to a more comprehensive search for possible world scenarios that are coherent with the speaker's utterance.

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In this study, we assessed these possibilities by using a well-known electrophysiological marker of semantic integration (the N400) in combination with a pharmacological manipulation of oxytocin levels across participants. Semantic integration is marked by a centrally distributed negative potential ~400 msec in EEG and by a left-lateralized N400m in magnetoencephalography (MEG; for alternative views of the N400's functional significance, see Kutas & Federmeier, 2011). Compared with sentences that are congruent with listeners' world knowledge (e.g., "Dutch trains are yellow and very crowded"), sentences violating world knowledge (e.g., "Dutch trains are white and very crowded") trigger a stronger N400/N400m signal after the onset of critical words (the N400/N400m effect; see Wang et al., 2012; Hagoort, Hald, Bastiaansen, & Petersson, 2004). This effect originates from the left inferior frontal and medial prefrontal regions (Nieuwland, 2012; Menenti, Petersson, Scheeringa, & Hagoort, 2009; Tesink et al., 2009; Hagoort et al., 2004). Here, we combined MEG and the pragmatic violation paradigm to isolate the N400m effect during speech comprehension and to characterize cortical sources of the N400m effect in listeners receiving either intranasally delivered oxytocin (24 international units) or placebo. We expected a significant N400m effect for the world knowledge contrast (incongruent > congruent) in the placebo group. For the oxytocin group, we would expect an enhanced N400m effect, if oxytocin increases cue salience and emphasizes the mismatch between world knowledge and word meanings. In contrast, if oxytocin reduces social anxiety and promotes the cognitive exploration of possible world scenarios, we would expect an attenuated N400m effect.

METHODS

This study was approved by the local research ethics committee (Committee on Research Involving Human Subjects, Arnhem-Nijmegen Region, The Netherlands).

Participants

Forty-five healthy native Dutch speakers (all men, age range 18–32 years, mean age 22 years) participated after providing written informed consent. Women were not recruited for this study because oxytocin administration might induce labor or abortion. All participants were right-handed. None of them had a history of significant neurological or psychiatric disorder. They were either paid or given course credits.

Study Design and Oxytocin Administration

This study used a between-participant double-blind randomized placebo-controlled design. We used the between-participant design rather than a within-participant design to avoid learning-induced between-session differences. Participants were randomly distributed into the oxytocin group and the placebo group. The oxytocin group received 24 international units of oxytocin via a nasal spray (Syntocinon spray; Novartis, Basel, Switzerland). The placebo group received an identically labeled saline solution via a nasal spray (sodium chloride of 8 mg/mL and benzalkonium chloride of 0.1 mg/mL).

The two groups were well matched in age, hormone levels, and personality traits (see Table 1). Cortisol and testosterone levels were measured through saliva samples collected (a) before the administration of oxytocin/placebo, (b) 15 min after the administration, and (c) at the end of the study day (~3.3 hr after the administration). A series of personality questionnaires were completed after the main task, including Empathizing & Systemizing Quotient (Baron-Cohen & Wheelwright, 2004), Interpersonal Reactivity Index (Davis, 1983), Need for Cognition Scale (Cacioppo, Petty, Feinstein, & Jarvis, 1996), and Social Anxiety Scale (Liebowitz, 1987).

Speech Comprehension Task

A speech comprehension task was carried out ~80 min after the administration of oxytocin or placebo. In this task, participants passively listened to sentences for comprehension. The same sentence materials have been used and described in detail by Van Berkum, van den Brink, Tesink, Kos, and Hagoort (2008). The content of the sentences was either congruent (50 trials, e.g., "Dutch trains are yellow and very crowded") or incongruent (50 trials, e.g., "Dutch trains are white and very crowded") with facts about the world. Cloze probability of the critical words was assessed in a cloze pretest with 16 native Dutch speakers (seven women, mean age 32 years) who did not participate in the MEG study. In the cloze pretest, participants were asked to read sentences that stopped immediately before the critical words (e.g., "Dutch trains are ____.") and to complete each sentence. The mean cloze probability was 51.3% (*SD* = 32.4%, range 12.5–100%) for the congruent critical words and 0% for the incongruent critical words (range = 0%). The congruent and incongruent variants of the same sentence were distributed into two different lists. No participant heard more than one variant.

In 120 additional filler trials, the sentence content was either congruent or incongruent with speaker characteristics derived from voice-based cues (60 trials per condition, e.g., "Before I leave I always check whether my make-up is still in place" in a female or male voice). We did not expect effects of speaker characteristics in the current population as previous studies have shown that healthy men do not show speaker characteristic effects (van den Brink et al., 2012).

Each trial began with a fixation cross at the center of the screen. A spoken sentence was presented 500 msec after the fixation onset. The fixation remained on the screen until 1000 msec after the sentence offset. Intertrial intervals varied from 3000 to 4000 msec. Participants were asked to avoid eye and other movements when

Table 1. Mean Demographic Data, Hormone Levels, and Questionnaire Scores (Standard Deviations) and Group Differences

Measures	*Placebo Group (n = 22)*	*Oxytocin Group (n = 23)*	*Group Difference*[a]
Age (years)	23.5 (3.4)	21.4 (2.1)	*ns*
Cortisol levels (nmol/L)			
Before oxytocin/placebo	9.994 (5.466)	9.716 (6.962)	*ns*
After oxytocin/placebo	9.363 (4.722)	9.169 (6.497)	*ns*
End of the day	6.804 (4.725)	7.128 (4.684)	*ns*
Testosterone levels (pg/mL)			
Before oxytocin/placebo	83.103 (55.455)	83.121 (43.005)	*ns*
After oxytocin/placebo	81.346 (53.142)	73.319 (47.196)	*ns*
End of the day	105.822 (104.259)	118.200 (166.335)	*ns*
Empathizing quotient	37.3 (12.6)	35.7 (11.0)	*ns*
Systemizing quotient	53.4 (14.8)	62.0 (15.8)	*ns*
Interpersonal reactivity index	57.9 (11.7)	59.7 (12.1)	*ns*
Need for cognition	11.5 (8.2)	9.3 (9.2)	*ns*
Social anxiety	27.3 (17.1)	30.8 (16.2)	*ns*

ns = not significant.

[a] p values of unpaired t tests, Bonferroni-corrected for multiple comparisons.

the fixation was visible. They underwent a practice block before the real blocks.

MEG and MRI Data Acquisition

Participants were seated in a dimly illuminated, magnetically shielded room. Their brain activity was recorded using a whole-head MEG with 275 axial gradiometer sensors (CTF275, VSM MedTech, Coquitlam, British Columbia; 1200-Hz sampling rate, 300-Hz analog low-pass filter). Head position relative to the MEG sensors was monitored throughout the recording using three coils placed at nasion and the left and right ear canal (Stolk, Todorovic, Schoffelen, & Oostenveld, 2013). After MEG recording, the participants were transferred to the MRI suite where high-resolution T1-weighted magnetization-prepared rapid-acquired gradient echo images were acquired on a Siemens (Berlin, Germany) Magnetom Avanto syngo 1.5-T scanner (176 sequential sagittal slices, 1730-msec repetition time, 2.95-msec echo time, 7° flip angle, 25.6×25.6 mm^2 field of view, $1 \times 1 \times 1$ mm^3 voxel size). The T1 images were used to construct participant-specific head models for MEG source reconstruction (see below).

MEG Data Preprocessing

MEG data were preprocessed and analyzed using the open-source FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). Two bad sensors were excluded from further analysis, resulting in 273 MEG sensors. Raw data were segmented into trials from −1000 to 1000 msec around the onset of critical words for further analyses. These analyses included the sensor-level event-related field (ERF) analysis, source reconstruction, and the frequency analysis in the alpha band. Trials contaminated by eye or other movement artifacts were visually identified and rejected. Approximately 92% of the trials were artifact-free and used for further analysis. There were no differences across congruency conditions (incongruent vs. congruent) or groups (oxytocin vs. placebo) in the number of artifact-free trials (repeated-measures ANOVA with Group and Congruency as factors, ps > .19).

ERF Analysis

We first analyzed the N400m signal in response to world knowledge congruent and incongruent words. ERFs of congruent and incongruent trials were computed separately and corrected with baseline measures between −200 and 0 msec to the critical word onset (Wang et al., 2012; Van Berkum et al., 2008). The ERFs were transformed to a planar gradient configuration for an optimal across-participant averaging and topographical interpretation (Bastiaansen & Knösche, 2000).

A whole-brain cluster-based permutation test (1000 randomizations, $p < .05$ corrected for multiple comparisons across 273 MEG sensors) was used to detect the N400m effect (incongruent > congruent) in each group. The permutation test was combined with a moving window approach (between 0 and 800 msec in steps of 50 msec) to detect the best time window for quantifying the N400m effect. Consistent with previous MEG studies (Wang et al., 2012; Mäkelä, Mäkinen, Nikkilä, Ilmoniemi, & Tiitinen, 2001), we observed the N400m effect between 450 and 650 msec over left frontotemporal sensors in the placebo group (see Results). The study-specific definition of the N400m window is independent of the analysis of oxytocin effects (see below). This definition has the advantage of optimizing the N400m estimate for the current cohort, considered that participants of different genders and empathy-related personality traits have different electrophysiological responses to pragmatic violations (van den Brink et al., 2012). Moreover, because sentences were presented auditorily, critical word information was not immediately available but extended in time. This might have contributed to a slightly later N400m effect than with a visual presentation of the sentences.

The whole-brain analysis was followed by an ROI analysis to examine the impact of oxytocin on N400m amplitude. For each participant, mean amplitudes of the N400m signal between 450 and 650 msec were averaged across 13 left frontotemporal sensors. The mean amplitudes were entered into a repeated-measures ANOVA with Congruency (incongruent vs. congruent) as a within-participant factor and Group (oxytocin vs. placebo) as a between-participant factor.

Source Reconstruction

Cortical sources of the N400m signal were reconstructed using a time-domain spatial filtering technique ("beamforming"; see Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997). This technique localizes sources of brain activity using adaptive spatial filters created separately for each grid location in a participant's brain. To this end, we segmented participants' T1 images and constructed participant-specific head models (Nolte, 2003). The T1 images were also used in combination with a template grid derived from the Montreal Neurological Institute (MNI) template to create participant-specific grids. The grid had a resolution of 1 cm, with grid positions matched across participants. On the basis of the head models and grid positions, participant-specific normalized lead field matrices were computed.

For each participant, a mean covariance matrix was computed from their MEG data, using full-length trials (from −200 to 800 msec) of both congruent and incongruent conditions for a more robust estimation. The covariance matrix, in combination with the participant-specific head model and lead field matrix, was used to construct a spatial filter for each grid position. Then trial-specific covariance matrices, computed on the 450- to 650-msec range of the trials, were projected through the spatial filters and averaged separately for each condition. This computation generated whole-brain mean source-level powers of the N400m signal for each condition.

We first examined systematic power differences between the incongruent and congruent conditions using a whole-brain cluster-based permutation test (1000 randomization, $p < .05$ corrected for multiple comparisons across 5780 grid positions). The placebo group showed greater power for incongruent than congruent words in the left inferior frontal gyrus (IFG), medial pFC, and right anterior temporal lobe (see Results).

The whole-brain analysis was followed by a source-level ROI analysis to examine the impact of oxytocin on cortical functioning. For each group, mean power values of the N400m signal were extracted from three box-shaped ROIs ($3 \times 3 \times 3$ cm^3) centered at the peaks of the left IFG cluster (MNI coordinates [−30, 20, −20]), medial pFC cluster (MNI coordinates [0, 50, 50]), and right anterior temporal cluster (MNI coordinates [60, 10, −30]). Similar to the sensor-level analysis, the mean power values were entered into repeated-measures ANOVAs with Congruency and Group as factors.

Finally, we examined how the effect of oxytocin in our ROIs changed over time. To this end, we distributed artifact-free trials into 10 smaller blocks, separately for each condition. Given that most artifacts occurred toward the end of the experiment, we combined the last three blocks into one, thus resulting in eight blocks for further analysis. Each block had ~4.6 trials (averaged across participants), except the last one. The congruent and incongruent conditions were matched in the number of artifact-free trials in every single block (paired-sample t tests, $ps > .16$). For the significant ROI, to analyze the block-by-block dynamics of the source-level N400m effect, the differences in the N400m signal power between the incongruent and congruent conditions were computed for each block and entered into a repeated-measures ANOVA with Block (eight levels) as a within-participant factor and Group (oxytocin vs. placebo) as a between-participant factor.

Frequency Analysis in the Alpha Band

We also investigated the impact of oxytocin on task-related alpha modulation. This analysis computed sensor level mean powers of alpha-band activity (8–13 Hz) by applying multitaper frequency transformation to the 0- to 1000-msec range of each trial. This time window was selected to cover the entire range of the critical words and for an optimal spectral resolution of 1 Hz. The task-related modulation of alpha power was measured as the relative change between the critical word alpha power and baseline alpha power to minimize influences of individual differences in absolute signal power and head position. The baseline alpha power was extracted from a similar time window before the critical word onset (from −1000 to 0 msec). We first detected task-related alpha modulation (critical word > signal baseline) in each condition and group using whole-brain cluster-based permutation tests (1000 randomizations, $p < .05$ corrected for multiple comparisons across 273 MEG sensors). We then compared the two groups for alpha modulation in each condition and for the differential alpha modulation between the incongruent and congruent conditions using whole-brain cluster-based permutation tests (1000 randomizations, $p < .05$ corrected for multiple comparisons across 273 MEG sensors).

RESULTS

Replication of the N400m Effect in the Placebo Group

Previous studies have repeatedly shown that, compared with congruent sentences, sentences violating world knowledge trigger a stronger left-lateralized MEG signal ~400 msec after the onset of critical words (Halgren et al., 2002; Helenius, Salmelin, Service, & Connolly, 1998). Consistent with these studies, a whole-brain cluster-based permutation test ($p < .05$ corrected) indicated that this study's placebo group showed a differential magnetic response that seemed to start early but became significant between 450 and 650 msec over 13 left frontotemporal MEG sensors for incongruent versus congruent critical words (the N400m effect; see the first row of Figure 1A). However, the same whole-brain search in combination with the moving window approach (between 0 and 800 msec in steps of 50 msec) revealed no statistically significant N400m effect in the oxytocin group (see the second row of Figure 1A).

Modulation of the N400m Effect by Oxytocin

An ROI analysis of mean amplitudes of the N400 signal between 450 and 650 msec, averaged across the 13 left frontotemporal MEG sensors, confirmed the absence of the N400m effect in the oxytocin group (see Figure 1B). Namely, a repeated-measures ANOVA revealed a significant interaction of Group and Congruency on N400m amplitude ($F(1, 43) = 11.48$, $p < .005$, partial $\eta^2 = 0.21$), suggesting that oxytocin administration significantly attenuated the N400m effect. As can be seen, the interaction was mainly due to a strong reduction in the N400m amplitude in the incongruent condition (oxytocin < placebo in the incongruent condition, $t(43) = 2.20$, $p < .05$, but not in the congruent condition, $p = .10$). Oxytocin made the incongruent condition behave as the congruent condition.

We also analyzed the N400m signal of filler sentences of which the content varied in terms of congruency with speaker characteristics (see Methods). We did not expect any effect of speaker characteristics in healthy male participants (van den Brink et al., 2012). Consistent with this expectation, we found no stronger N400m potential for speaker characteristic incongruent versus congruent sentences in either the placebo or oxytocin group. In the Van den Brink et al. study, it was found that the N400 effect to speaker characteristics was dependent on the participants' Empathizing Quotient scores. The Empathizing Quotient scores of the participants in this study were in the same range as those of the male participants in the Van den Brink et al. study who failed to show an N400 effect. The findings in our study suggest that oxytocin administration did not significantly modulate the detection of mismatches between social and semantic cues.

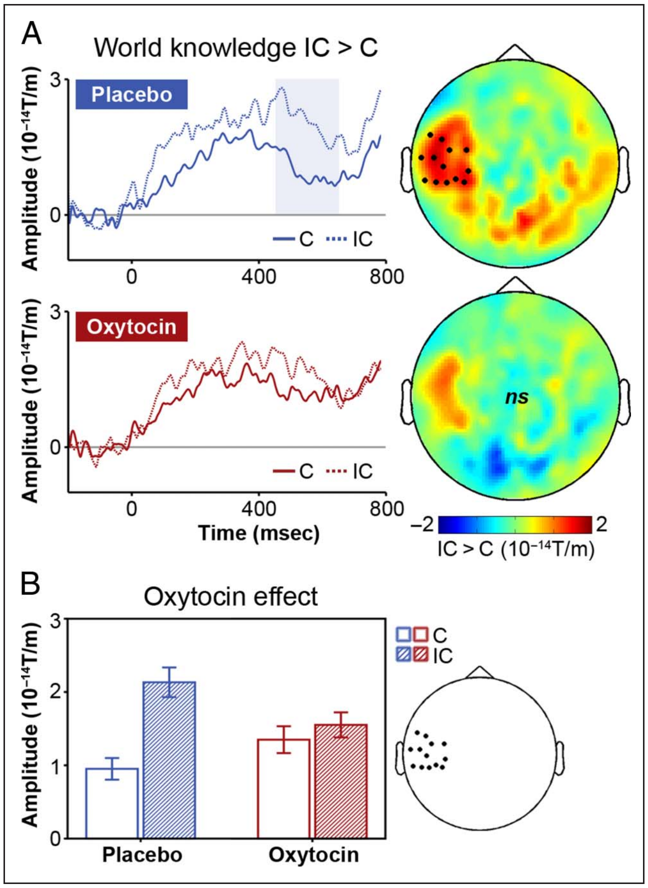

Figure 1. (A) The placebo group showed a stronger N400m signal between 450 and 650 msec (light blue area) over 13 left frontotemporal MEG sensors for world knowledge incongruent words (IC, dotted line) than congruent words (C, solid line; $p < .05$ corrected). A whole-brain search revealed no such N400m effect in the oxytocin group. The ERFs are planar-gradient transformed and averaged across significant MEG sensors. The topography shows the sensors with significant mean amplitude differences of the N400m signal (IC > C; black dots). For the oxytocin group, the condition difference was not significant (*ns*). (B) A sensor-level ROI analysis confirmed the absence of the N400m effect in the oxytocin group. Bars indicate mean amplitudes of the N400m signal averaged across the left frontotemporal MEG sensors depicted on the head projection. Error bars indicate standard errors.

Source-Level Effects of Oxytocin

Having replicated the sensor-level N400m effect in the placebo group, we reconstructed cortical sources of the N400m signal in the same group of participants and compared the power of those sources across conditions using a source-level cluster-based permutation test ($p < .05$

corrected). This whole-brain search revealed a greater N400m signal power for world knowledge incongruent than congruent words in the left IFG/temporal lobe (peak in MNI coordinates [−30, 20, −20], $t(21) = 5.31$), medial pFC (peak [0, 50, 50], $t(21) = 5.19$), and right anterior temporal lobe (peak [60, 10, −30], $t(21) = 3.89$; see Figure 2A).

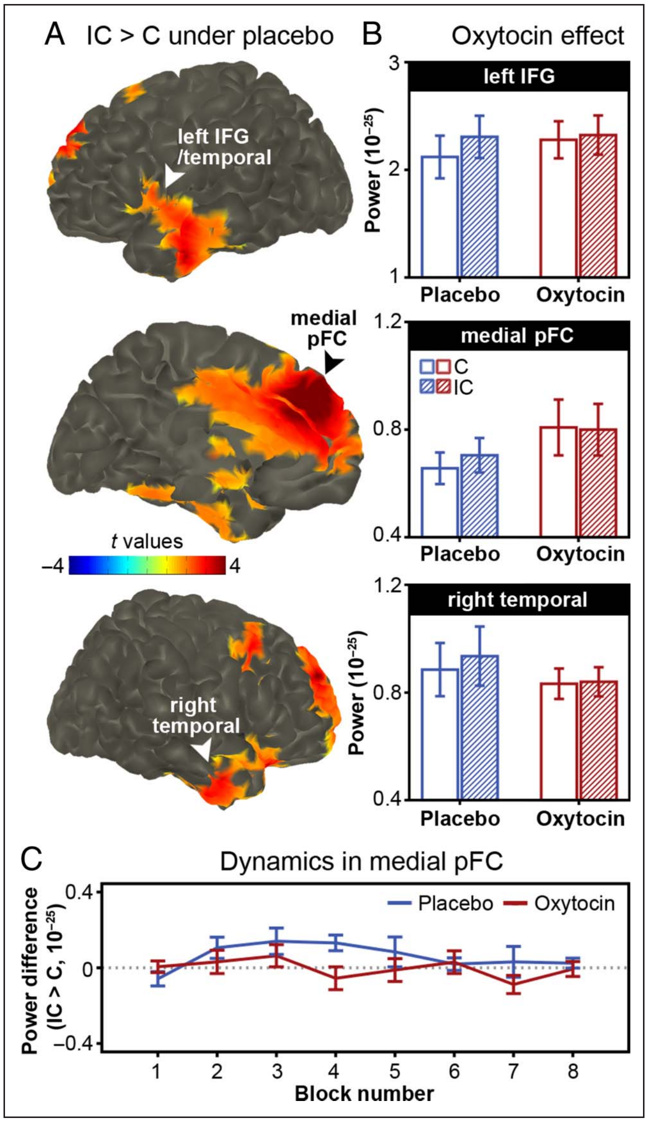

Figure 2. (A) Source reconstruction of the N400m effect, under placebo. The source-level analysis revealed greater N400m signal power for world knowledge incongruent (IC) than congruent (C) words in the left IFG/temporal lobe, medial pFC, and right anterior temporal lobe ($p < .05$ corrected). (B) A source-level ROI analysis confirmed the absence of the N400m effect in the oxytocin group, with the interaction between group and congruency reaching statistical significance in the medial pFC. Bars indicate mean values of the N400m signal power extracted from the left IFG, medial pFC, and right temporal lobe separately for each group and condition. Error bars indicate standard errors. (C) The analysis of block-by-block dynamics indicated the absence of the N400m effect in the medial pFC under oxytocin throughout the experiment. Lines represent the mean differences of the N400m signal power (IC > C) in eight sequential trial blocks. Error bars indicate standard errors.

Following the same strategy as in the sensor-level analysis, we then performed an ROI analysis on each cortical source separately, using repeated-measures ANOVAs, to test for interactions between Group and Congruency on the N400m signal power. This analysis revealed a significant interaction between oxytocin and semantic integration in the medial pFC ($F(1, 43) = 4.87$, $p < .05$, partial $\eta^2 = 0.10$), consistent with the sensor-level findings. Although the same trend was visible in the other two ROIs, the analysis failed to reach statistical significance in the left IFG ($p = .14$) or right anterior temporal lobe ($p = .13$; see Figure 2B).

An analysis of source-level neural activity in the left auditory cortex suggested that this neural modulation was cortically and functionally specific and was not due to overall changes in sensory processing as a result of oxytocin administration. Namely, there were no interactions between group and congruency on the signal power evoked in the left auditory cortex (MNI coordinates [−50, −40, 20]) in the N400m time window (450–650 msec) or in an earlier auditory processing time window (90–100 msec) in which a strong auditory response can be seen (Todorovic, van Ede, Maris, & de Lange, 2011).

State-like Modulation by Oxytocin

The lack of source-level N400m effect in the oxytocin group may be driven by late reductions of an initially present N400m effect or by a systematic change of semantic integration in a state-like manner. To understand the temporal dynamics of the oxytocin effect on semantic integration, we analyzed the medial pFC N400m effect in a block-by-block fashion (see Figure 2C). We computed the differences in the medial pFC N400m signal power between the incongruent and congruent conditions for each group and compared the two groups using a repeated-measures ANOVA with Group and Trial block (eight levels) as factors. Consistent with the abovementioned findings, this analysis revealed a main effect of Group ($F(1, 43) = 4.25$, $p < .05$, partial $\eta^2 = 0.09$). However, there was no statistically significant main effect of Block or interaction between Group and Block (ps > .24). In addition, a block-wise one-sample t-test approach did not show a statistically significant N400m effect under oxytocin for any of the blocks. These results suggest that oxytocin administration significantly attenuated the medial pFC N400m effect throughout the experiment, modulating semantic integration in a state-like manner.

No Effect of Oxytocin on General Attentional Modulation

We finally examined whether oxytocin led to an overall reduction of attention. Alpha-band (8–13 Hz) activity is a well-established electrophysiological marker of attention (Klimesch, 2012). We detected significant task-related modulations of alpha-band activity (i.e., relative changes of alpha power, 0–1000 msec after critical word onset vs. −1000 to 0 msec before onset baseline) over posterior MEG sensors for each group and condition ($p < .05$ corrected). There was no difference between groups in alpha modulation for the congruent or incongruent condition or in differential alpha modulation between the incongruent and congruent conditions. These findings suggest that the absence of the N400m effect is unlikely due to a lack of attention or a reduction in the depth of processing in the oxytocin group.

DISCUSSION

To the best of our knowledge, this study is the first to explore the neuromodulatory effect of oxytocin on semantic integration during speech comprehension. By using MEG in combination with a well-established pragmatic violation paradigm, this study confirms that sentences violating the listener's world knowledge elicit a strong N400m effect from the left inferior frontal cortex, right anterior temporal cortex, and medial pFC. The novel finding of this study is that oxytocin administration significantly attenuates the N400m effect, at both sensor and source levels. The absence of the N400m effect is unlikely due to a lack of early sensory or semantic processing or a general downregulation of attention in the oxytocin group, given that the two groups were comparable in their MEG responses to the congruent condition. Moreover, the placebo and oxytocin groups did not differ in demographics, hormone levels, and personality traits (see Table 1). The oxytocin-related effects can, therefore, not be ascribed to these factors.

The results of source reconstruction of the N400m effect are consistent with previous findings from functional MRI studies that world knowledge incongruent sentences trigger greater regional brain activations than congruent sentences in left inferior frontal regions and medial pFC (Nieuwland, 2012; Menenti et al., 2009; Tesink et al., 2009; Hagoort et al., 2004). The presence of both medial pFC and left inferior frontal cortex is also consistent with Halgren et al. (2002), which used an equivalent current dipole modeling approach and showed that the N400m effect spreads from the left posterior superior temporal cortex to the left inferior frontal cortex and further to the frontopolar and anterior orbital cortices. A recent meta-analysis of 51 studies showed that language tasks with high semantic processing demands reliably activate the medial pFC in addition to the left inferior frontal cortex (Hagoort & Indefrey, 2014).

The cortical sources of the N400m effect are not completely identical with the scalp distribution of the same effect. Namely, the cortical sources of the N400m effect include the medial pFC and right anterior temporal lobe in addition to the left inferior frontal and temporal regions, whereas the scalp distribution of the N400m effect is mainly left lateralized. This mismatch may result from differences in the sensor- and source-related analyses, with the former being more prone to individual differences in brain size and shape. It is also possible that the neural sources in the medial pFC and right anterior temporal lobe show less consistent time-locking to the critical words, such that the neural activation of these regions is better captured by the signal power of the N400m interval than raw signal amplitude. For the purpose of this study, it is important to emphasize that the location of the effects is largely overlapping with known language-relevant regions (cf. Hagoort & Indefrey, 2014). At the same time, the most crucial finding is that the processing of semantic integration as measured by our MEG recording is modulated by oxytocin. Hereafter, we will discuss what might drive this modulatory effect.

A similar reduction of the N400 effect as in the oxytocin group has been observed in previous studies when readers see world knowledge anomalies in a supporting discourse context (Menenti et al., 2009; Hald, Steenbeek-Planting, & Hagoort, 2007; Nieuwland & Van Berkum, 2006). In this case, the specific discourse context provides a possible world scenario, which makes the world knowledge anomalies more acceptable (e.g., Dutch trains are painted in white for a particular event). In the current study, listeners would have to reach such possible world scenarios through a deeper and more exhaustive exploration of the conceptual space. Our findings support the motivational account of oxytocin effect that the listener receiving oxytocin may allocate more computational resources for the search of alternative possible world scenarios. This hypothesis is consistent with findings of animal studies that oxytocin can promote social exploration via reducing social anxiety (Chang & Platt, 2014; Ebitz et al., 2013; Ring et al., 2006; Bale et al., 2001; Windle et al., 1997). It is also consistent with findings of human studies in creativity that healthy men treated with oxytocin display more flexible thinking, more original ideas, and better performance in creative problem-solving tasks (De Dreu et al., 2014). The "creativity" in language comprehension and problem solving may both come from the motivation-promoting effect of oxytocin. In short, oxytocin might promote listeners to assign a positive truth value to possible scenarios, instead of determining the truth value only on the basis of knowledge about state of affairs in the real world.

Additional analyses make it unlikely that the oxytocin modulation of the N400m effect is due to a general lack of attention or a reduction in the depth of processing in the oxytocin group. This hypothesis would predict that oxytocin altered the processing of both congruent and incongruent sentences (in terms of electrophysiological responses), given that oxytocin altered the processing in a state-like manner (see Figure 2C) and participants would not know the condition of a particular sentence until they hear the critical word. This prediction is not supported by our analysis of alpha-band activity, a well-established electrophysiological marker of attention (Klimesch, 2012). Namely, we showed that the task significantly modulated alpha-band activity over posterior MEG sensors in each group and condition and that the two groups were matched in terms of task-related alpha-band modulation in both congruent and incongruent trials. As a result, the differential alpha-band power between incongruent and congruent trials was the same for both groups. These findings indicated that the attention-related neurophysiolgical state of the oxytocin group was matched with that of the placebo group throughout the whole epoch. This observation is not compatible with a general attentional modulation interpretation of the current results but supports our interpretation that oxytocin significantly attenuated the N400m effect by making the incongruent sentences more plausible.

This study used the intranasal delivery that has been used in many recent studies exploring the role of oxytocin in social cognition. It is worth noting that intranasally delivered oxytocin may influence cognition and behavior through multiple pathways, including the olfactory pathway that targets the amygdala and pFC, the trigeminal pathway that targets the brain stem, and the peripheral pathway from which oxytocin enters the systemic circulation (Quintana, Alvares, Hickie, & Guastella, 2015). Recent studies suggest that oxytocin delivered to the brain stem or systemic circulation may facilitate the recognition of affective cues (Kemp et al., 2012; Quintana, Guastella, Outhred, Hickie, & Kemp, 2012). Further studies are needed to understand the pathways under the motivational mechanisms of oxytocin.

This study has potential limitations. First, we focused on the impact of oxytocin on online sentence processing, but we did not monitor the behavioral consequence of sentence interpretation. In the current task, participants listened in a naturalistic way to sentences for comprehension but were not explicitly asked to judge the congruency of the sentences or to indicate their judgment. Future studies should incorporate laboratory tasks or more ecological tests to examine the effect of oxytocin on offline language performance. Second, we recruited only male participants because of logistical complications in applying oxytocin in women. However, previous animal and human studies have reported gender-specific responses to oxytocin (Kubzansky, Mendes, Appleton, Block, & Adler, 2012; Domes et al., 2007, 2010) and an interaction between estrogen and oxytocin (McCarthy, McDonald, Brooks, & Goldman, 1996). Future studies need to examine whether the motivational effect of oxytocin differs in men and women.

In conclusion, we explored the neuromodulatory effect of intranasally delivered oxytocin on semantic integration during speech comprehension. We observed that oxytocin administration in healthy men significantly attenuated the N400m effect in response to world knowledge anomalies. The results suggest that oxytocin may have a motivational role in language comprehensions, that is, promoting the search for possible world scenarios that can make the content of the sentence more plausible or even true.

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REFERENCES

Aoki, Y., Yahata, N., Watanabe, T., Takano, Y., Kawakubo, Y., Kuwabara, H., et al. (2014). Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. *Brain, 137,* 3073–3086.

Bale, T. L., Davis, A. M., Auger, A. P., Dorsa, D. M., & McCarthy, M. M. (2001). CNS region-specific oxytocin receptor expression: Importance in regulation of anxiety and sex behavior. *Journal of Neuroscience, 21,* 2546–2552.

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: An investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders, 34,* 163–175.

Bastiaansen, M. C. M., & Knösche, T. R. (2000). Tangential derivative mapping of axial MEG applied to event-related desynchronization research. *Clinical Neurophysiology, 111,* 1300–1305.

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

Cacioppo, J. T., Petty, R. E., Feinstein, J. A., & Jarvis, W. B. G. (1996). Dispositional differences in cognitive motivation: The life and times of individuals varying in need for cognition. *Psychological Bulletin, 119,* 197–253.

Chang, S. W., & Platt, M. L. (2014). Oxytocin and social cognition in rhesus macaques: Implications for understanding and treating human psychopathology. *Brain Research, 1580,* 57–68.

Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology, 44,* 113–126.

De Dreu, C. K., Baas, M., Roskes, M., Sligte, D. J., Ebstein, R. P., Chew, S. H., et al. (2014). Oxytonergic circuitry sustains and enables creative cognition in humans. *Social Cognitive and Affective Neuroscience, 9,* 1159–1165.

De Dreu, C. K., & Kret, M. E. (2016). Oxytocin conditions intergroup relations through upregulated in-group empathy, cooperation, conformity, and defense. *Biological Psychiatry, 79,* 165–173.

Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D. F., & Herpertz, S. C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry, 62,* 1187–1190.

Domes, G., Lischke, A., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., et al. (2010). Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology, 35,* 83–92.

Ebitz, R. B., Watson, K. K., & Platt, M. L. (2013). Oxytocin blunts social vigilance in the rhesus macaque. *Proceedings of the National Academy of Sciences, U.S.A., 110,* 11630–11635.

Hagoort, P., Hald, L., Bastiaansen, M., & Petersson, K. M. (2004). Integration of word meaning and world knowledge in language comprehension. *Science, 304,* 438–441.

Hagoort, P., & Indefrey, P. (2014). The neurobiology of language beyond single words. *Annual Review of Neuroscience, 37,* 347–362.

Hagoort, P., & van Berkum, J. (2007). Beyond the sentence given. *Philosophical Transactions of the Royal Society, Series B, Biological Sciences, 362,* 801–811.

Hald, L. A., Steenbeek-Planting, E. G., & Hagoort, P. (2007). The interaction of discourse context and world knowledge in online sentence comprehension. Evidence from the N400. *Brain Research, 1146,* 210–218.

Halgren, E., Dhond, R. P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J. D., et al. (2002). N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *Neuroimage, 17,* 1101–1116.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry, 54,* 1389–1398.

Helenius, P., Salmelin, R., Service, E., & Connolly, J. F. (1998). Distinct time courses of word and context comprehension in the left temporal cortex. *Brain, 121,* 1133–1142.

Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., et al. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry, 61,* 498–503.

Hu, J., Qi, S., Becker, B., Luo, L., Gao, S., Gong, Q., et al. (2015). Oxytocin selectively facilitates learning with social feedback and increases activity and functional connectivity in emotional memory and reward processing regions. *Human Brain Mapping, 36,* 2132–2146.

Jackendoff, R. (2002). *Foundations of language: Brain, meaning, grammar, evolution*. Oxford, UK: Oxford University Press.

Kemp, A. H., Quintana, D. S., Kuhnert, R. L., Griffiths, K., Hickie, I. B., & Guastella, A. J. (2012). Oxytocin increases heart rate variability in humans at rest: Implications for social approach-related motivation and capacity for social engagement. *PLoS One, 7,* e44014.

Klimesch, W. (2012). α-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences, 16,* 606–617.

Kubzansky, L. D., Mendes, W. B., Appleton, A. A., Block, J., & Adler, G. K. (2012). A heartfelt response: Oxytocin effects on response to social stress in men and women. *Biological Psychiatry, 90,* 1–9.

Kumsta, R., & Heinrichs, M. (2013). Oxytocin, stress and social behavior: Neurogenetics of the human oxytocin system. *Current Opinion in Neurobiology, 23,* 11–16.

Kutas, M., & Federmeier, K. D. (2011). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology, 62,* 621–647.

Liebowitz, M. R. (1987). Social phobia. *Modern Problems of Pharmacopsychiatry, 22,* 141–173.

Mäkelä, A. M., Mäkinen, V., Nikkilä, M., Ilmoniemi, R. J., & Tiitinen, H. (2001). Magnetoencephalographic (MEG) localization of the auditory N400m: Effects of stimulus duration. *NeuroReport, 12,* 249–253.

McCarthy, M. M., McDonald, C. H., Brooks, P. J., & Goldman, D. (1996). An anxiolytic action of oxytocin is enhanced by estrogen in the mouse. *Physiology & Behavior, 60,* 1209–1215.

Menenti, L., Petersson, K. M., Scheeringa, R., & Hagoort, P. (2009). When elephants fly: Differential sensitivity of right and left inferior frontal gyri to discourse and world knowledge. *Journal of Cognitive Neuroscience, 21,* 2358–2368.

Nieuwland, M. S. (2012). Establishing propositional truth-value in counterfactual and real-world contexts during sentence comprehension: Differential sensitivity of the left and right inferior frontal gyri. *Neuroimage, 59,* 3433–3440.

Nieuwland, M. S., & Van Berkum, J. J. (2006). When peanuts fall in love: N400 evidence for the power of discourse. *Journal of Cognitive Neuroscience, 18,* 1098–1111.

Nolte, G. (2003). The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Physics in Medicine and Biology, 48,* 3637–3652.

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience, 2011,* 156869.

Quintana, D. S., Alvares, G. A., Hickie, I. B., & Guastella, A. J. (2015). Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model. *Neuroscience & Biobehavioral Reviews, 49,* 182–192.

Quintana, D. S., Guastella, A. J., Outhred, T., Hickie, I. B., & Kemp, A. H. (2012). Heart rate variability is associated with emotion recognition: Direct evidence for a relationship between the autonomic nervous system and social cognition. *International Journal of Psychophysiology, 86,* 168–172.

Ring, R. H., Malberg, J. E., Potestio, L., Ping, J., Boikess, S., Luo, B., et al. (2006). Anxiolytic-like activity of oxytocin in male mice: Behavioral and autonomic evidence, therapeutic implications. *Psychopharmacology, 185,* 218–225.

Stolk, A., Todorovic, A., Schoffelen, J. M., & Oostenveld, R. (2013). Online and offline tools for head movement compensation in MEG. *Neuroimage, 68,* 39–48.

Tesink, C. M., Buitelaar, J. K., Petersson, K. M., van der Gaag, R. J., Teunisse, J. P., & Hagoort, P. (2011). Neural correlates of language comprehension in autism spectrum disorders: When language conflicts with world knowledge. *Neuropsychologia, 49,* 1095–1104.

Tesink, C. M., Petersson, K. M., van Berkum, J. J., van den Brink, D., Buitelaar, J. K., & Hagoort, P. (2009). Unification of speaker and meaning in language comprehension: An fMRI study. *Journal of Cognitive Neuroscience, 21,* 2085–2099.

Todorovic, A., van Ede, F., Maris, E., & de Lange, F. P. (2011). Prior expectation mediates neural adaptation to repeated sounds in the auditory cortex: An MEG study. *Journal of Neuroscience, 31,* 9118–9123.

Unkelbach, C., Guastella, A. J., & Forgas, J. P. (2008). Oxytocin selectively facilitates recognition of positive sex and relationship words. *Psychological Science, 19,* 1092–1094.

Van Berkum, J. J., van den Brink, D., Tesink, C. M., Kos, M., & Hagoort, P. (2008). The neural integration of speaker and message. *Journal of Cognitive Neuroscience, 20,* 580–591.

van den Brink, D., Van Berkum, J. J., Bastiaansen, M. C., Tesink, C. M., Kos, M., Buitelaar, J. K., et al. (2012). Empathy matters: ERP evidence for inter-individual differences in social language processing. *Social Cognitive and Affective Neuroscience, 7,* 173–183.

Van Veen, B. D., van Drongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering, 44,* 867–880.

Veening, J. G., de Jong, T. R., Waldinger, M. D., Korte, S. M., & Olivier, B. (2015). The role of oxytocin in male and female reproductive behavior. *European Journal of Pharmacology, 753,* 209–228.

Wang, L., Jensen, O., van den Brink, D., Weder, N., Schoffelen, J. M., Magyari, L., et al. (2012). Beta oscillations relate to the N400m during language comprehension. *Human Brain Mapping, 33,* 2898–2912.

Windle, R. J., Shanks, N., Lightman, S. L., & Ingram, C. D. (1997). Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology, 138,* 2829–2834.