Future parents: Childhood experiences, oxytocin and emotion recognition skills

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Chapter 3

Oxytocin effects on mind reading are moderated by experiences of parental love withdrawal: An fMRI study.

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Abstract

The neuropeptide oxytocin has been shown to stimulate a range of social behaviors. However, recent studies indicate that the effects of intranasal oxytocin are more nuanced than previously thought and that contextual factors and individual characteristics moderate the beneficiary oxytocin effects. In this randomized-controlled trial we examine the influence of intranasally administered oxytocin on neural activity during mind-reading with fMRI, taking into account harsh caregiving experiences as a potential moderator. Participants were 50 women who received a nasal spray containing either 16 IU of oxytocin or a placebo and had reported how often their mother used love withdrawal as a disciplinary strategy. Participants performed an adapted version of the Reading the Mind in the Eyes Test (RMET), a task which requires individuals to infer mental states by looking at photographs of the eye region of faces. We found that oxytocin enhanced neural activation in the superior temporal gyrus (STG) and insula during the RMET. Moreover, oxytocin increased RMET performance outside the scanner. However, the oxytocin induced changes in STG activation and RMET performance were only brought about in potentially less socially proficient individuals who had low RMET performance, that is, participants reporting higher levels of maternal love withdrawal.

Introduction

The ability to infer others' mental states, thought, feelings and intentions, also referred to as mind-reading or mental state reasoning, is a key component of human social functioning and is regarded as uniquely human (Premack & Woodruff, 1978). Previous research has shown that mind-reading can be facilitated by oxytocin (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), a neuropeptide that is involved in social affiliation (Carter, 1998). However, other studies indicate that the prosocial effects of oxytocin are dependent on context and individual characteristics, such as personality (Bartz et al., 2010a) and childhood experiences (Bakermans-Kranenburg, Van IJzendoorn, Riem, Tops, & Alink, 2012; Bartz, Zaki, Bolger, & Ochsner, 2011; Van IJzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011b). In the current study, we examine whether the effects of oxytocin on neural activity during mind-reading are moderated by unsupportive caregiving experiences. To our knowledge, this is the first randomized-controlled trial examining the influence of intranasally administered oxytocin on the neural mechanisms underlying mind-reading, taking into account childhood experiences as a potential moderator.

Individuals attempt to comprehend the mental state of others and make predictions about how others feel, think and behave by reading subtle visual and verbal cues that give information on the emotional state of the other. One important source of visual information is the eye region (Langton, Watt, & Bruce, 2000). More than other facial features, the eyes represent a special area providing a wealth of social information (Itier & Batty, 2009). Because of the important role of the eyes in social communication, mental state reasoning has been assessed with the Reading the Mind in the Eyes Test (RMET), a task which requires individuals to infer mental states by looking at photographs of the eye region of faces (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). The RMET is considered an advanced theory of mind test, since participants have to put themselves into the mind of other persons, and attribute a mental state to them (Vellante et al., 2012). The test has been used to distinguish between healthy individuals and individuals with impairments in social cognition, such as patients with autism (Baron-Cohen et al., 1997; Baron-Cohen et al., 1999), borderline personality disorder (Frick et al., 2012) and schizophrenia (Russell et al., 2000). In addition, performance on the RMET has been associated with measures of empathy (Vellante et al., 2012), and has adequate test-retest reliability ($r = .60$) (Hallerback, Lugnegard, Hjarthag, & Gillberg, 2009).

Neuro-imaging studies have consistently shown that the RMET activates the inferior frontal gyrus (IFG), the superior temporal gyrus (STG), the superior temporal sulcus (STS), the temporal poles, and the insula. The STS, STG, and temporal poles are brain regions implicated in theory of mind (Gallagher & Frith, 2003; Hein & Knight, 2008). The IFG is part

of the mirror neuron system and is, in concert with the anterior insula, involved in empathy, emotion recognition, and in the processing of facial emotional expressions (Bernhardt & Singer, 2012; Carr, Lacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Keuken et al., 2011; Liakakis, Nickel, & Seitz, 2011). Beyond the involvement of these regions in the RMET, studies have shown that the degree of activation in these regions during mind-reading is related to RMET performance. For example, individuals with autism have poor performance on the RMET and show reduced activation of the insula and IFG compared with healthy controls when inferring mental states from the eyes (Baron-Cohen et al., 1999).

Furthermore, studies indicate that performance on the RMET is influenced by intranasal administration of oxytocin (Domes et al., 2007). Oxytocin is a neuropeptide that is well known for its role in lactation, pregnancy, initiation of maternal care, and parenting (Carter, 1998; Insel, 2010). A substantial number of studies on the beneficial effects of oxytocin on social cognition and behavior have been published over the past ten years (Van IJzendoorn & Bakermans-Kranenburg, 2012). These studies show that oxytocin stimulates a range of social behaviors, including trust, empathy, and sensitive parenting (Graustella & MacLeod, 2012). However, recent research indicates that the effects of oxytocin are more nuanced than previously thought and that social context and individual differences are two important factors shaping the effects of oxytocin (Bakermans-Kranenburg et al., 2012; Bartz et al., 2011). For example, oxytocin only enhances trust when partners are known or believed to be reliable (Declerck, Boone, & Kiyonari, 2010; Mikolajczak et al., 2010). De Dreu et al (2010) found that intranasal oxytocin enhanced in-group altruism, but at the same time increased defensive reactions toward out-group members. Thus, oxytocin may drive a 'tend and defend' response, especially when out-group threat is high (De Dreu, 2012; De Dreu, Greer, Handgraaf, Shalvi, & Van Kleef, 2012).

In addition to contextual factors, individual differences in caregiving experiences have also been shown to influence the prosocial effects of oxytocin (Bakermans-Kranenburg et al., 2012). Van IJzendoorn et al (2011b) showed that intranasal oxytocin increased willingness to donate money to a charity only in participants who had experienced lower levels of maternal love withdrawal, a disciplinary strategy that involves withholding love and affection when a child misbehaves or fails at a task. In contrast, intranasal oxytocin was ineffective for participants with higher levels of love withdrawal. Similarly, a previous study showed that oxytocin increased prosocial helping behavior toward an excluded person, but only in participants with lower levels of love withdrawal (Riem, Bakermans-Kranenburg, Huffmeijer, & Van IJzendoorn, 2013). Excessive use of love withdrawal is considered psychological maltreatment (Euser, Van IJzendoorn, Prinzie, & Bakermans-Kranenburg, 2010) and has been related to high concern over mistakes, low emotional well-being and feelings of rejection and resentment toward the parents (Elliot & Thrash, 2004; Goldstein

& Heaven, 2000; Renk, McKinney, Klein, & Oliveros, 2006). In addition, harsh parenting experiences may interfere with emotion recognition and the processing of emotions (Sullivan, Carmody, & Lewis, 2010) and may lead to the development of poor theory of mind skills (Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003; Pears & Fisher, 2005). High levels of love withdrawal may therefore hinder the understanding of other peoples' mental states.

The current study is the first to examine the effects of intranasal oxytocin on neural activity during the Reading the Mind in the Eyes Test with functional Magnetic Resonance Imaging (fMRI), taking into account harsh caregiving experiences as a potential moderator. We were specifically interested in effects of oxytocin on the insula, IFG, and STG, because the RMET activates these brain regions (Adams et al., 2009; Mascaro, Rilling, Negi, & Raison, 2013; Moor et al., 2012) and because previous studies have shown that oxytocin affects neural activity in these regions during exposure to emotional stimuli (Domes et al., 2010; Riem et al., 2011). Specifically related to mind-reading, Pincus et al (2010) showed that intranasal oxytocin enhances activation in the IFG and anterior STG during the RMET, although this effect was not significant when compared with the control condition of gender identification. We expected that maternal use of love withdrawal would hinder mental state attribution, leading to lower scores on the RMET. In addition, we expected that intranasal oxytocin would increase RMET performance and activation of the insula, IFG and STG during mental state attribution, potentially moderated by experiences of maternal use of love withdrawal.

Method

Participants

Female participants were selected for this study because of the lack of studies investigating oxytocin effects in females (Bos, Panksepp, Bluthe, & van Honk, 2012). A total of 343 female undergraduate students from the departments of education and child studies, and psychology at Leiden University participated in the first phase of the study. In this phase, the participants completed online questionnaires on experienced parenting and some demographic details. One participant was excluded due to random responses. Five females with children of their own were also excluded. One hundred eighty six students participated in the second phase of the study, which was designed to examine behavioral and cardiac responses to infant crying. Fifty-four participants with scores ranging from low to high on an experienced parenting questionnaire were selected to participate in the third phase of the study, consisting of a computer game designed to study prosocial helping behavior towards an excluded adult (without an fMRI component, Riem et al., 2013) and the current fMRI study. Participants were screened for MRI contraindications, psychiatric or neurological

disorders, hearing problems, pregnancy, and alcohol and drug abuse. Four participants were excluded from the analyses due to excessive head movement during fMRI scanning, resulting in a total sample size of 50 participants for the current study. They were randomly assigned to the oxytocin or the placebo condition (n = 25 oxytocin, n = 25 placebo). The mean age of the participants was 19.62 years (SD =1.47, range 18-27). The majority (72 %) of the participants used oral contraceptives. Written informed consent was obtained from all participants. Permission for this study was obtained from the Ethics Committees of the Institute of Education and Child Studies of Leiden University and of the Leiden University Medical Centre.

Procedure

Participants were invited for the fMRI study preferably in the luteal phase of their menstrual cycle. For two participants it was not possible to determine menstrual phase, because of use of Mirena intrauterine device.

A between-subject design was used to study the effects of oxytocin. Approximately one hour before the start of fMRI data acquisition participants took 6 puffs of nasal spray containing oxytocin (16 IU total) or 6 puffs of a placebo spray under supervision of the experimenter. Salivary oxytocin levels have been shown to remain elevated more than seven hours after administration of nasal spray containing 16 IU of oxytocin (Van IJzendoorn, Bhandari, Van der Veen, Grewen, & Bakermans-Kranenburg, 2012) and effects of 16 IU of oxytocin on social behavior and neural activity have been reported in previous studies (Riem et al., 2011; Van IJzendoorn & Bakermans-Kranenburg, 2012). Drug administration was double-blind. After nasal spray administration, the participants were familiarized with the task during practice trials outside the MRI scanner.

Maternal love withdrawal

The questionnaire on maternal use of love withdrawal contained 8 items of the Withdrawal of Relations subscale of the Children's Report of Parental Behavior Inventory (CRPBI; Beyers & Goossens, 2003; Schludermann & Schludermann, 1983). Because it is in particular the use of maternal love withdrawal that has been related to low emotional well-being in adolescence and adulthood (Elliot & Thrash, 2004; Renk et al., 2006), we focused on maternal caregiving only. The questionnaire was completed online during the first phase of the study. Participants rated how well each of the 8 statements described their mother (e.g., ''My mother is a person who, when I disappoint her, tells me how sad I make her'') on a 5-point scale ranging from 1 = *not applicable* to 5 = *fully applicable*. The scores did not differ for participants in the oxytocin or placebo condition, $t(48) = -0.10$, $p = .92$.

Experimental task

Participants performed an adapted version of the Reading the Mind in the Eyes Task (RMET) (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The task consisted of 36 photographs depicting the eye region of faces. Two mental states words accompanied each photograph and participants were asked to select the word that best described what the person in the photograph was thinking or feeling. The selection of the two mental state words was based on a pilot study with 20 women who were administered the original version of the RMET with four words. The correct word and the word that was least often chosen were selected as the mental state words in the current fMRI study. Each photograph was presented for 5 s (interstimulus time 1-2.5 s), once in a mental state attribution condition and once in a control condition, in which participants were asked to indicate the gender of the person in the photograph. The photographs were presented in blocks of 6 trials. Participants were asked to select the correct mental state word or to indicate whether the person in the photograph was male or female by pressing buttons with the right hand. Correct words were counterbalanced to right and left side. After fMRI data acquisition, the original version of the RMET with four mental state words was administered. RMET performance of participants in the placebo group was very similar to previously reported RMET scores of other female student samples (Baron-Cohen et al., 2001).

fMRI data acquisition

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva TX MRI system (Philips Medical Systems, Best, the Netherlands) in the Leiden University Medical Center. First, a T1-weighted anatomical scan was acquired (flip angle = 8°, 140 slices, voxel size .875 x .875 x 1.2 mm). For fMRI, a total of 224 T2*-weighted whole-brain echoplanar images were acquired (repetition time = 2.2 s; echo time = 30 ms, flip angle = 80°, 38 transverse slices, voxel size 2.75 x 2.75 x 2.75mm (+ 10% interslice gap)).

fMRI data analysis

Data analysis was carried out using FEAT (FMRI Expert Analysis Tool) version 5.98, part of FSL (Smith et al., 2004). The following pre-statistics processing was applied: motion correction (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 8.0 mm, and high-pass temporal filtering (highpass filter cutoff = 100.0 s). Functional scans were registered to the high-resolution EPI-images, which were registered to the T1-weighted images, which were registered to standard space (Jenkinson et al., 2002).

In native space, functional activation was examined using general linear model analysis. Each condition (mental state, gender) was modeled separately as a square-wave

function. Each predictor was then convolved with a double gamma hemodynamic response function and its temporal derivative was added to the model, giving four regressors. To examine regions involved in mental state attribution we contrasted the mental state attribution condition with the gender condition (mental state > gender).

The first-level contrast images and the corresponding variance images were transformed to standard space and submitted to second-level mixed-effects group whole brain analyses. Group means were tested using one-sample t-tests and we tested for group differences using two-sample t-tests on these contrasts with the oxytocin versus placebo group comparison (Oxytocin > Placebo and Oxytocin < Placebo). We included menstrual cycle (follicular or luteal phase) and use of oral contraceptives as confound regressors in the model in the analyses of the group means and group differences. The statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p<.05$.

Region of Interest (ROI) analyses were conducted with *a priori* specified regions of interest based on previous fMRI studies using the Reading the Mind in the Eyes Task (Adams et al., 2009; Moor et al., 2012). These regions were the anterior insula, the inferior frontal gyrus pars opercularis, and the anterior superior temporal gyrus, anatomically defined using the Harvard–Oxford cortical atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Mean Z-values for the left anterior STG, left anterior insula, and left IFG were calculated (anatomically defined using the Harvard–Oxford cortical atlas) for each participant with Featquery in order to examine whether experiences with maternal love withdrawal moderated the effects of oxytocin. In addition, mean Z-values for significantly activated voxels in the left anterior STG and left anterior insula were calculated for visualization purposes. Hierarchical regression analyses were conducted to predict STG and insula activation during mental attribution compared with the gender identification condition with menstrual cycle and use of oral contraceptives in the first step, condition (oxytocin versus placebo) and experienced love withdrawal (centered) in the second step, and the interaction between condition and love withdrawal in the third step.

Results

The RMET mental state attribution condition was contrasted with the gender attribution/identification condition in order to identify brain regions involved in mental state reasoning. The whole brain analysis revealed four large clusters of activation in the placebo group, with peak voxels in the bilateral inferior frontal gyrus, paracingulate cortex and occipital fusiform gyrus. Consistent with previous studies, the pattern of activation included the bilateral temporal pole, the superior temporal sulcus, the middle temporal gyrus, the superior

temporal gyrus, the orbitofrontal cortex, the fusiform gyrus, the insula, the thalamus, the amygdala, and the left putamen (see Figure 1). See Table 1 for an overview of the cluster sizes and the coordinates and Table S1 for the local maxima within these clusters.

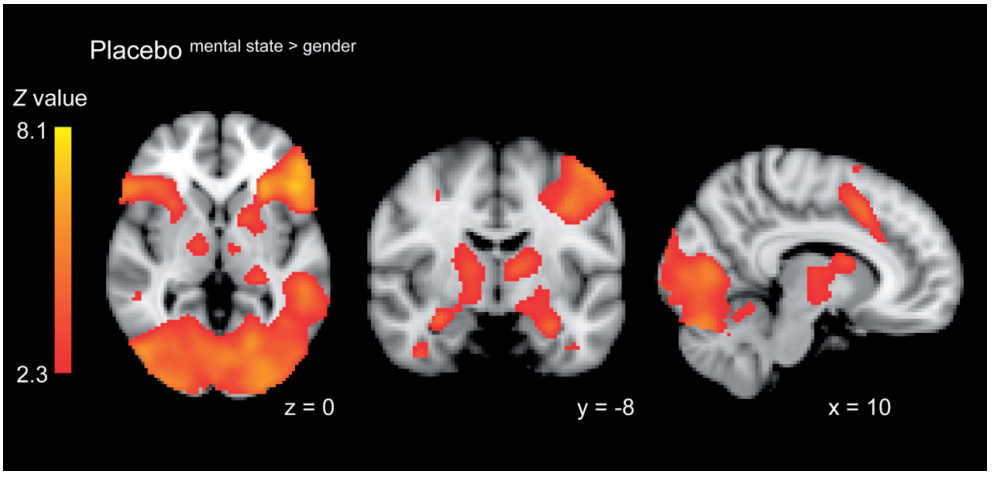

Figure 1. Significant activation during mental state attribution compared with the gender condition in the placebo group. Statistical images were thresholded with clusters determined by $Z > 2.3$ and a cluster-corrected significance threshold of $p < 0.05$.

To examine the effects of oxytocin on brain activation during mental state reasoning we contrasted the oxytocin group with the placebo group (Oxytocin $^{\text{Mental state > Gender}}$ > Placebo $^{\text{Mental state > Gender}}$ and Oxytocin $^{\text{Mental state > Gender}}$ < Placebo $^{\text{Mental state > Gender}}$). The whole brain analysis did not reveal significant differences in brain activation between the oxytocin and placebo group. However, region of interest analyses showed that oxytocin significantly increased activation in the left insula (cluster size = 140, peak $Z = 3.12$, MNI coordinates (mm) = -34, 10, -2) and the left superior temporal gyrus (cluster size = 238, peak $Z = 3.30$, MNI coordinates (mm) = -50, 0, -16), extending toward the superior temporal sulcus (see Figure 2). Region of interest analyses with the left inferior frontal gyrus, right inferior frontal gyrus, right insula and right STG did not reveal significant differences between the oxytocin and the placebo group.

Hierarchical regression analyses were conducted in order to examine whether experiences with maternal love withdrawal moderated the effects of oxytocin. The results of the regression analyses are displayed in Table 2. For left STG activation the model was significant ($F(5,44) = 4.75$, $p = .001$). Condition and love withdrawal significantly predicted STG activation (condition: $ß = -.29$, $p = .02$; love withdrawal: $ß = .27$, $p = .04$). In addition, there was a significant interaction between condition and love withdrawal ($ß = -.34$, $p =$

Table 1. *MNI coordinates, cluster size, and Z-max values for significantly activated clusters*

		MNI coordinates				
Contrast	Brain region	x	y	z	Cluster size	Peak *Z*
Placebo Mental state > Gender	L Occipital Fusiform Gyrus	-40	-70	-16	25617	7.65
	L Inferior Frontal Gyrus	-52	14	24	10654	8.14
	R Inferior Frontal Gyrus	56	26	12	3408	6.10
	L Paracingulate Gyrus	-4	14	44	1757	7.22
	L Insula	-28	26	0	616	6.11[a]
	R Insula	40	26	0	488	4.30[a]
Oxytocin Mental state > Gender	L Inferior Frontal Gyrus	-48	20	20	37592	7.92
	R Inferior Frontal Gyrus	58	26	10	2808	5.90
	L Paracingulate Gyrus	-2	12	46	2555	6.68
	L Insula	-38	26	-8	954	6.56[a]
	R Insula	46	24	-6	437	4.35[a]
	L Superior Temporal Gyrus	-48	4	-26	529	4.49[a]
	R Superior Temporal Gyrus	52	12	-18	195	4.72[a]

$p < .05$, corrected by whole brain cluster threshold ($Z > 2.3$); use of oral contraceptives and menstrual cycle included as confound regressors in the model. [a] Region of interest analysis, $p < 0.05$, corrected by cluster threshold ($Z > 2.3$).

.01). To explore the interaction, we created four groups: participants reporting higher versus lower love withdrawal in the oxytocin group, participants reporting higher versus lower love withdrawal in the placebo group (median split). A priori contrasts showed that oxytocin significantly increased STG activation for participants reporting higher levels of love withdrawal ($t(46) = 3.16$, $p = .003$) but no significant effects of oxytocin were found for participants reporting lower levels of love withdrawal ($t(46) = -0.21$, $p = .84$) (see Figure 3). For left insula activation, the model was not significant ($F(5,44) = 2.31$, $p = .06$). There were no significant effects of condition ($ß = -.18$, $p = .19$) or love withdrawal ($ß = .07$, $p = .62$), and no significant interaction between condition and love withdrawal ($ß = -.21$, $p = .13$). For left

Table 2. *Hierarchical regression analyses with menstrual cycle, oral contraceptives, condition (placebo/oxytocin), maternal love withdrawal and the interaction between condition and love withdrawal as predictors and mean Z-values of left superior temporal gyrus (STG), left insula, and left inferior frontal gyrus (IFG) activation as outcomes*

	STG			Insula			IFG		
	B	ß	R^2	B	ß	R^2	B	ß	R^2
Step 1			0.06			0.12			0.14
Menstrual cycle	0.05	0.01		-0.61	-0.21		-1.14	-0.34*	
Oral contraceptives	-0.57	-0.23		-0.59	-0.26		-0.27	-0.11	
Step 2			0.24			0.16			0.15
Condition (Oxytocin vs Placebo)	-0.64	-0.29*		-0.36	-0.18		0.23	0.10	
Love withdrawal	0.39	0.27*		0.09	0.07		0.08	0.05	
Step 3			0.35			0.21			0.20
Condition x love withdrawal	-0.97	-0.34**		-0.55	-0.21		-0.68	-0.23	

* $p < .05$, ** $p < .01$, Betas derived from the final block of the regression model.

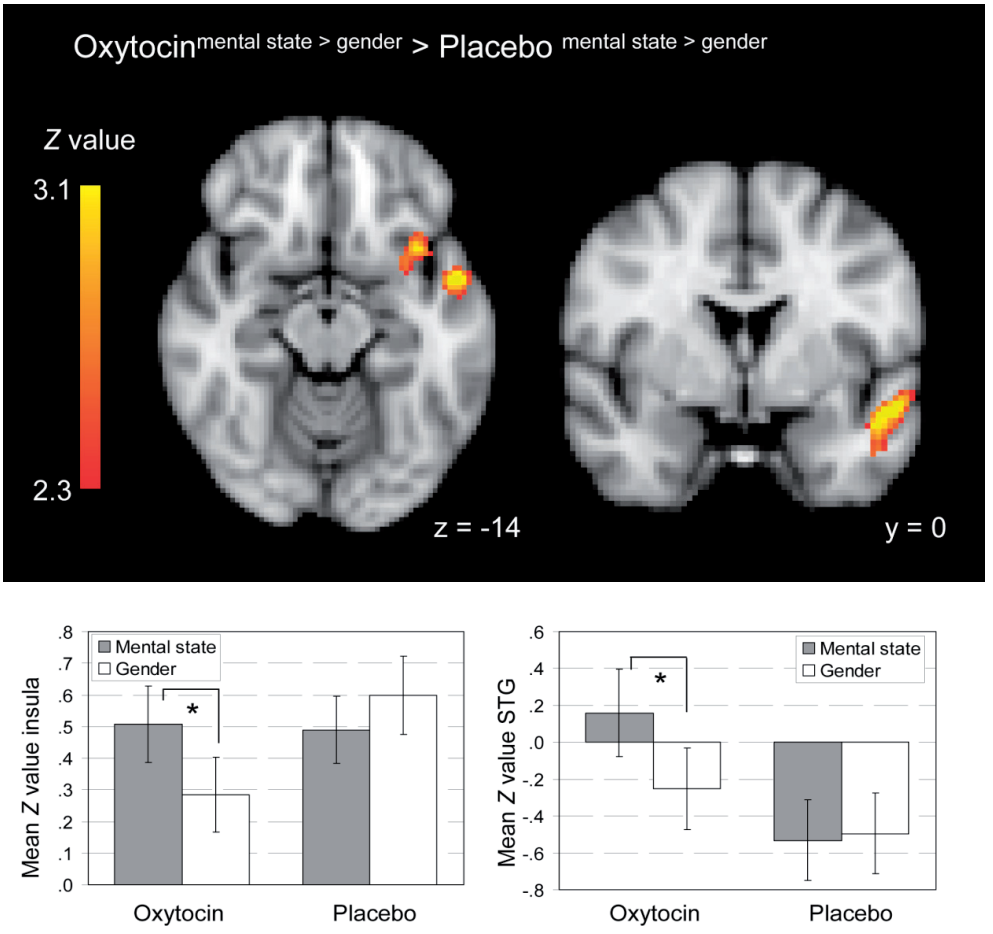

Figure 2. a) Oxytocin effect on superior temporal gyrus and insula activation (the right side of the brain corresponds with the left hemisphere and vice versa, region of interest analysis, $p < 0.05$, corrected by cluster threshold $Z > 2.3$) and b) mean Z values and SEs of left insula and left superior temporal gyrus activation for the mental state and gender condition. * $p < .05$.

IFG activation, the model was not significant either ($F(5,44) = 2.26$, $p = .07$). There were no significant effects of condition ($ß = .10$, $p = .48$) or love withdrawal ($ß = .05$, $p = .71$), and no significant interaction between condition and love withdrawal ($ß = -.23$, $p = .10$).

Effects of oxytocin on performance on the original RMET tested outside the scanner were examined. The correlation between performance on the original RMET and the adapted fMRI version was $r = .24$, $p = .10$. There was no significant difference in performance on the original RMET between the placebo group and the oxytocin group ($t(48) = -0.04$, $p = .97$). Univariate analysis of variance was conducted with RMET performance as dependent

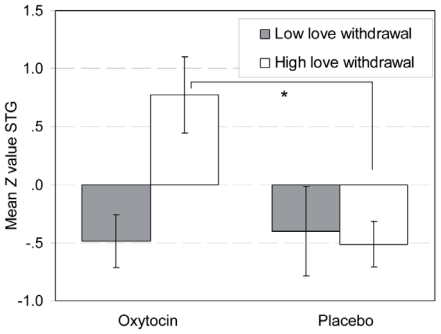

Figure 3. Z values (*M, SE*) of left STG activation during the mental state condition compared with the gender condition for participants reporting lower versus higher love withdrawal in the placebo group and participants reporting lower versus higher love withdrawal in the oxytocin group. * $p < .01$.

variable, condition (placebo, oxytocin) and love withdrawal (higher love withdrawal, lower love withdrawal, median split) as between-subjects factors. There were no significant effects of condition ($F(1,46) = 0.01$, $p = .94$) and love withdrawal ($F(1,46) = 0.87$, $p = .36$), but the interaction between condition and love withdrawal was significant ($F(1,46) = 6.62$, $p = .01$). Participants with higher levels of love withdrawal in the oxytocin condition showed better RMET performance than participants with higher levels of love withdrawal in the placebo condition (oxytocin: $M = 29.25$, $SD = 2.01$, placebo: $M = 27.00$, $SD = 4.24$, $d = 0.68$). However, participants with lower levels of love withdrawal in the oxytocin condition showed poor performance compared with participants with lower levels of love withdrawal in the placebo condition (oxytocin: $M = 27.77$, $SD = 3.81$, placebo: $M = 30.17$, $SD = 1.75$, $d = 0.81$). Correlations between love withdrawal and RMET performance were examined in order to examine whether experiences of maternal use of love withdrawal hinder mental state attribution. There was a significant negative correlation between love withdrawal and RMET score for participants in the placebo group ($r = -.41$, $p < .05$). More experiences of love withdrawal were related to worse RMET performance. However, this association was absent in the oxytocin group ($r = .09$, $p = .67$). The difference between the correlation coefficients was significant ($p = .04$).

Discussion

In this study we examined the influence of intranasal oxytocin on neural activity during the Reading the Mind in the Eyes Test with fMRI, taking into account harsh caregiving experiences as a potential moderator. We found that intranasal oxytocin enhanced activation in the insula and the STG, extending toward the STS, during mental state

attribution compared with gender identification. This is consistent with previous studies showing that these regions are activated during the RMET (Adams et al., 2009; Mascaro et al., 2013; Moor et al., 2012) and can be affected by intranasal oxytocin administration (Pincus et al., 2010; Riem et al., 2011). Enhanced insula, STS, and STG activation might facilitate mental state attribution, since these regions are implicated in empathy and theory of mind (Bernhardt & Singer, 2012; Gallagher & Frith, 2003; Hein & Knight, 2008). However, the effects of oxytocin on STG were moderated by harsh caregiving experiences. Oxytocin enhanced STG activation only in individuals who experienced higher levels of maternal love withdrawal. Individuals who reported lower levels of maternal love withdrawal did not show increased STG activation after oxytocin administration. Moreover, influences of maternal love withdrawal on the effects of oxytocin on RMET performance outside the scanner were also found. Oxytocin enhanced RMET performance in individuals with higher levels of love withdrawal, but decreased RMET performance in individuals with lower levels of love withdrawal.

Our finding that the effects of oxytocin on STG activation and RMET performance are moderated by experiences of love withdrawal is in line with studies showing that the effects of oxytocin are dependent on context and individual characteristics (Bakermans-Kranenburg et al., 2012; Van IJzendoorn et al., 2011b). For example, effects of oxytocin have been found to be moderated by attachment anxiety, with less anxiously attached individuals remembering their mother as more caring and close after oxytocin administration, but more anxiously attached individuals remembering their mother as less caring and close after oxytocin administration (Bartz et al., 2010b). More specifically related to emotion recognition and mental state reasoning, Bartz et al. (2010a) showed that intranasal oxytocin improves empathic accuracy only in less socially proficient individuals. Similarly, beneficiary oxytocin effects on RMET performance have been found in individuals with high alexithymia, but not in individuals with low alexithymia (Luminet, Grynberg, Ruzette, & Mikolajczak, 2011). In addition, Domes et al (2007) found that oxytocin improved RMET performance for difficult items, but not for easy items. Thus, oxytocin may improve mental state reasoning when people have difficulty inferring others' mental states, thoughts, or feelings, either because they are less socially proficient or because the social cues that give information on the emotional state of the other are subtle or ambiguous.

Interestingly, we found that oxytocin enhanced STG activation and RMET performance only in individuals reporting higher levels of maternal love withdrawal. Individuals who experienced maternal use of love withdrawal might be less socially proficient compared with individuals with a supportive family background, since harsh parenting experiences place children at increased risk for developing poor theory of mind skills (Cicchetti et al., 2003; Pears & Fisher, 2005). Indeed, we found that maternal love

withdrawal was negatively correlated with RMET performance, supporting our hypothesis that maternal love withdrawal hinders mental state attribution. No relation between love withdrawal and RMET performance was found in the oxytocin condition, indicating that intranasal oxytocin compensates for deficits in socio-cognitive functioning in individuals with harsh caregiving experiences. These findings are in line with previous studies showing that the effects of oxytocin are a function of the baseline socio-emotional abilities of the subject (Bartz et al., 2010a; Luminet et al., 2011). Intranasal oxytocin might help individuals who are less attuned to social information and fail to interpret social cues at baseline (Bartz et al., 2010a; Bartz et al., 2011).

Our finding that oxytocin enhances STG activation and RMET performance only in individuals with higher levels of love withdrawal is in contrast with previous studies that found that intranasal oxytocin enhances social behavior only in individuals with a supportive family background. For example, Van IJzendoorn et al (2011b) found that oxytocin increased donating to a charity in individuals with lower levels of love withdrawal, but not in individuals with higher levels of love withdrawal. Similarly, in a previous study (Riem et al., 2013) with the same sample as in the current study, we showed that oxytocin increased prosocial helping behavior toward an experimenter who was socially excluded during a virtual ball tossing game, but only in individuals reporting lower levels of love withdrawal.

There may be at least two explanations for these contrasting findings. First, the moderating influence of harsh caregiving experiences on the effects of oxytocin may be dependent on the outcome that is at stake. Intranasal oxytocin might not enhance prosocial behavior in individuals with higher levels of love withdrawal because these negative childhood experiences may have resulted in an insecure internal working model (Bowlby, 1969/1982), which predisposes individuals to see social relationships in an even more negative light after oxytocin administration (Bartz et al., 2010b). However, in contrast to prosocial *behavior*, intranasal oxytocin might still affect outcomes related to socio-cognitive processing such as mental state attribution in individuals with negative caregiving experiences. Second, differences in the timing of intranasal oxytocin administration between studies might explain the seemingly contrasting findings. In the current study, time between oxytocin administration and data acquisition was shorter compared with previous studies on the moderating influence of love withdrawal on the effects of oxytocin (Riem et al., 2013; Van IJzendoorn et al., 2011b). Salivary oxytocin levels have been shown to remain elevated for more than seven hours, which can be explained by the feed forward mechanism of the oxytonergic system, with increased oxytocin levels leading to more production of oxytocin (Van IJzendoorn et al., 2012). However, harsh caregiving experiences affect methylation of genetic areas regulating the oxytocin system (McGowan et al., 2009;

Van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011a), which might in turn lead to an altered feed forward mechanism. Thus, effects of intranasal oxytocin might be more short-lived in individuals who experienced harsh parenting. This may explain why in the current study with a short interval between administration and testing we found oxytocin effects in individuals reporting higher levels of love withdrawal, whereas in studies with a longer time between administration and testing no effects of oxytocin in these individuals were found. Future studies should examine the mechanism underlying the differential effects of oxytocin in individuals with different family background and may clarify how contextual and individual characteristics in tandem modulate the effects of oxytocin.

One limitation of our study is that the use of a between-subject design implies the risk of pre-existing differences between the placebo and oxytocin group. Randomization and double-blind application have decreased this risk substantially. Another limitation is that the findings of the current study can only be generalized to women without children. Effects of oxytocin on neural activation during the RMET might be different in men and women with children. Further, the use of self-reported maternal love withdrawal is another limitation of our study. Interview assessments or observations of experiences with the parents might yield more valid data. Lastly, we found that oxytocin reduced RMET performance in individuals with lower levels of love withdrawal, which is in contrast to previous studies indicating that oxytocin enhances empathy and emotion understanding (Bartz et al., 2010a; Domes et al., 2010). Replication of this finding is needed to examine whether oxytocin indeed can have negative effects on mental state attribution.

In sum, this study is the first randomized-controlled trial examining the effects of intranasally administered oxytocin on the neural mechanisms underlying mind-reading, taking into account family background as a potential moderator. We found that oxytocin enhanced neural activation in empathy-related brain regions during the RMET. Moreover, oxytocin increased RMET performance outside the scanner, indicating that it facilitates mental state attribution. However, the oxytocin induced changes in STG activation and RMET performance were moderated by family background. The positive effects of oxytocin were only brought about in potentially less socially proficient individuals who had low RMET performance, that is, individuals who experienced higher levels of maternal love withdrawal. Our findings are in line with studies showing that individual characteristics shape the effects of oxytocin on social cognition (Bakermans-Kranenburg et al., 2012; Bartz et al., 2010b; Riem et al., 2013; Van IJzendoorn et al., 2011b) and that the effects of oxytocin are a function of the baseline socio-emotional abilities of the participant (Bartz et al., 2010a; Luminet et al., 2011). Oxytocin seems to be most helpful for individuals who are less attuned to subtle social cues that give information on the emotional state of the other.

Table S1. *MNI coordinates and Z-max values for local maxima within the significantly activated clusters during mental state attribution compared with gender identification*

			MNI coordinates			
Contrast	Cluster	Brain region	x	y	z	Peak *Z*
Placebo Mental state > Gender	1	L Occipital Fusiform Gyrus	-40	-70	-16	7.65
	1	L Lateral Occipital Cortex	-30	-90	-10	7.06
	1	R Occipital Fusiform Gyrus	34	-66	-20	7.01
	1	L Temporal Fusiform Cortex	-40	-40	-20	6.93
	1	L Temporal Occiptal Fusiform Cortex	-38	-50	-18	6.71
	1	R Occipital Pole	24	-96	-6	6.62
	2	L Inferior Frontal Gyrus	-52	14	24	8.14
	2	L Inferior Temporal Gyrus	-42	0	42	7.40
	2	L Frontal Operculum Cortex	-48	28	-4	6.81
	2	L Frontal Pole	-50	38	-4	6.79
	2	L Inferior Frontal Gyrus	-46	28	4	6.59
	2	L Insula	-28	26	0	6.11
	3	R Inferior Frontal Gyrus	56	26	12	6.10
	3	R Inferior Frontal Gyrus	56	20	20	5.13
	3	R Inferior Frontal Gyrus	44	12	26	4.69
	3	R Temporal Pole	54	14	-16	4.31
	3	R Insula	30	16	0	4.08
	3	R Precentral Gyrus	60	20	34	4.06
	4	L Paracingulate Gyrus	-4	14	44	7.22
	4	L Superior Frontal Gyrus	-8	16	66	3.31
	4	L Paracingulate Gyrus	-8	24	32	3.22
	4	R Anterior Cingulate Gyrus	12	24	28	3.17
	4	R Paracingulate Gyrus	12	22	32	3.16
	4	R Superior Frontal Gyrus	8	12	68	2.73
Oxytocin Mental state > Gender	1	L Inferior Frontal Gyrus	-48	20	20	7.92
	1	L Middle Temporal Gyrus	-54	-48	6	7.08
	1	L Superior Temporal Gyrus	-46	26	-4	7.04
	1	L Orbitofrontal Cortex	-40	26	-10	6.73
	1	L Precentral Gyrus	-42	0	44	6.62
	1	L Temporal Fusiform Cortex	-42	-42	-22	6.47
	2	L Inferior Frontal Gyrus	58	26	10	5.90
	2	R Temporal Pole	52	14	-18	5.81
	2	R Frontal Operculum Cortex	36	24	2	4.24
	2	R Inferior Frontal Gyrus	40	12	24	3.82
	2	R Precentral Gyrus	30	8	28	3.13
	3	L Paracingulate Gyrus	-2	12	46	6.68
	3	L Juxtapositional Lobule Cortex	-4	8	50	6.64
	3	L Superior Frontal Gyrus	-6	14	56	6.28
	3	L Superior Frontal Gyrus	-6	34	50	3.75
	3	R Anterior Cingulate Gyrus	12	16	32	3.49
	3	L Anterior Cingulate Gyrus	-10	22	30	2.81

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