



## Oxytocin reduces neural activity in the pain circuitry when seeing pain in others



Peter A. Bos<sup>a,b,\*</sup>, Estrella R. Montoya<sup>a,1</sup>, Erno J. Hermans<sup>c,d</sup>, Christian Keysers<sup>e,f</sup>, Jack van Honk<sup>a,b,g</sup>

<sup>a</sup> Department of Psychology, Utrecht University, Heidelberglaan 1, 3584 CS Utrecht, The Netherlands

<sup>b</sup> Department of Psychiatry and Mental Health, University of Cape Town, Groote Schuur Hospital, Observatory, Cape Town, South Africa

<sup>c</sup> Radboud University Medical Centre, Donders Institute for Brain, Cognition, and Behaviour, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>d</sup> Radboud University Medical Centre, Department for Cognitive Neuroscience, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>e</sup> Department of Neuroscience, University Medical Center Groningen, University of Groningen, Antonius Deusinglaan 2, 9713 AW, The Netherlands

<sup>f</sup> The Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands

<sup>g</sup> Institute of Infectious Diseases and Molecular Medicine, Groote Schuur Hospital, Observatory, Cape Town, South Africa

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### ABSTRACT

Our empathetic abilities allow us to feel the pain of others. This phenomenon of vicarious feeling arises because the neural circuitry of feeling pain and seeing pain in others is shared. The neuropeptide oxytocin (OXT) is considered a robust facilitator of empathy, as intranasal OXT studies have repeatedly been shown to improve cognitive empathy (e.g. mind reading and emotion recognition). However, OXT has not yet been shown to increase neural empathic responses to pain in others, a core aspect of affective empathy. Effects of OXT on empathy for pain are difficult to predict, because OXT evidently has pain-reducing properties. Accordingly, OXT might paradoxically decrease empathy for pain. Here, using functional neuroimaging we show robust activation in the neural circuitry of pain (insula and sensorimotor regions) when subjects observe pain in others. Crucially, this empathy-related activation in the neural circuitry of pain is strongly reduced after intranasal OXT, specifically in the left insula. OXT on the basis of our neuroimaging data thus remarkably decreases empathy for pain, but further research including behavioral measures is necessary to draw definite conclusions.

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### Introduction

Empathy refers to a plethora of capacities and qualities, ranging from automatically reading motives, intentions and feelings from bodily cues of others, to vicariously experiencing pain and distress when others are hurt (Decety, 2011; Keysers et al., 2010; Panksepp and Panksepp, 2013; Panksepp, 1998; Preston and de Waal, 2002). Empathy thus covers a cognitive–affective continuum (Panksepp and Panksepp, 2013), with on the one end the cognitive-empathic “mind reading” abilities, and on the other the social-affective properties, wherein empathy for pain is a key evolutionarily conserved form of empathy (Decety, 2011; Panksepp and Panksepp, 2013; Panksepp, 2009; Preston and de Waal, 2002). Human neuroimaging studies have revealed that experiencing physical and social pain, and witnessing the pain of others result in overlapping activity in the brain (Decety, 2011; Keysers et al., 2010; Lamm et al., 2011; Preston and de Waal, 2002), a shared neural circuitry that comprises the insula, the anterior and middle cingulate cortex (ACC; MCC), and the primary and secondary somatosensory cortices

(SI, SII) (Hayes and Northoff, 2012; Keysers et al., 2010; Lamm et al., 2011; Singer et al., 2004).

The neuropeptide oxytocin (OXT) is considered a robust facilitator of empathy (Bos et al., 2012; Panksepp and Panksepp, 2013; Zak et al., 2007). This notion stems from observations of beneficial effects of intranasal oxytocin (OXT) on cognitive aspects of empathy, including the processing of social information (e.g. Hurlemann et al., 2010; Unkelbach et al., 2008), mind reading (Domes et al., 2007; Guastella et al., 2010; Theodoridou et al., 2013), and emotion recognition (Bartz et al., 2010). However, studies investigating the effects of intranasal OXT on empathy for pain are scarce, and the findings are inconclusive. Two studies used subjective ratings to painful stimuli to investigate empathy for pain in others (Abu-Akel et al., 2015; Shamay-Tsoory et al., 2013). In these studies, OXT had no main effect on empathy for pain ratings, but altered the ratings dependent on condition. In the first study, OXT only increased empathy for pain ratings towards others when participants were instructed to adopt the perspective of another, but not when adopting a self-perspective (Abu-Akel et al., 2015), an effect the authors ascribe to OXT's effect on increased self-other distinctiveness (Colonnello et al., 2013). In the second study Israeli Jews observed Jews, Arabs, and Europeans in painful situations (Shamay-Tsoory et al., 2013). Although OXT did not increase empathy for pain ratings, in the placebo condition there were reduced empathy ratings

\* Corresponding author at: Department of Psychology, Utrecht University, Heidelberglaan 1, 3584 CS Utrecht, The Netherlands.

E-mail address: [p.a.bos@uu.nl](mailto:p.a.bos@uu.nl) (P.A. Bos).

<sup>1</sup> These authors contributed equally.

for Arabs in painful situations which were normalized after OXT (Shamay-Tsoory et al., 2013). This selective normalization towards out-group members due to OXT however does not concur with increased self-other distinctiveness, and seems to contrast to previously reported effects of increased in-group preferences after OXT administration (e.g. De Dreu et al., 2010). However, De Dreu used implicit social behavioral measures, whereas self-reports are prone to socially desirable responses (Kämpfe et al., 2009; Zhou et al., 2003), which might have played a role in the experimental setting of Shamay-Tsoory et al. (2013). Only one neuroimaging study wherein participants were told that their romantic partner was receiving an electric shock showed no significant effects on empathy for pain in the pain matrix after intranasal OXT compared to placebo (Singer et al., 2008). Conceivably, the use of romantic partners and pain stimuli that cannot be directly observed (i.e. electric shocks), and thus also depend on cognitive empathic abilities, might have complicated findings.

In sum, there is substantial evidence for beneficial effects of OXT on cognitive empathy (Bartz et al., 2011; Bos et al., 2012; Domes et al., 2007; Theodoridou et al., 2013), but convincing evidence for effects of OXT on empathy for pain is lacking. If OXT increases empathy for pain, it should increase activity in the shared brain circuit of pain and empathy for pain, when individuals are observing pain in others. However, research in both rodents and humans show that OXT also has pain-reducing properties (Lee et al., 2009; Rash and Campbell, 2014; Rash et al., 2013). With regard to the shared neural circuitry of feeling pain and seeing pain in others (Keysers et al., 2010; Lamm et al., 2011), OXT might contrariwise decrease empathy for pain.

Furthermore, research in both animals and humans show that effects of OXT can be strongly context-dependent (Bartz et al., 2011; Bos et al., 2012). OXT facilitates pair bonding in monogamous rodent species (Ross and Young, 2009), but also increases maternal aggression towards intruders (Campbell, 2008). In humans, under certain conditions, OXT can increase glee over misfortune of others (Shamay-Tsoory et al., 2009), and strengthen in-group preferences (De Dreu et al., 2010, 2011). Thus, if OXT increases or decreases empathy for pain, it could very well do so differently towards in- and out-group members. A recent line of studies demonstrate that observation of pain in people from a different racial background leads to attenuated empathic responses in motor regions (Avenanti et al., 2010) and in the cingulate cortices (Azevedo et al., 2012; Xu et al., 2009), but whether OXT would increase rather than reduce such differences is currently unknown. The above described study by Abu-Akel et al. (2015) showed normalization of decreased empathy for pain ratings towards a hated out-group (Arabs) but not to a more neutral out-group (Europeans). Although it is unclear how subjective pain ratings towards others relate to empathic neural responses, it might be that a possible selective effect for the out-group will be reduced after OXT. Based on OXT studies applying implicit social behavioral measures (De Dreu et al., 2010, 2011), increased in-outgroup effects can be expected.

To critically address these matters, we investigated empathic neural responses in 24 white male subjects (mean age 23.1) after administration of intranasal OXT (24 IU) and placebo in a randomized within-subject design. Functional magnetic resonance imaging (fMRI) was used to measure neural responses to short movie clips displaying hands of different individuals with a white and black skin color (see Fig. 1A), which were punctured by a needle (pain condition) or touched by a cotton swab (control condition). Hands of individuals with white and black skin were chosen as respective in- and out-group stimuli, with regard to the above described studies showing that the effects of OXT may depend on in- and out-group dynamics (Bartz et al., 2011; Bos et al., 2012). Finally, as in other empathy for pain experiments (Keysers et al., 2014; Lamm et al., 2011; Meffert et al., 2013), to focus on vicarious pain representations, participants were given innocuous and moderate electroshocks on their hands while in the scanner and were asked to report the painfulness of each shock. We then identified voxels in this pain localizer experiment, in which brain activity during

shock experience was positively correlated with reported painfulness, and used this network as our search volume while exploring activity to seeing pain in others. To limit the burden on the participants undergoing the OXT and placebo treatment, the pain localizer was collected in a separate sample of participants.

## Materials and methods

### Participants

Main Experiment: 24 healthy Caucasian Dutch males (age range 19–27; mean age 23.1) were recruited at the university campus of Utrecht University. Participants were free of medication, had no history of psychiatric, neurological, or endocrine abnormalities and did not smoke. The experimental protocol was approved by the ethics committee of the University Medical Center Utrecht and was in accordance with the latest declaration of Helsinki. The study is registered in the WHO-approved Dutch Clinical trial register (TC1454). The participants gave written informed consent and received payment afterwards. Pain Localizer: see section on pain localizer.

### Oxytocin administration

The setup of the study followed a within-subject, double-blind, placebo-controlled, counterbalanced crossover design in which 24 IU of OXT was administered (Syntocinon nasal spray; Defiante Farmacêutica, S.A.). Participants self-administered 3 puffs (a 4 IU) per nostril under supervision of the experiment leader. The placebo consisted of a NaCl solution produced by the pharmacist of the University Medical Centre Utrecht in accordance with GCP guidelines.

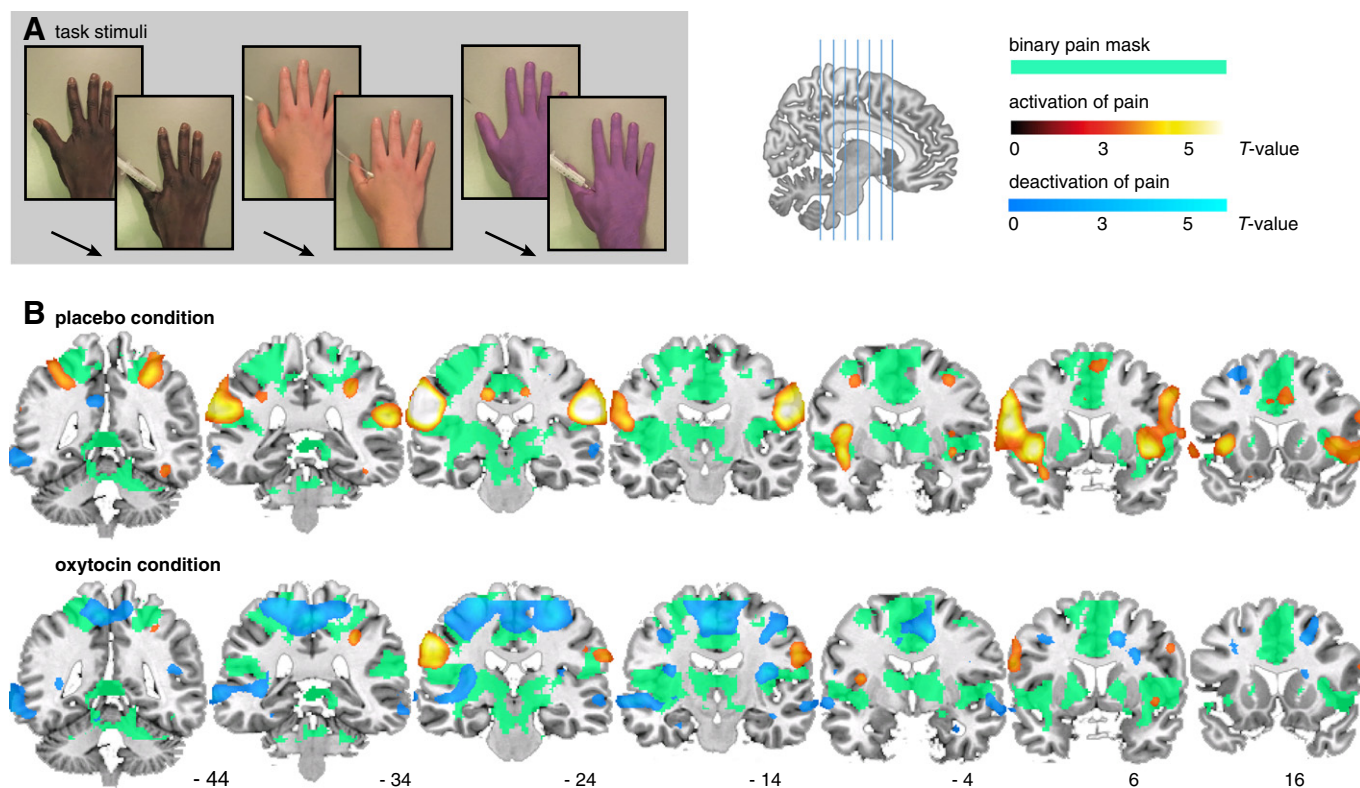
### Experimental task

The task was based on Avenanti et al. (2010) and consisted of 2.5 s movie clips of male right hands that were either punctured by a needle (pain condition) or touched by a cotton swab (control condition). For the in- and out-group conditions, 3 white and 3 black hands were used respectively. Since any effect of the black hands in our white participant group could be explained by reduced familiarity with black hands, following Avenanti et al. (2010) we also included a purple hand condition. The purple hand condition was created by painting a white, a black, and an additional hand of intermediate skin color using Grimas make-up (code 601; [www.grimas.nl](http://www.grimas.nl)). Movies were recorded using a JVC-handycam recorder and were converted to movie frames using Adobe Premiere Elements software. Frames were selected such that the tip of the needle (or cotton swab) could be seen on the first frame and that it touched the skin of the hand at approximately 1 s. E-prime software (version 1.2; <http://www.pstnet.com>) was used to present the stimuli.

Every stimulus was presented 5 times on a grayscale background, yielding 15 stimulus presentations for all 6 conditions and 90 stimulus presentations in total throughout the task which were randomly presented. In between the stimuli a black fixation cross was presented on a grayscale background with an average duration of 5 s that varied between 3 and 8 s. In 10% of the trials, the fixation cross changed color upon which participants were instructed to press a button. This was to ensure that participants were attending to the stimuli throughout the task.

### Procedure

Participants were scanned at the same time of day on two separate days with an interval of at least 72 h. Before administration participants were screened for alcohol and drug use, were given brief explanations of the task and gave written informed consent.



**Fig. 1.** A) Pictures of the first and last frames of the movie clips. From left to right: the black hand in the pain condition, the white hand in the non-pain condition, and the purple hand in the pain condition. B) Coronal brain slices of the anatomical pain mask (in green), and the T-maps for the contrast of pain versus non-pain in the placebo and oxytocin conditions (placebo: upper panel; oxytocin: lower panel) which are overlaid onto a T1-weighted canonical image. Activation for pain is plotted in yellow–red color scale, deactivation for pain is plotted in blue scale. Accompanying MNI-coordinates on the Y-axis are presented below, and all T-maps are thresholded at  $P < 0.005$  (uncorrected) for illustration purposes only (see Table 1 for inferential statistics).

The participants then self-administered the nasal spray under supervision of the experiment leader and were seated in a waiting room until asked to proceed to the scanner. Participants were screened using an MRI-checklist and a metal detector, and were instructed to position themselves on the scanner bed as comfortable as possible and to try to relax. Head movement was minimized by foam pads which were placed between the RF-coil and participants' head. Instructions and task images were back-projected onto a translucent screen positioned near the participants' feet. Participants also received a button-box in their left or right hand to respond to the color-change of the fixation cross. Hand side was held constant over both sessions and was counterbalanced with drug order. Further instructions during the scan session were given by intercom. The time interval between OXT administration and the start of the task was kept constant at approximately 55 min (min: 47; max 60; SD: 4.6), a time interval consistent with most studies showing effects of OXT on behavior published so far (Bos et al., 2012).

After the second session, participants were debriefed and given payment. They were further asked to guess which day they received the OXT and to fill out an explicit race bias questionnaire, which allowed us to exclude participants with openly racial attitudes. Analysis of the debriefing questionnaire indicated that our participants did not hold openly racist attitudes. Neither were they aware on when they received OXT or placebo (binomial:  $P = 0.31$ ).

#### fMRI data collection and analyses

Scanning was performed on a 3 Tesla Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands). Before the functional scans, a high resolution anatomical T1-weighted scan with the following parameters was obtained for co-registration and normalization

purposes: 3.8 ms echo time, 8.4 ms repetition time,  $288 \times 288 \times 175$  mm field of view, 175 sagittal slices, flip angle of  $8.0^\circ$ , voxel size 1.0 mm isotropic. Blood oxygen level dependent (BOLD-) response was measured with functional T2\*-weighted images, of which 490 were obtained throughout the task. The 2D-EPI-SENSE sequence had the following parameters: echo time 23 ms, repetition time 1.4 s,  $208 \times 256$  mm field of view, 30 slices, flip angle of  $70^\circ$ , voxel size 4.0 mm isotropic, SENSE-factor  $R = 2.4$  (anterior–posterior).

Preprocessing and subsequent analyses were performed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Functional scans of both sessions were motion corrected to the first dynamic scan and slice-time corrected to the middle slice. The anatomical scan was then coregistered to the mean functional scan. Subsequently, using unified segmentation, the structural scan was segmented and normalization parameters were estimated. Using these normalization parameters, all volumes were normalized to a standard brain template (MNI) and were resliced at 2 mm isotropic voxel size. Smoothing with an 8 mm full width at half maximum gaussian kernel was applied to the normalized functional volumes.

A general linear model (GLM) was applied to both sessions to investigate the effects of the pain and control stimuli, and the interaction with drug administration. For both sessions, neural responses to the presentation of the stimuli are modeled using 2.5 s boxcar function convolved with a hemodynamic response function (HRF) as implemented in the SPM8 software.

For both sessions, seven regressors were entered into the model, six for the effects of interest (pain and control conditions for the white hand, black hand, and purple hand), and one regressor modeling the button press in response to the color change of the fixation cross. Additionally, realignment parameters and a discrete cosine transform high pass filter with a cut-off of 128 s were entered into the analyses to



reduce unexplained variance. For the group analyses contrast maps of all conditions versus rest were computed.

In the first analysis, we investigated the effects of the pain and control stimuli and the interactions with hand color. The contrast maps of the placebo condition were entered into a factorial  $2 \times 3$  ANOVA with pain (pain or control) and hand color (white, black, or purple) as separate factors. In the second analysis, in which we investigated the effect of drug on the neural correlates of pain, contrast maps of the drug and placebo condition were entered into a  $2 \times 2 \times 2$  factorial ANOVA with drug (OXT or placebo), pain (pain of control), and hand color (white or black) as separate factors. Since the purpose of the purple hand condition in this task was to show that differences appearing between the white and black hands in the placebo condition were not caused by less familiarity of our participants with the black hands, this condition was omitted in the second group analysis.

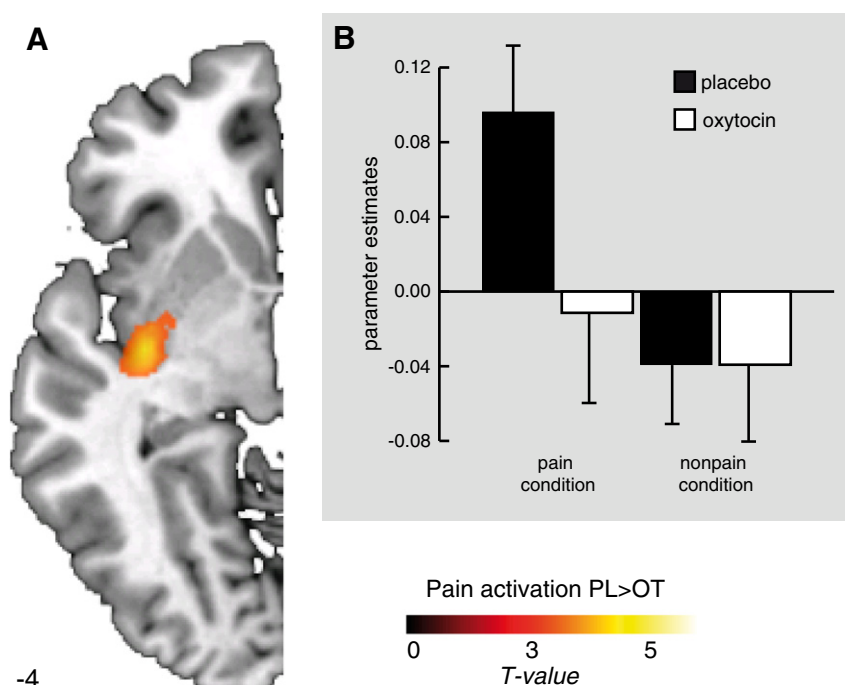
All calculated linear contrasts were masked by a binary brain mask of neural activation in response to pain sensation, restricting our analysis to only include neural regions that are also activated during actual pain sensation (see below: pain localizer). Within this mask, only activations are reported that survive a voxel-wise  $P < .05$  Family Wise Error (FWE) correction for peak level. In addition, we tested for any additional activation outside the mask for all contrasts at the same corrected threshold, and report these effects in supplementary Table S1. In all analyses order was entered as a between subject factor, and was removed from the analyses if it showed not significant. To link activation patterns to anatomy, the significant voxels were inspected with the Anatomy Toolbox for SPM (Eickhoff et al., 2007) or the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002) if the region was not included in the probabilistic cytoarchitectonic maps of the Anatomy toolbox. Also, based on previous studies investigating neural empathic responses towards pain, the following regions of interest were defined: insula, anterior and mid cingulate cortex (ACC; MCC), and the primary and secondary somatosensory cortices (SI; SII) (Hayes and Northoff, 2012; Keyers et al., 2010; Lamm et al., 2011; Singer et al., 2008). For these regions, small volume voxel-wise corrections (SVC) were applied to bilateral anatomically

defined regions based on probabilistic cytoarchitectonic atlas in the Anatomy toolbox. The contrasts were first masked with the binary pain mask to assure that the reported voxels are also activated during pain experience. Next, small volume corrections (FWE  $P < .05$ ) were applied for each of the anatomical ROIs as defined using the Anatomy Toolbox for SPM. The anatomical masks for the anterior and mid cingulate cortex, and the bilateral insula were based on the AAL template (Tzourio-Mazoyer et al., 2002), as these are not incorporated in the Anatomy toolbox. Also, for illustration purposes only, we extracted the parameter estimates of left insula and plotted these in Fig. 2B to display the effect of OXT in the pain condition.

#### Pain localizer

Thirty volunteers, not included in the main study, participated in this localizer, (14 males, 16 females, age  $24.8 \pm 4.37$ , mean  $\pm$  s.d.). All participants were healthy, right-handed, had no history of neurological or psychiatric disorders, and provided with written informed consent. This study was approved by the Ethics Committee of the University of Amsterdam, the Netherlands.

In one acquisition run, sixteen noxious and sixteen innocuous 0.5 s electroshocks were applied in a pseudo-randomized order (i.e. no more than two consecutive shocks of the same intensity were delivered consecutively). Stimuli consisted of 100 Hz train of electrical pulses, 2 ms each, lasting 0.5 s each, using an MRI-compatible electrical stimulator attached on the back of the right hand on the 4th musculus interossei, stimulation area  $16 \text{ mm}^2$ , through two bipolar surface electrodes. After 2 to 5 s (randomized interval) participants were asked to evaluate how painful each electroshock was by moving a cursor on a 10 point visual analog scale on the screen using three buttons of an MRI compatible button-box placed next to their left hand. Two buttons were used to move the slider left and right on the visual scale on the screen and the third button was for confirmation. The pain intensity scale was a 10 point scale (1: not painful at all; 10: most intense imaginable pain), with the starting point set randomly for each trial to disentangle the number of button presses from the rating. Participants took



**Fig. 2.** A) Axial brain slice of the T-map for the contrast OXT < placebo in the pain condition only. The T-map is thresholded at  $P < 0.005$  (uncorrected) for illustration purposes only and was overlaid onto a T1-weighted canonical image (see Table 1 for inferential statistics). B) Bar-graph of the extracted parameter estimates of the anatomically defined left insula for the pain and non-pain conditions in both drug sessions, aggregated over both in- and out-group stimuli.

on average 3.4 s to do this rating. The next trial then started after a randomized intertrial interval between 8 and 12 s long. Before the scanning we measured the pain threshold from the participant. We started from a 0.2 mA current that was then increased until maximally 6.0 mA in 0.1 mA steps (Singer et al., 2004). Participants were instructed to evaluate how painful the stimulation was on a 10-point scale. We then chose the current corresponding to a rating of 7 for the painful condition and of 2 for the painless condition (Singer et al., 2004). The current selected was  $0.75 \pm 0.14$  mA (mean  $\pm$  s.e.m) for the painless and  $2.12 \pm 0.77$  mA for the painful condition.

A Phillips Achieva 3.0 Tesla MRI scanner was used for image acquisition as in the main experiment. We used a T2\*-weighted echo-planar sequence with 32 interleaved 3.5 mm thick axial slices and a 0.35 mm gap for functional imaging (TR = 1700 ms, TE = 27.6 ms, flip angle = 73°, FOV = 240 mm  $\times$  240 mm, 80  $\times$  80 matrix of 3.5 mm isotropic voxels). At the end of the functional scanning, a T1-weighted anatomical image (1  $\times$  1  $\times$  1 mm) covering the whole brain, was acquired. Preprocessing was performed as for the main experiment.

The data was analyzed by a GLM at the first level including one predictor for all 32 electrical stimulations with a parametric modulator for the subjective rating of pain. A second predictor contained the rating period, from onset of the rating screen until the end of the button presses. All predictors were modeled as box-cars and convolved with the HRF. Six additional predictors of no interest, resulting from the realignment procedure, were entered to account for translations and rotations of the head (none of the included participants had head motion parameters exceeding the acquired voxel-size). At the second level, we then identified voxels where the parametric modulator for

subjective pain report was positive and non-zero (i.e. BOLD signal correlated positively with pain report). Results were thresholded at  $P < 0.05$  (FWE-corrected) to generate a binary mask to be used as search-space for the main experiment.

## Results

In the placebo condition we found that within the pain localizer, compared to control stimuli, the needle puncturing the hand (averaged over hand-color) results in strong bilateral activation of SI and SII, the insula, and MCC, and the inferior frontal gyrus (Table 1; Fig. 1B upper panel). These are important regions of the brain's pain matrix and have shown activation both during the experience of pain, as well as perceiving another person in pain (Keysers et al., 2010; Lamm et al., 2011). There was no increased activation for the control stimuli compared to the pain stimuli within the pain localizer mask (Table 1).

Next, within the same pain localizer mask, we addressed the effect of OXT. An overall interaction between drug administration and pain condition as separate factors (t-contrast: placebo (pain–nonpain)–oxytocin (pain–nonpain); Table 1), showed a significant effect in the secondary somatosensory cortices, the insula, and the MCC (all regions;  $P < 0.05$ , SVC at FWE). The opposite t-contrast of the interaction between drug and pain (oxytocin (pain–nonpain)–placebo (pain–nonpain)) did not result in significant effects in or outside the pain mask. To break down the positive interaction between OXT administration and condition, we performed direct t-tests within the OXT condition, and between the OXT and placebo conditions. The interaction was driven by reduced activation for the pain stimuli in the OXT condition (Table 1), as the

**Table 1**  
Inferential statistics of fMRI data for placebo and oxytocin session separately and combined.

Anatomical region		MNI coordinates			Voxels	Peak T	P-value*
		x	y	z			
Placebo session incl. purple hand condition							
Activation of pain: (pain black + pain white + pain purple)–(no pain black + no pain white + no pain purple)							
SII	R	60	–22	26	283	7.58	<0.001
	L	–58	–22	24	243	7.05	<0.001
		–56	–22	36	30	6.68	<0.001
Inferior temporal cortex	R	48	–64	–2	63	6.52	<0.001
Insula	L	–40	10	–2	74	5.33	0.004
	R	42	2	–2	20	5.15	0.009
SI	R	32	–44	54	111	4.10	0.029**
	L	–58	–20	38	36	5.60	<0.001**
Middle cingulate cortex	L	–14	–26	40	6	4.11	0.019**
Main effect of hand color: (black pain + black no pain + purple pain + purple no pain)–(2 white pain + 2 white no pain)							
Fusiform gyrus	R	26	–66	–18	1	4.80	0.035
Oxytocin session							
Activation of pain: (pain black + pain white)–(no pain black + no pain white)							
Middle temporal cortex	R	46	–62	0	63	5.47	0.002
SII	L	–56	–22	22	17	3.97	0.02**
SI	L	–58	–22	40	11	4.05	0.033**
Deactivation of pain: (no pain black + no pain white)–(pain black + pain white)							
Primary motor cortex	L	–4	–38	56	12	5.05	0.012
Middle cingulate cortex	R	12	–2	44	2	4.82	0.029
	L	–4	–34	52	1	4.70	0.046
Supplementary motor area	L	–24	–28	70	27	4.92	0.020
	L	–8	–12	54	14	4.83	0.029
SII	R	38	–16	18	2	4.96	0.047
SI	L	–24	–30	70	254	4.62	0.004**
Insula	R	36	–16	18	69	4.69	0.001**
	L	–34	–20	18	82	4.18	0.009**
Oxytocin and placebo session							
Interaction: (placebo (pain black + pain white)–placebo (no pain black + no pain white))–oxytocin ((pain black + pain white)–oxytocin (no pain black + no pain white))							
SII	R	58	–24	24	66	4.09	0.014**
	L	–4	–38	54	15	4.13	0.017**
Middle cingulate cortex	R	12	2	44	35	3.82	0.046**
	L	–38	–12	–6	55	4.14	0.011**
Pain condition: placebo (pain black + pain white)–oxytocin (pain black + pain white)							
Insula	L	–36	–12	–4	17	3.95	0.021**

\* Voxel-wise corrected within pain mask at FWE  $P < 0.05$ .

\*\* Small volume corrected for ROI at same threshold.

contrast in the OXT condition shows significant deactivation in the pain condition compared to the control condition in the MCC and SII (both regions;  $P < 0.05$  at FWE), the insula and SI (both regions;  $P < 0.05$ , SVC at FWE; Table 1, Fig. 1B lower panel). The pain condition did also elicit activation after OXT, but to a much lesser extent compared to the robust activation observed in the placebo condition, as only small parts of the SI and SII were significantly activated ( $P < 0.05$ , SVC at FWE). Finally, a direct test between drug conditions in the pain condition showed that the left insula was significantly reduced after OXT administration compared to placebo ( $P < 0.05$ , SVC at FWE; Fig. 2), whereas the opposite contrast in the non-pain condition showed no significant effects. Thus, our analysis showed that in the placebo condition looking at the pain stimuli resulted in strong bilateral activation of the pain circuitry, while opposite effects appeared after OXT, that is, deactivation of this circuitry to the pain stimuli. The analysis further showed that selectively in response to the pain stimuli, the insula was significantly decreased after the OXT administration.

With regard to the in-out-group effects of OXT described in the introduction, we also investigated whether there were effects of hand color on the neural responses to pain, and if OXT had selective effects on in- and out-group hands. Overall, the only effect of hand color in the present data was a main effect in the placebo condition, in which the right fusiform gyrus activated stronger in response to black and purple hands compared to white hands ( $P < 0.05$  at FWE). This effect was however not specific for the pain or control condition, and might therefore reflect increased visual processing of more unfamiliar stimuli. Thus, in contrast to previous findings (Azevedo et al., 2012; Xu et al., 2009), we did not observe differences in the ACC to in- and out-group hands in pain. To investigate the effect of hand color on the effect of OXT, we calculated the interactions with hand color, drug administration, and pain condition. None of the calculated interactions with hand color and drug showed significant effects, indicating that our drug effects were independent of hand color. Additionally, there were no significant effects of order on the data, or any effects of drug outside the pain mask (Table S1).

## Discussion

Multiple studies have shown effects of OXT promoting cognitive, conscious and deliberate aspects of social information processing (Hurlmann et al., 2010; Unkelbach et al., 2008), including mind reading and emotion recognition (Bartz et al., 2010; Domes et al., 2007; Guastella et al., 2010; Theodoridou et al., 2013). As a result, OXT is widely considered to be a facilitator of empathy (Bos et al., 2012; Domes et al., 2007; Hurlmann et al., 2010; Panksepp and Panksepp, 2013; Zak et al., 2007). Here, using pharmaco-fMRI, we investigated the effects of intranasal OXT on empathy for pain by measuring neural empathic responses to pain observed in others. Whereas in the placebo condition we show strong neural responses in the pain circuitry to seeing pain in others, an opposite pattern of decreased activation to observed pain appears in the OXT condition. Specifically activation to pain in the insula, a core region in empathic processing (Jabbi et al., 2007; Singer et al., 2004), is significantly reduced after OXT. In the case of increased empathy for pain, OXT administration was expected to result in increased neural empathic responses when observing pain in others. The data however clearly show an opposite pattern of reduced neural empathic responses to the pain of others. This observation might relate to previous findings of reduced pain related neural activation in anticipation to threat when subjects were holding the hand of their partner (Coan et al., 2006). Social support in the form of hand holding, and even looking at pictures of a beloved one, has also shown to decrease subjective ratings of painful stimulation (Master et al., 2009). A study that measured physiological stress responses (i.e. cortisol elevations) in response to social stress shows that especially the combination of social support with OXT administration reduces stress responding (Heinrichs et al., 2003).

Previous studies investigating the effect of OXT on empathy for pain have either used subjective measures without neuroimaging (Abu-Akel et al., 2015; Shamay-Tsoory et al., 2013), or used a neuroimaging paradigm wherein pain could not be directly observed and thus depended in part on cognitive empathic capacities (Singer et al., 2008). The lack of consistency between our observed reduction in neural empathic responses to pain, and the context-dependent effects found with empathy ratings, brings forth the question to what extent these different measures are dissociated. In this light, a limitation of the current neuroimaging study is that no other measures were used, that is, subjective ratings but especially implicit behavioral indices of empathy for pain. This would have allowed us to investigate the relation between behavioral indexes of empathy and neural empathic responses to pain in others, and should be incorporated into future studies to provide for definite conclusion.

Nonetheless, the current results shed new light on the effects of OXT on empathy by suggesting that it has opposite effects on cognitive empathy and empathy for pain. Cognitive empathy and empathy for pain have been known to dissociate in clinical groups (Decety et al., 2013; Keysers et al., 2014; Meffert et al., 2013; Richell et al., 2003), with autistic individuals showing impaired cognitive but preserved affective empathy (Keysers and Gazzola, 2014; Keysers et al., 2014). Psychopathic individuals on the other hand seem to have preserved cognitive but impaired spontaneous affective empathy (Decety et al., 2013; Meffert et al., 2013). Also, from an evolutionary point of view, deliberate cognitive and spontaneous affective empathy have very different functions and costs (Keysers and Gazzola, 2014; Keysers et al., 2014): while the former allows you to get information about others without direct motivational consequences, the latter motivates you to incur the cost of costly helping. It is therefore not surprising, that evolution would have equipped our brain with ways to modulate these routes separately.

Importantly, our findings involve a specific form of affective empathy: empathy for pain. The processing of pain is neurobiologically regulated by the opioid system (Sprenger et al., 2006; Wager et al., 2007), and the neural circuitries of pain and empathy for pain are shared (Keysers et al., 2010; Lamm et al., 2011). A parsimonious and plausible hypothesis is that the reduced neural empathic responses to pain we show after intranasal OXT involve up-regulation of opioid receptor function (Barceló et al., 2012; Gu and Yu, 2007; Russo et al., 2012; Yang et al., 2011) and correspond to OXT's pain-reducing properties (Gu and Yu, 2007; Lee et al., 2009; Rash and Campbell, 2014; Rash et al., 2013). Variation in opioid sensitivity has been shown to predict reported distress and neural responses for experienced social pain (Way et al., 2009), but whether opioids reduce empathy for pain has not been investigated. Irrespective of the exact underlying mechanisms, if the current findings are indeed brought forth by the pain reducing effect of OXT, the effects might very well be selective for empathy for pain as measured in the current study. In that case, it might not translate to other forms of affective empathy that rely on different neural circuits, or subjective measures of empathy for pain.

Although our pain-stimuli elicited robust activation of the pain matrix, we did not see a modulatory effect of hand color on this activation, or an interaction of hand color with the effect of OXT. The absence of such effects is inconsistent with previous studies showing effects of race on ACC activation when seeing pain in others (Azevedo et al., 2012; Xu et al., 2009). Two explanations could account for these differences. The first is that cultural differences in how people with a dark skin color are perceived in the participants in the separate studies could affect the data. For example, in Italy, where the study of Azevedo et al. (2012) was performed, black African immigrants form a much disliked immigrant group, whereas in the Netherlands traditional immigrants (and thus out-group) are mainly of Moroccan and Turkish origin. The study by Shamay-Tsoory et al. (2013) with subjective ratings described in the introduction indicate that attitudes of the participants play a role in empathic responding (i.e. disliked out-groups result in



other responses than a neutral out-group). The inclusion of in-out-group categories other than ethnical distinctions in future studies could answer the question considering the ubiquity of our findings. Alternatively, variation in methodology between the studies could also account for the different findings. In the current study, we controlled for attendance to the stimuli by having participants press a button when the fixation cross changed color (in 10% of the trial), whereas the previous studies employed a passive viewing paradigm (Azevedo et al., 2012; Xu et al., 2009). In anticipation of a possible motor response, our attention check will have resulted in preparatory motor activation in the ACC/MCC during the fixation cross. A study investigating the interaction between motor responding and neural empathic responses to pain showed these processes are strongly interdependent, and subserved by the ACC and MCC (Morrison et al., 2007). According to the authors, the functional role of the ACC and MCC responses to seeing pain in others is possible to 'poise the observer on the knife-edge between the execution and suppression of a motor response'. In our paradigm, the increased activity during the baseline period might have reduced sensitivity in detecting differences in the BOLD-response during the presentation of the pain and non-pain stimuli, and as such, obscure possible in-out-group differences. Interestingly, the study by Morrison et al. (2007) also showed that activation of the insula, where we observed the clearest effects of OXT (see Fig. 2), was fully independent of (pre)motor preparation and execution. This is in line with the view that the insula is critical for the affective component of empathic responding (Craig, 2009; Jabbi et al., 2007; Lamm et al., 2011; Singer et al., 2004).

OXT is proposed as medication in a broad range of emotional disorders, but this is not always based on sound evidence (Miller, 2013). OXT might have beneficial effects in disorders characterized by impaired cognitive empathy, such as autism. Indeed, in a meta-analytic review covering 19 clinical OXT trials in various emotional disorders only studies on autism showed a promising effect size (Bakermans-Kranenburg and Van IJzendoorn, 2013). Since lack of empathy for pain is primary to psychopathy, our data suggest that the use OXT in psychopathic individuals may not be advisable (Liu et al., 2012). As such, our findings add to the increasing evidence showing that OXT's effects strongly depend on personal and contextual factors (Bartz et al., 2011; Bos et al., 2012). The data further reveal a dissociation of the facilitating and inhibiting effects on OXT in cognitive empathy and affective empathy for pain. Further fundamental insights into the effects of OXT on the human social brain and behavior are necessary to better inform clinical strategies (Miller, 2013). Herein the differences in the effects of OXT on cognitive and affective empathy might be a critical factor. However, further OXT administration research, which also includes behavioral measures is necessary to draw more definite conclusions.

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