



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



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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

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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). 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.

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