

Effects of Oxytocin and Prosocial Behavior on Brain Responses to Direct and Vicariously Experienced Pain

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In this study, we tested the validity of 2 popular assumptions about empathy: (a) empathy can be enhanced by oxytocin, a neuropeptide known to be crucial in affiliative behavior, and (b) individual differences in prosocial behavior are positively associated with empathic brain responses. To do so, we measured brain activity in a double-blind placebo-controlled study of 20 male participants either receiving painful stimulation to their own hand (self condition) or observing their female partner receiving painful stimulation to her hand (other condition). Prosocial behavior was measured using a monetary economic interaction game with which participants classified as prosocial ($N = 12$) or selfish ($N = 6$), depending on whether they cooperated with another player. Empathy-relevant brain activation (anterior insula) was neither enhanced by oxytocin nor positively associated with prosocial behavior. However, oxytocin reduced amygdala activation when participants received painful stimulation themselves (in the nonsocial condition). Surprisingly, this effect was driven by “selfish” participants. The results suggest that selfish individuals may not be as rational and unemotional as usually suggested, their actions being determined by their feeling anxious rather than by reason.

Keywords: empathy, pain, prosocial behavior, oxytocin, amygdala

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Social neuroscience has started uncovering the neural mechanisms underlying our capacity for empathy, that is, our capacity to share and understand the feelings of others (de Vignemont & Singer, 2006). The present study extends previous research on empathy in addressing two distinct, currently unresolved questions. It investigates (a) whether empathic brain responses can be enhanced by oxytocin (OT), a neuropeptide that has been found to be involved in the modulation of social affiliative and approach behavior; and (b) whether individual differences in empathic brain responses differ as a function of the type of prosocial behavior observed in a standard economic trust game.

Past endeavors in neuroscientific research on empathy have focused on the question concerning how we (our brains) know what it feels like for another person to experience pain in the absence of any stimulation to our own body. Theoretical conceptualizations of empathy (Decety & Jackson, 2004; Decety & Lamm, 2006; de Vignemont & Singer, 2006; Gallese, 2003; Preston & de Waal, 2002) suggest that we understand other people's affective states via activation of neural networks usually involved in processing our own affective states. Indeed, several human fMRI studies have provided evidence for a role of such shared neural networks that enable one to feel what it feels like for another person to actually experience pain, touch, or disgust when one merely observes or imagines the other person experiencing pain, touch, or disgust—but receives no such stimulation oneself (Avenanti, Buetti, Galati, & Aglioti, 2005; Avenanti, Paluello, Bufalari, & Aglioti, 2006; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007; Cheng et al., 2007; Gu & Han, 2007; Jabbi, Swart, & Keysers, 2007; Jackson, Brunet, Meltzoff, & Decety, 2006; Jackson, Meltzoff, & Decety, 2005; Keysers et al., 2004; Lamm, Batson, & Decety, 2007; Moriguchi et al., 2007; Morrison & Downing, 2007; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; Saarela et al., 2007; Singer et al., 2004, 2006; Wicker et al., 2003).

In an early study, Singer et al. (2004), for example, investigated empathy for pain when participants received pain themselves or

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witnessed their partners receiving pain. The authors showed that the affective components of the pain matrix (anterior insula [AI] and anterior cingulate cortex [ACC]), activated when participants received pain, were also activated vicariously for their partner's pain. This pattern of results has proven to be robust and was seen using different pain stimuli and situations as well as when people empathized with strangers (Botvinick et al., 2005; Jackson et al., 2005; Lamm et al., 2007; Morrison et al., 2004; Singer et al., 2006). Some studies have also provided evidence for a positive correlation between magnitude of empathy-related activation and individual differences as measured by questionnaires such as Davis's (1980) Interpersonal Reactivity Index (Jabbi et al., 2007; Lamm et al., 2007; Singer et al., 2004, 2006). Empathic brain responses are not only positively correlated with trait measures of empathy, but also with online unpleasantness ratings (Cheng et al., 2007; Jackson et al., 2005; Saarela et al., 2007). Furthermore, these empathy-related brain activations appear to be modulated by factors such as the intensity of pain applied to the other (Avenanti et al., 2006), cognitive appraisal (Lamm et al., 2007), previous experience with the empathy-inducing stimulus (Cheng et al., 2007), and perceived fairness of the other (Hein & Singer, 2008; Singer et al., 2006). However, to the best of our knowledge, no study has ever looked at whether such empathic brain responses can also be modulated by pharmacological interventions, for example, by the administration of OT.

In nonhuman mammals, the neuropeptide OT has been shown to play a central role in social behavior. More specific, research has shown that it is associated with the ability to form social attachments and with affiliation, including parental care, pair bonding, sexual behavior, and social memory (Carter, 1998; Insel & Young, 2001; Lim & Young, 2006; Young & Wang, 2004). In addition, OT has been found to also decrease stress responses and anxiety in social interactions (Bale, Davis, Auger, Dorsa, & McCarthy, 2001; Neumann, Kromer, Toschi, & Ebner, 2000; Parker, Buckmaster, Schatzberg, & Lyons, 2005). Receptors for the neuropeptide OT are distributed in various brain regions (Landgraf & Neumann, 2004), including limbic regions such as the amygdala (Huber, Veinante, & Stoop, 2005).

Recent research has shown that neuropeptides cross the blood-brain barrier after intranasal administration (Born et al., 2002), thus providing a useful method for studying the central nervous system effects of OT in humans as well (Heinrichs & Domes, 2008). Recent studies using this method have suggested that OT is also a potent modulator in the processing of social behavior in humans (for a review, see Heinrichs & Domes, 2008). Specifically, OT has been found to reduce endocrine and psychological responses to social stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), to modulate social memory (Heinrichs, Meinschmidt, Wippich, Ehlert, & Hellhammer, 2004), and to increase trust, generosity, and the ability to infer the mental states of another person ("mind reading") (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Zak, Stanton, & Ahmadi, 2007). In general OT has been assumed to play a crucial role in overcoming natural avoidance of proximity and facilitate approach behavior (e.g., Kosfeld et al., 2005). Even though empathy is generally believed to be closely related to prosocial, affiliation, and bonding behavior (for a discussion, see, e.g., Preston & de Waal, 2002) and has been suggested to be enhanced by OT in the literature (e.g., Zak et al.,

2007), this assumption has never explicitly been tested within the context of an empathy paradigm. Thus, to examine the effects of OT on empathy, we used the empathy-for-pain paradigm previously described by Singer et al. (2004).

We hypothesized that if OT really enhances empathy, its effect should be revealed in an increase in subjective ratings of empathic feelings as well as in increased activity in empathic brain responses in AI and ACC when participants are exposed to another person's suffering (other condition). If, however, as accumulating new evidence suggests, OT effects are mostly mediated via the amygdala, effects of OT should be observed in the nonempathy condition when people receive pain (self condition), but not in the empathy condition. Thus, previous studies examining empathy for pain (Singer et al., 2004, 2006; see also, Lamm et al., 2007) have shown enhanced activation of amygdala in the self but not in the other condition. This prediction would not be in line with the suggested social effects of OT but would be in line with recent fMRI studies testing the effect of exogenously administered OT on brain activation in humans exposed to emotional stimuli that showed attenuated activation in amygdala after OT administration (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes, Heinrichs, Glascher, et al., 2007; Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008). Note, however, that these studies chose paradigms using mostly social stimuli known to activate the amygdala such as fearful facial expressions. Using the present paradigm, we compare for the first time a social condition not involving amygdala responses and a nonsocial condition activating amygdala.

In addition to the investigation of modulatory effects on empathic brain responses induced by OT, we investigated a second distinct but also unresolved question regarding the empathic brain: Can we find evidence for the proposed association between individual differences in empathic brain responses and prosocial behavior? Prosocial behavior is a broad construct that includes helping behavior, cooperation, and altruism (Penner, Dovidio, Piliavin, & Schroeder, 2005). Behavioral studies in the context of developmental psychology indeed have suggested that empathic concern is, albeit weakly, correlated with helping behavior (Eisenberg, Miller, et al., 1989). However, when empathy motivates helping behavior and when it leads to distress and withdrawal remains unclear (Batson & Shaw, 1991; de Vignemont & Singer, 2006; Eisenberg, Fabes, et al., 1989). One problem related to psychological research on prosocial behavior is often the lack of experimentally controlled laboratory tasks for the quantitative assessment of prosocial behavior. In the context of economics research, by contrast, prosocial behavior is operationalized in terms of choices people make in interactive games with monetary incentives. *Prosocial behavior*, or *altruism*, is then defined as costly acts that increase another person's benefits (Fehr & Fischbacher, 2003). In this study, we used a well-known economic game, the trust game (Ashraf, Bohnet, & Piankov, 2006; Berg, Dickhaut, & McCabe, 1995), to assess differences in prosocial behavior. In the trust game, Player 1 has the opportunity to send money to Player 2, knowing that every unit sent will be doubled by the experimenter and in the hope that Player 2 will send more money back. Player 2 then decides how much money to send back to Player 1, knowing that he can maximize his own profit by not sending any at all. On the basis of this decision, Player 2 can be classified as prosocial (conditional cooperators) or selfish (personal income maximizers).

We expected that these individual differences in trust game behavior predicted individual differences in empathic brain responses expected to be observed in AI and ACC.

Method

Participants

We scanned 21 healthy, right-handed, male participants who were asked to come to the scanning sessions with their romantic partner. One participant was excluded from the analysis due to data loss. The participants ranged in age from 20 to 31 with a mean age of 24.6 years ($SD = 3.2$). All participants gave informed consent and the study was approved by the local research ethics committee.

Procedure

Participants came for two sessions scheduled, on average, 10 days apart ($M = 10.4$ days, $SD = 4.33$, minimum [min.] = 2, maximum [max.] = 14). In a first step, OT or a placebo was administered with a nasal spray. It has been shown that neuropeptides pass the blood–brain barrier reliably after intranasal application (Born et al., 2002). Several studies using this method have reported OT-dependent effects on either behavior or brain function (Baumgartner et al., 2008; Domes, Heinrichs, Michel et al., 2007; Heinrichs et al., 2003, 2004; Kirsch et al., 2005; Kosfeld et al., 2005; Petrovic et al., 2008; Pitman, Orr, Lasko, 1993). The spray was administered to participants four times with a delay of 45 s between administrations, each administration consisting of one inhalation of the spray into each nostril. Each inhalation contained approximately 4 IU; participants thus received a total of 32-IU OT in the OT condition. Session (OT, placebo) order was randomized using a double-blind procedure. Scanning began roughly 45 min after spray administration ($M = 45.8$, $SD = 2.7$, min. = 42, max. = 55).

The empathy-for-pain paradigm was similar to the one used in Singer et al. (2004). In brief, by means of a system of mirrors, participants saw their own and their partner's hand lying on a tilted board. Pain electrodes were attached to the dorsum of their hands. On a screen they saw an arrow pointing to one of the hands, indicating whether the participant or his partner would be stimulated next. The color of the arrow indicated whether the stimulation would be painful or nonpainful. In contrast to Singer et al., the self and other conditions were blocked. In the self condition, to prevent the participants' experience of the effect of OT on pain processing from altering their empathic response, participants started with the empathy condition. Also, after each trial of painful or nonpainful stimulation to self or other, participants indicated how they felt about the stimulation by rating the degree of unpleasantness/pleasantness on an analogue rating scale ranging from -10 (*very unpleasant*) to $+10$ (*very pleasant*).

Behavioral and Questionnaire Measures

All participants filled out the Interpersonal Reactivity Index (IRI; Davis, 1980), a questionnaire used to assess empathy, and the State–Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), which is used to assess anxiety level. Prosocial behavior was assessed using a trust game, for which the participants were randomly paired with an anonymous player from

the University of Nottingham, who had played the game several weeks before at the School of Economics. The Nottingham players' decisions were kept in anonymous envelopes and used as the Player 1 decisions. The participants in London (who were the ones being scanned) were Player 2s. (For more details, see Supplementary Material A). Both players received an endowment of £5. Player 1s decided whether they wanted to keep their money or transfer it to Player 2. The experimenter then doubled the amount of money transferred. Player 2s decided whether they wanted to transfer their money given that (a) Player 1 had transferred his or her money or that (b) Player 1 had not transferred his or her money. After this decision, each Player 2 was paired at random with a Player 1 and paid according to the two players' decisions. Later, Player 2s were classified as "prosocial" if they had decided to cooperate if Player 1 had cooperated. They were classified as "selfish" if they had decided to keep the money even if Player 1 had sent their money. Thus, "selfish participants" had chosen to optimize their own reward at Player 1's expense and to keep their £5 even though they had received £10 from Player 1 (who consequently was left with no money at all).

Image Acquisition and Analysis

The imaging data (T_2^* -weighted echo planar images, EPI) measuring blood oxygen level dependent (BOLD) contrast were acquired using a 1.5-Tesla Siemens Sonata system. To reduce inhomogeneities in amygdala and orbitofrontal cortex, we used a sequence with axial slices tilted by 30° and a flip angle of 90° that reduces signal dropout due to susceptibility-induced field inhomogeneities in amygdala and orbitofrontal cortex (O'Doherty, Deichmann, Critchley, & Dolan, 2002). Our field of view covered the whole brain in 44 planes. We had a TR of 3.96 s (90 ms per slice). Each run began with six "dummy" volumes discarded for analyses. At the end of each scanning session, a T1-weighted structural image was acquired.

The data were preprocessed and analyzed with SPM5 (Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm). Scans were first realigned, normalized, and spatially smoothed by a 10 mm full-width half-maximum Gaussian kernel (6 mm at the first level, 8 mm at the second level). A high-pass filter (with a cut-off at 128 s) was applied to the time series. The data was then analyzed in an event-related fashion. The experiment constituted a $2 \times 2 \times 2$ factorial design with the first factor representing the drug condition (OT vs. placebo), the second factor the pain condition (pain vs. no pain), and the third factor the target condition (self vs. other). The conditions for each participant were modeled within a fixed effects general linear model. The resulting beta estimate maps were then taken to a second-level group analysis and the significance of contrasts of interest assessed within a random effects framework to allow statistical inference across the population. On the second level, one-sample t tests were used to assess the main effects of pain, drug, and target and the interaction between the three factors. Unpaired two-sample t tests were used to assess the difference in activation between the selfish and prosocial participants. In addition, linear contrasts between pain and no pain for self and other in the placebo condition were computed to assess both the pain matrix and empathic brain responses. Shared pain-related networks in self and other were assessed by computing a conjunction analysis on (pain vs. no pain)

in self and (pain vs. no pain) in other in the placebo condition alone. Regression analyses were computed to assess correlations between empathic brain responses and subjective unpleasantness ratings. Inclusive masking procedures (set on a threshold of $p < .05$, uncorrected) were used in the regression analysis to restrict activation to the brain areas observed in the simple contrast of: other \times (pain versus no pain). Effects of OT were assessed by computing the contrasts: OT \times (pain versus no pain) – placebo \times (pain versus no pain) and placebo \times (pain versus no pain) – OT \times (pain versus no pain).

We report results in a priori regions of interest at $p < .001$ uncorrected for multiple comparisons with an extent threshold of minimally eight contiguous voxels, except for the pain matrix (pain vs. no pain in self in the placebo condition) in which a slightly higher threshold was used ($p < .0001$, uncorrected). Small volume corrections (SVC) were applied for an anatomically defined mask around bilateral amygdala, defined according to the Wake Forest University (WFU) PickAtlas software (<http://fmri.wfubmc.edu/cms/software>).

Results

Behavioral Results

Table 1 provides descriptive statistics for the full sample as well as for subsamples of prosocial participants and selfish participants for age, education, and IRI and STAI scores. Subjective unpleas-

Table 1
Descriptive Characteristics of the Total and the Two Subsamples

	All ^a	Prosocial ^b	Selfish ^c	Prosocial versus selfish ^d
Age				
<i>M</i>	24.60	25.33	22.67	$p = .11$
<i>SD</i>	3.22	3.28	2.94	
Education				
<i>M</i>	5.60	5.75	5.67	$p = .95$
<i>SD</i>	2.34	2.73	1.97	
IRI, total score				
<i>M</i>	62.60	61.63	64.92	$p = .26$
<i>SD</i>	7.50	8.89	2.87	
IRI, perspective taking				
<i>M</i>	16.10	16.08	17.17	$p = .62$
<i>SD</i>	4.17	3.99	4.71	
IRI, fantasy scale				
<i>M</i>	15.50	14.88	15.92	$p = .59$
<i>SD</i>	3.59	3.34	4.54	
IRI, empathic concern				
<i>M</i>	19.25	18.83	19.50	$p = .64$
<i>SD</i>	2.69	2.86	2.74	
IRI, personal distress				
<i>M</i>	11.75	11.83	12.33	$p = .78$
<i>SD</i>	3.46	3.76	2.66	
State anxiety				
<i>M</i>	33.00	31.58	36.67	$p = .22$
<i>SD</i>	7.86	6.67	10.07	
Trait anxiety				
<i>M</i>	35.83	36.38	34.17	$p = .54$
<i>SD</i>	7.31	7.95	4.79	

Note. Education = years of education after age 16; IRI = Interpersonal Reactivity Scale.

^a $N = 20$. ^b $n = 12$. ^c $n = 6$. ^d Unpaired t tests, two-tailed.

antness ratings were computed as the difference between average ratings in the pain minus the no-pain condition. The unpleasantness ratings of one of the participants were not used for the analysis due to a lack of reliable ratings. The average unpleasantness ratings are depicted in Figure 1. They were significantly higher in the self than in the other condition, placebo: $t(19) = 4.20$, $p < .01$; OT: $t(19) = 3.32$, $p < .01$. There was no significant difference between the average unpleasantness ratings in the placebo and the OT condition, self: $t(19) = .20$, $p = .85$; other: $t(19) = .85$, $p = .41$. Individual differences in empathy (IRI) and anxiety (STAI) were not correlated with unpleasantness in any condition.

Next, we classified participants based on their behavior in the trust game. Of the 20 participants in our study, we observed 12 prosocial participants who reciprocated the other's trust and 6 selfish participants who maximized their income regardless of their partner's behavior. Two participants were not classifiable according to this distinction, as they decided to send their money to Player 1 even though Player 1 had not sent any money to them. To test whether the two types differed with respect to their behavioral unpleasantness ratings, we performed a $2 \times 2 \times 2$ analysis of variance (ANOVA) with prosociality (prosocial/selfish) as a between-subjects factor and drug (OT/placebo) and target (self/other) as within-subject factors. This ANOVA did not show any differences for the prosociality and drug factors, but did show a significant difference for the target factor, $F(1, 16) = 21.7$, $p < .001$, with higher pain ratings when the participants received pain as compared to empathizing with the pain of others. None of the interaction terms were significant. Unpaired t comparisons revealed that the two types neither differed on scores for the different subscales of the IRI nor on scores of the STAI (see Table 1). In sum, prosocial and selfish participants did not show any major behavioral differences.

Brain Imaging Results

Empathy. To identify the pain matrix, we computed a contrast between painful and nonpainful stimulation trials for the self in the placebo condition (placebo: self [pain–no pain]). We observed a typical pattern, shown in previous pain studies (e.g., Singer et al., 2004, 2006), involving activation in SI and SII; posterior, mid, and anterior insula; operculum; dorsal and rostral parts of ACC; pre-SMA; cerebellum; amygdala; and the ventral striatum (see Supplementary Material, Table 1). Also in line with previous findings, the comparison of brain activation in participants observing their partner receiving painful versus nonpainful stimulation (placebo: other [pain–no pain]) revealed activation in right AI extending into the operculum as well as activation foci in thalamus and left lingual gyrus (see also Table 2). A conjunction analysis testing for shared activation between the self and the other condition (placebo: self [pain–no pain] + other [pain–no pain]) showed activation in the right thalamus and the right AI (see Table 2 and Figure 2) confirming previous findings of a critical role for AI in empathy for pain.

To test whether individual differences in subjectively perceived unpleasantness correlated with empathic brain responses, we performed a regression analysis with the subjective ratings using the contrast (placebo: other [pain–no pain]). This revealed a correlation with the right AI/operculum and the ACC (see Table 2 and

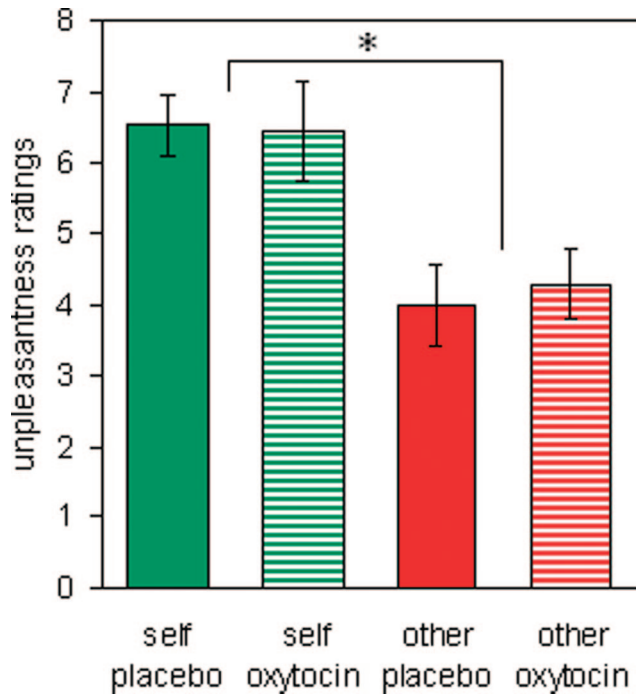


Figure 1. Subjective unpleasantness ratings: Average unpleasantness ratings for the conditions self (green) and other (red), placebo (filled), and oxytocin (shaded) with error bars (SEM), * $p < .01$.

Figure 3). A comparable regression analysis with the IRI did not reveal any significant correlation in empathy-relevant brain areas, neither for the IRI total nor for any of the subscales. Overall, however, these results replicate previous findings of an important role of AI and ACC in empathic brain responses elicited when observing another person suffering pain (de Vignemont & Singer, 2006; Singer et al., 2004, 2006).

OT. To test the effects of OT on both pain-related processing in the self as well as on empathic brain responses, we compared pain-related activation (pain–no pain) in self and other in the placebo compared to the OT condition. Table 3 provides an overview of the results. For the self condition, higher activation for the OT compared to placebo condition (self: OT [pain–no pain] – placebo [pain–no pain]) were found mainly in orbitofrontal regions. In line with previous findings showing a reduction of amygdala response due to the administration of OT, the reverse contrast (self: placebo [pain–no pain] – OT [pain–no pain]) revealed higher activation in the right amygdala extending into ventral striatum and the midbrain in the placebo compared to the OT condition. With respect to the other condition, right OFC activation was observed for the contrast (other: OT [pain–no pain] – placebo [pain–no pain]). However, contrary to our hypothesis of OT-induced enhancement of activation in empathy-relevant brain networks, no significant activation was observed when testing for significantly higher activation in the placebo compared to the OT condition for others (other: placebo [pain–no pain] – OT [pain–no pain]). To ensure we were not missing OT-related modulation in empathy-relevant brain regions due to insufficient power, we lowered the threshold to $p < .01$, but still no difference in the

magnitude of activation in the right AI or ACC was observed between the two drug conditions.

Prosociality. The second goal of this study was to investigate whether there is a predictive link between prosocial behavior and empathic brain responses. To this end, we first focused only on the placebo condition and compared brain responses in the self and other condition for the prosocial and selfish participants (see Table 4). In the self condition, prosocial participants showed higher activation in medial PFC (placebo, self: prosocial [pain–no pain] – selfish [pain–no pain]). Selfish participants, on the other hand, showed higher activation in right TPJ, SFG, and cerebellum (placebo, self: selfish [pain–no pain] – prosocial [pain–no pain]). In contrast to the hypothesis that prosocial as compared to selfish participants show higher activation in empathy-relevant brain areas, the contrast (placebo, other: prosocial [pain–no pain] – selfish [pain–no pain]) did not show significant activation, neither in right AI nor in ACC nor in any other brain regions. To assure again that this lack of differential findings was not based on a lack of power, we lowered the threshold to $p < .01$, but could not detect any significant differences in empathy-relevant brain areas between prosocial and selfish participants.

Based on our two independent observations of OT effects on amygdala responses in the self condition and effects of prosocial types on amygdala responsivity to impending pain in self, we finally also tested whether the effects of OT in the self condition were different for prosocial and selfish participants (see Table 5). This three-way interaction of pain versus no pain, OT versus placebo, and prosocial versus selfish participants indeed revealed significant activation in amygdala and mPFC. These activations and associated contrast estimates for the peak in the triple interaction within the amygdala are depicted in Figure 4. As Figures 4 illustrates, the three-way interaction is attributable to high activations in the amygdala for selfish participants in the placebo con-

Table 2
Empathic Brain Responses and Regression Analysis

Region	Cluster size	x	y	z	Z scores
Pain minus no pain in other, placebo					
R AI	15	30	27	6	3.51
R operculum	30	54	24	6	3.61
R AI ^a		45	21	0	3.36
R thalamus	26	6	-12	3	4.15
L lingual gyrus	8	-18	-57	-6	3.56
Conjunction of pain minus no pain in self and other, placebo					
R AI	19	33	27	6	3.59
R AI ^a		42	21	-3	3.22
R thalamus	26	6	-12	3	4.13
Regression of unpleasantness ratings on pain minus no pain in other, placebo					
Operculum/AI	28	57	24	3	4.69
Operculum/AI ^a		48	24	12	3.25
ACC	11	-9	12	39	4.07

Note. $p < .001$, uncorrected; cluster size > 7 voxels. R = right; L = left; AI = anterior insula; ACC = anterior cingulate cortex.

^a Sub-maxima within a cluster.

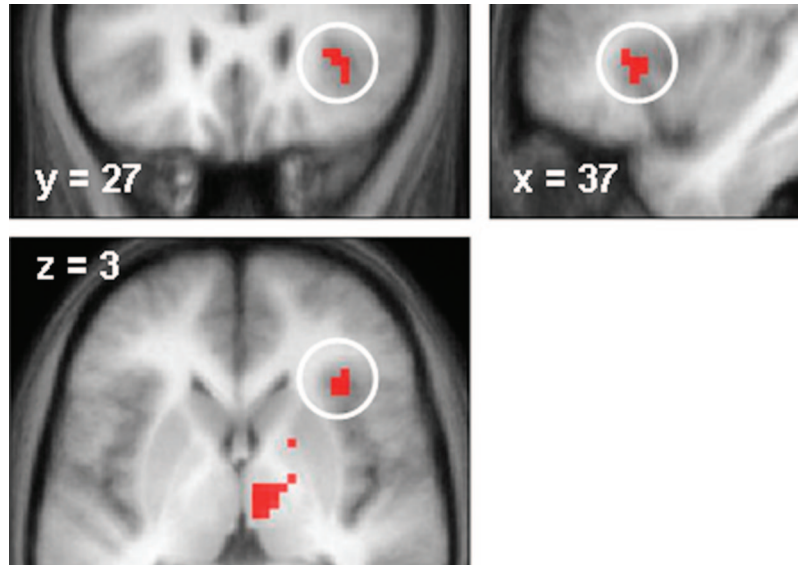


Figure 2. Empathic brain responses: Activation in the right anterior insula (AI) revealed by conjunction analyses depicting shared activation in painful versus nonpainful trials in the self and other placebo condition. Threshold is set at $p < .001$, uncorrected.

dition which are suppressed in the OT condition. Based on these findings, we tested the hypothesis that activation in the amygdala is higher for selfish than prosocial participants using a lowered threshold for the contrast (placebo, self: selfish [pain–no pain] – prosocial participants [pain–no pain]). Indeed, we found a significantly higher activation in the right amygdala for the selfish participants on a threshold of $p < .002$. An inspection of the betas in mPFC revealed that this three-way interaction was due to selfish participants showing decreased activation in the self placebo condition and an increased activation in the self OT condition, which is the opposite of the previously described amygdala pattern (see Supplementary Material, Figure 1).

Discussion

The aim of this study was twofold: First, using a classical empathy paradigm, we wanted to test the hypothesis that administration of OT enhances empathy. If OT enhances empathic brain responses as studies reporting enhancing effects of OT on trust, approach, bonding, and affiliative behavior in animals and humans suggest, we should observe an increase in brain activity in empathy-relevant brain regions, namely ACC and AI. However, if OT-induced effects are mostly mediated via the amygdala as recent fMRI studies suggested (Baumgartner et al., 2008; Domes, Heinrichs, Glascher et al., 2007; Kirsch et al., 2005; Petrovic et al.,

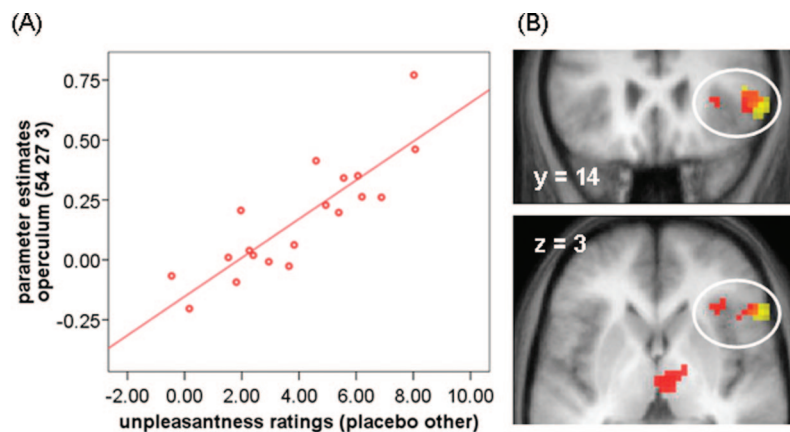


Figure 3. Individual differences in empathic brain responses: (A) Correlation of parameter estimates in the anterior insula/operculum for (pain vs. no pain) in the placebo other condition and subjective unpleasantness ratings. (B) Activation revealed in anterior insula/operculum for the contrast (pain vs. no pain) in the placebo other condition (red) and for the regression analysis of unpleasantness ratings on the contrast (pain vs. no pain) in the placebo other condition (yellow). Threshold is set at $p < .001$, uncorrected.

Table 3
Effects of Oxytocin for (Pain Versus No Pain) in Self and Other

	Cluster size	x	y	z	Z scores
Self oxytocin > placebo					
R medial OFC	27	18	27	-24	4.65
R medial OFC	25	15	66	-12	3.42
R medial OFC ^a		6	60	-9	3.25
R lateral OFC	8	45	42	-15	3.29
Self placebo > oxytocin					
R amygdala/striatum	18	24	0	-12	3.92*
Midbrain	27	6	-9	-12	3.88
Other oxytocin > placebo					
No significant activation					
Other placebo > oxytocin					
R OFC	8	27	27	-18	3.99

Note. $p < .001$, uncorrected (except where noted otherwise); family wise error corrected after small volume correction, cluster size > 7 voxels. R = right; OFC = orbitofrontal cortex.

^a Sub-maxima within a cluster.

* $p < .05$.

2008), we should observe an effect of OT in the nonsocial self condition, that is, when participants process nociceptive stimuli but not in the social empathy condition. This latter hypothesis is derived from previous studies in which amygdala has been shown to be activated in the self condition (Singer et al., 2004, 2006), but not when empathizing with another person.

The second goal of the study was to test another implicit, but never tested, assumption about the empathic brain, namely that individual differences in prosocial behavior predict empathic brain responses. If the hypothesis is true, we should find enhanced empathy-relevant activation in AI and ACC in prosocial as compared to selfish participants as measured in a standard economic trust game.

Our results neither revealed that OT enhances empathic responses nor that the prosocial participants showed higher empathic brain responses. Rather, in line with previous OT studies (Baum-

Table 4
Effects of Prosociality for (Pain Versus No Pain) in Placebo for Self

	Cluster size	x	y	z	Z scores
Self prosocial > selfish					
Medial PFC	14	-6	63	0	3.57
Medial PFC ^a		-12	69	0	3.35
Self selfish > prosocial					
R TPJ	18	54	-36	30	3.87
R SFG	8	27	30	57	3.69
R cerebellum	13	42	-75	-27	3.56
R amygdala	11	21	-3	-15	2.85*
Other prosocial > selfish					
No significant activation					
Other selfish > prosocial					
No significant activation					

Note. $p < .001$, uncorrected (except where noted otherwise); cluster size > 7 voxels. PFC = prefrontal cortex; R = right; TPJ = temporoparietal junction; SFG = superior frontal gyrus.

^a Sub-maxima within a cluster.

* $p < .002$, uncorrected.

Table 5
Effects of Oxytocin in Prosocial and Selfish Participants

	Cluster size	x	y	z	Z scores
Self placebo > oxytocin, prosocial > selfish					
Medial PFC	21	-9	63	0	4
L fronto-insular PFC	18	-33	42	-3	3.52
L fronto-insular PFC ^a		-27	33	-6	3.32
Self placebo > oxytocin, selfish > prosocial					
R amygdala	19	15	-9	-18	3.57*
L amygdala	8	-21	-9	-24	3.59

Note. Table depicts three-way interactions for the factors drug, pain, and prosociality in the self condition. $p < .001$, uncorrected (except where noted otherwise). Family wise error corrected after small volume correction, cluster size > 7 voxels. PFC = prefrontal cortex; L = left; R = right.

^a Sub-maxima within a cluster.

* $p < .05$.

gartner et al., 2008; Domes, Heinrichs, Glascher et al., 2007; Kirsch et al., 2005), we demonstrated a modulation by OT of amygdala activation when participants processed nociceptive stimulation in the self condition. Activity in amygdala in the self condition was lower after OT was administered exogenously compared to the placebo condition. Surprisingly, this effect seems to have been driven by the selfish participants alone: selfish, but not prosocial, participants showed enhanced amygdala activation when confronted with nociceptive stimulation and hence an OT-induced reduction.

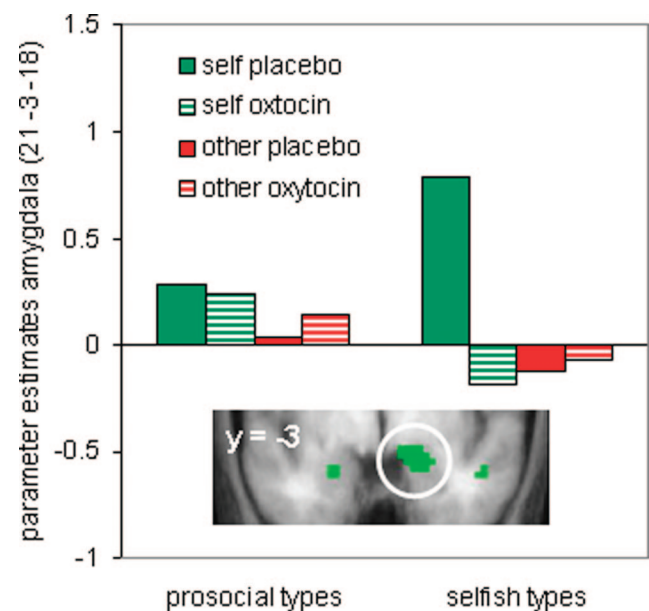


Figure 4. Effects of oxytocin and types on amygdala: The bar diagram illustrates parameter estimates derived from the right amygdala (21, -3, 18) revealed in the three-way interaction (pain, drug, prosociality) in self. Contrast estimates on the contrast (pain vs. no pain) are shown for the self (green) and the other (red) in the placebo (filled), and oxytocin (shaded) conditions, separately for prosocial and selfish participants. Threshold is set at $p < .001$, uncorrected.

Empathic Brain Responses and Prosocial Behavior

The results of the analyses focusing on brain activation elicited when participants either received nociceptive stimulation (self condition) or vicariously experienced their partner's pain (other condition) largely replicated previous results obtained with a similar paradigm (e.g., Singer et al., 2004, 2006). The pain matrix encompassed a complex network including primary and secondary somatosensory cortices; posterior, mid, and anterior parts of the insular cortices; operculum; dorsal and rostral parts of the ACC; pre-SMA; cerebellum; amygdala; and the ventral striatum. When participants empathized with their partners in pain, activation was observed in right AI extending into operculum and the right thalamus.

The anterior parts of the insular cortices are the most consistently reported areas in studies on empathy for pain (Botvinick et al., 2005; Jackson et al., 2005; Lamm et al., 2007; Morrison et al., 2004; Singer et al., 2004, 2006). Previous findings showed correlations of individual differences in empathic brain responses in AI and ACC with behavioral and questionnaire measures of empathy (Cheng et al., 2007; Jackson et al., 2005; Saarela et al., 2007; Singer et al., 2004, 2006). Consistent with these studies, we also found a positive correlation of activations in right AI/operculum and ACC with subjective unpleasantness ratings assessed after each stimulation trial. Thus, participants who felt more unpleasant about their partners experiencing pain also showed higher activation in these empathy-relevant brain areas. In contrast to the Singer et al. (2004, 2006) studies, the correlations between individual differences in empathy questionnaires (IRI) and empathic brain networks did not reach significance in this study (nonsignificant correlations between the IRI and empathic brain responses were also reported in Jackson et al., 2005; Lamm et al., 2007). We also failed to demonstrate enhanced ACC activation in the empathy condition in our sample despite the fact that we observed a positive correlation of activation in ACC and individual differences in unpleasantness ratings. This lack of increased ACC activation on a group level during the empathy condition parallels the findings of the Singer et al. (2006) study, which also only found reliable activation in ACC for the female participants (see also Singer et al., 2004), not for the male participants. Taking all empathy-for-pain studies into account, the AI seems to be more reliably activated across both genders than the ACC.

Despite the observation of reliable individual differences in empathic brain responses, we were still not able to find evidence to support the assumption that prosocial behavior predicts differences in empathic brain responses. Prosocial as compared to selfish participants (as assessed with a sequential trust game) did not differ in magnitude of brain responses in AI and ACC. As is the case for null findings, there are multiple interpretations for the lack of a difference in empathy between prosocial and selfish participants. First, because there were only six selfish participants, an obvious explanation for the lack of an effect is small sample size. On the other hand, other performed analyses showed reliable effects of prosociality (prosocial vs. selfish) in other brain regions (e.g., amygdala) using the same threshold. Second, a lack of an association between empathy and prosocial behavior may reflect the measure used to assess prosociality. Even though we used one of the most widely applied measures of prosociality in economics, it may nevertheless be insufficient in differentiating between dif-

ferent facets of prosocial behavior. In fact, we used the strategy method in the trust game (i.e., participants were to state what they would in the event of every possible action of the other player), which is weighted toward what is often referred to as *cold reasoning*, in which emotional involvement is low (Brosig, Weimann, & Yang, 2003). Empathy, however, is more related to *hot reasoning*, in which emotions are integral to decision making. In addition, the decision to engage in conditional cooperation or defection in this trust game may reflect what economists call *fairness preferences* rather than empathic motivation. In other words, participants may base their decision on social norms (e.g., "if someone offers me cooperation, I should reciprocate") rather than on an empathic feeling driven by an imaginative representation of the other's emotions and a felt concern for the other.

Future research might focus usefully on the development of adequate behavioral measures that are able to differentiate between different forms of prosociality and their underlying motivation so that, for example, fairness-based cooperative behavior can be distinguished from empathy-based helping behavior. This speaks to the simple fact that prosocial behavior is so far at best a vaguely defined construct that encompasses many different forms of other-regarding behavior. The development of new laboratory tasks is needed to differentiate between subcomponents of prosocial behavior and their relation to empathy.

Empathic Brain Responses and Effects of OT

We also failed to find evidence for an OT-induced increase in subjective empathy ratings or enhanced activation in empathy-relevant brain regions such as AI and ACC. In contrast and in line with previous findings showing that exogenously administered OT in humans primarily affects amygdala activation (Baumgartner et al., 2008; Domes, Heinrichs, Glascher et al., 2007; Ferguson, Aldag, Insel, & Young, 2001; Huber et al., 2005; Kirsch et al., 2005), we observed an OT-induced reduction of amygdala activation elicited by the anticipation and processing of noxious stimuli in the self condition.

Inspection of previous studies using a similar empathy-for-pain paradigm (Singer et al., 2004, 2006) confirmed that, on a group level, enhanced amygdala activation is typically observed when participants anticipate and experience pain (self condition), but not when they empathize with the pain of others (other condition). Furthermore, using their paradigm, Lamm et al. (2007) also reported activation in the amygdala that was stronger when the participants were asked to imagine the pain from a first-person as compared to a third-person perspective. As a consequence, amygdala activation would not be expected in the empathy condition. In the present paradigm, the short prestimulus interval between flashes indicative of impending pain and the circle indicative of actual receipt of nociceptive stimulation does not allow us to infer whether amygdala activation reflects an anticipatory anxiety response or the actual processing of pain itself. The literature on amygdala function seems to suggest that the amygdala is rather involved in anticipatory fear processing rather than in pain processing itself (Adolphs, 2002; LeDoux, 2003; Peyron, Laurent, & Garcia-Larrea, 2000; Rosen & Donley, 2006; but see Zald, 2003). For example, in a study by Phelps et al. (2001), participants showed increased amygdala activation in response to the sight of a symbol indicative of a possible future noxious stimulation, and

this response was observed even though the painful stimulation never actually occurred.

Reduced amygdala activation due to OT has been shown in previous fMRI studies using a similar protocol to exogenously apply OT via a nasal spray (Baumgartner et al., 2008; Domes, Heinrichs, Glascher et al., 2007; Kirsch et al., 2005; Petrovic et al., 2008). However, the present study revealed an interesting new result that throws light on the interpretation of OT effects. Previous behavioral and imaging results of OT studies mostly have been discussed in the context of a specific effect of OT for social stimuli and behavior. Thus, OT in animals has been shown to be associated with attachment and affiliative behavior including pair bonding, maternal care, and sexual bonding (Campbell, 2007; Carter, 1998; Insel & Shapiro, 1992; Insel & Young, 2001; Lim & Young, 2006; Pedersen, 1997). In humans, exogenously administered OT has been shown to reduce psychosocial stress responses (Heinrichs et al., 2003), increase trusting behavior (Kosfeld et al., 2005), enhance generosity in a social interaction task (Zak et al., 2007), and improve mindreading ability (Domes, Heinrichs, Michel et al., 2007). The results of the present study demonstrate an effect of OT on amygdala response elicited by upcoming noxious stimulation that does not have a social component. Similarly, Kirsch et al. observed OT-based reduction of amygdala responses both when participants were presented with fearful faces but also when they viewed nonsocial but fearful scenes. These results might suggest that the common denominator is fear-elicited amygdala activation rather than activation elicited by social stimuli. However, socially salient stimuli such as facial emotional expressions seem to be potent drivers of amygdala activation. Carefully designed future studies will have to further investigate the relationship between the effects of OT on amygdala activation and social context.

Empathic Brain Responses, Prosocial Participants, and the Effects of OT

Surprisingly, the three-way interaction between pain/no pain, OT/placebo, and prosocial/selfish for the self condition also revealed amygdala activation. This effect seems to have been driven by the selfish participants alone. As compared to prosocial participants, selfish participants showed significantly higher activation in the amygdala for pain versus no pain in the self placebo condition. Consistently, when testing painful versus nonpainful trials in the self placebo condition for prosocial participants only, no significant amygdala activation was observed. Consequently, OT was not able to reduce amygdala responses in the group of prosocial participants.

Even though heightened amygdala reactivity in selfish participants, reduced by OT, was not hypothesized a priori, this finding could have important implications for economic theory if replicable. In economic game theory, selfish participants are usually conceived of as rational players who seek to maximize their own reward and do not care about another player's reward. The observation that selfish participants show stronger amygdala reactivity to noxious stimulation points in a completely different direction. As described above, amygdala responses are known to play an important role in emotion and fear processing (Adolphs, 2002; LeDoux, 2003; Rosen & Donley, 2006). A recent meta-analysis shows that patients with different anxiety disorders have heightened activity in the amygdala (Etkin & Wager, 2007). Moreover,

the strength of amygdala activation has been linked to dispositional traits such as neuroticism and negative attributional style (Fischer, Tillfors, Furmark, & Fredrikson, 2001; Haas, Omura, Constable, & Canli, 2007). These findings can be interpreted as indicating that amygdala responsiveness reflects a bias toward threat-related responses (Bishop, 2007). Accordingly, our results of heightened amygdala responses to noxious stimuli could suggest that selfish people are actually rather high in anxiety and more biased toward threat-related responses rather than nonemotional, rational people.

This interpretation would suggest that selfishness is related to anxiety and mistrust toward others. Within this frame of reference, selfish behavior may be the result of a strategy to avoid anticipated negative outcomes. We acknowledge that such an interpretation does not preclude the existence of two types of selfish participants, one being completely rational, coldblooded, reward maximizing and the other overly vigilant and anxious. In the present small sample, we could not detect significant differences between scores in state and trait anxiety for the two types. To validate the plausibility of such a hypothesis and generalize the present findings to the entire population, future behavioral studies will have to test different trust and anxiety tasks in a much larger and heterogeneous sample and future fMRI studies will have to replicate the observation of enhanced amygdala responses in egoistic types in the context of other fear-related paradigms. If replicable these findings may help a better understanding of the mechanisms and motivations underlying trusting and cooperative behavior in human societies and may have also important implication for the advancement of institutional designs.

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Call for Nominations

The Publications and Communications (P&C) Board of the American Psychological Association has opened nominations for the editorships of **Developmental Psychology**, **Journal of Consulting and Clinical Psychology**, and **Psychological Review** for the years 2011–2016. Cynthia García Coll, PhD, Annette M. La Greca, PhD, and Keith Rayner, PhD, respectively, are the incumbent editors.

Candidates should be members of APA and should be available to start receiving manuscripts in early 2010 to prepare for issues published in 2011. Please note that the P&C Board encourages participation by members of underrepresented groups in the publication process and would particularly welcome such nominees. Self-nominations are also encouraged.

Search chairs have been appointed as follows:

- **Developmental Psychology**, Peter A. Ornstein, PhD, and Valerie Reyna, PhD
- **Journal of Consulting and Clinical Psychology**, Norman Abeles, PhD
- **Psychological Review**, David C. Funder, PhD, and Leah L. Light, PhD

Candidates should be nominated by accessing APA's EditorQuest site on the Web. Using your Web browser, go to <http://editorquest.apa.org>. On the Home menu on the left, find "Guests." Next, click on the link "Submit a Nomination," enter your nominee's information, and click "Submit."

Prepared statements of one page or less in support of a nominee can also be submitted by e-mail to Emnet Tesfaye, P&C Board Search Liaison, at etesfaye@apa.org.

Deadline for accepting nominations is January 10, 2009, when reviews will begin.