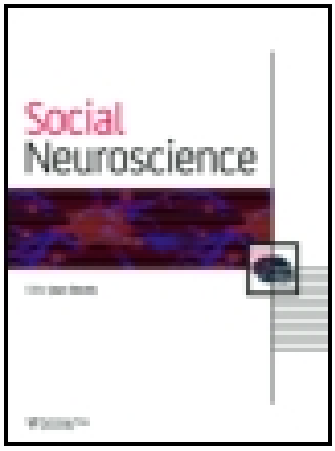

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Oxytocin increases empathy to pain when adopting the other- but not the self-perspective

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Oxytocin increases empathy to pain when adopting the other- but not the self-perspective

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There is growing evidence that the neuropeptide oxytocin (OT) facilitates various forms of sensitivity to others, but the mechanism by which OT enhances empathy in humans is unclear. In this study, we examined whether OT increases empathy by the way of blurring the distinction between self and other, or by enhancing the difference between self and other. In this double-blind, placebo-controlled, within-subject crossover design, empathic responses of healthy participants were compared when imagining oneself (i.e., self-perspective empathy) versus when imagining the other (i.e., other-perspective empathy) in painful and nonpainful situations. Under OT treatment, participants expressed more empathy when imagining others than when imagining oneself in pain. This was in contrast to the placebo condition where there were no differences between the empathic responses during the self- and the other-perspective. We propose that the modulatory effect of OT on empathy when taking the other-perspective may be mediated by its role in self- and other-distinctiveness and corollary by its role in increasing salience to social agents and cues.

Keywords: Oxytocin; Empathy; Pain; Perspective-taking; Self and other.

Empathy is an essential aspect of human nature in that it facilitates social interactions, attachment, and connections with other people (Decety & Svetlova, 2012). This ability, which generally has been defined as an emotional response to another's individual distress, requires an accurate understanding of another's mental state or frame of reference (Batson, 2009b). As such, empathy includes both cognitive and affective components (Decety & Jackson, 2004; Shamay-Tsoory, 2011). Affective empathy refers to the capacity to experience affective reactions to the observed experiences of others, and involves several related underlying processes such as emotional contagion, emotion recognition, and shared pain. Cognitive empathy, on the other hand, pertains to the capacity to engage in the cognitive process of adopting another's point of view, and involves making inferences regarding the other's affective and cognitive mental states. Research investigating interpersonal empathy has shown that people exhibit a stronger empathic response toward those who they perceive as similar to themselves (Brown, Bradley, & Lang,

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2006; Sturmer, Snyder, Kropp, & Siem, 2006), and that empathy seems to be evoked more easily when the other is identified as an individual with whom they share a common denominator (Echols & Correll, 2012; Hein, Silani, Preuschoff, Batson, & Singer, 2010). Research thus suggests that empathic concern is motivated by shared neural representations between self and other (Decety & Jackson, 2004; Decety & Sommerville, 2003; Lamm, Nusbaum, Meltzoff, & Decety, 2007; Perry, Bentin, Ben-Ame Bartal, Lamm, & Decety, 2010; Preston & De Waal, 2002).

In contrast, a different line of research suggests that empathy is less due to self–other merging (or a blurring in the distinction between the two), but rather that it is motivated by the recognition that the self is distinct from the other (in need), and that one's experience is distinct from the experience of others (Batson, Early, & Salvarani, 1997; Jackson, Brunet, Meltzoff, & Decety, 2006; Lamm, Batson, & Decety, 2007). Results from these studies underscore the notion that the perspective that one takes (i.e., self- vs. other-perspective) could lead to different empathic perceptions of others in need. Research comparing self-perspective empathy versus other-perspective empathy suggests that individuals tend to confer higher and faster pain ratings during self-perspective condition (Jackson et al., 2006; Van Der Heiden, Scherpiet, Konicar, Birbaumer, & Veit, 2013). For example, using a variant of the "empathy for pain" paradigm, Jackson et al. (2006) showed that participants significantly rated higher the pain they imagined themselves experiencing than the pain they imagined others experiencing in similar situations. Interestingly, these differences were associated with both shared and differential neural activations. The parietal operculum, anterior cingulate cortex, and anterior insula were more active during both the self- and other-perspective conditions. Imagining oneself in pain was associated with activation in the secondary somatosensory cortex, anterior cingulate cortex, and the middle insula, and imagining others was associated with activations in the precuneus/posterior cingulate and the temporo-parietal junction, regions that are critically involved in inferring and representing self and other mental states. The authors accordingly proposed that differences in the empathic ratings between the two conditions are likely attributable to the different forms of perspective-taking one adopts during imagining oneself versus imagining the other in distress, which suggests that empathy involves an awareness of self- and other-distinctiveness (see Lamm, Decety, & Singer, 2011 and Reniers, Völlm, Elliott, & Corcoran, 2014).

This interface between the self and the other has been the topic of socio-endocrinological research in light of the realization of the role of the neuropeptide oxytocin (OT) in socio-affiliative behavior. Oxytocin is a neurohypophyseal peptide that primarily acts as a neuromodulator in the brain and can cross the blood–brain barrier when administered intranasally (Born et al., 2002). A growing body of empirical research has shown that the administration of OT can modulate trust, cooperation, generosity, recognition of affective states, attachment, as well as perspective-taking or mentalizing abilities (for review see Bethlehem, Van Honk, Auyeung, & Baron-Cohen, 2013). Oxytocin has also been implicated to play a role in empathetic behaviors whereby it is assumed to confer an enhancing effect on empathy (Abu-Akel, Fischer-Shofty, Levkovitz, Decety, & Shamay-Tsoory, 2014; Rosenfeld, Lieberman, & Jarskog, 2011; Smith, Porges, Norman, Connelly, & Decety, 2014; Striepens, Kendrick, Maier, & Hurlemann, 2011). Studies investigating the enhancing effect of OT on empathy have yielded mixed results, however. Some studies reported that OT selectively enhanced in men affective empathy (but not cognitive empathy) (Hurlemann et al., 2010) and selectively improved empathic accuracy in less socially proficient men (Bartz et al., 2010). In contrast, OT did not have an effect on the empathic responses in male participants when they received a signal indicating that their romantic female partners were in pain (Singer et al., 2008). A more recent study also reported no influence of OT on affective empathy toward an unknown person, but found it to influence men's performance on an implicit perspective-taking task (Theodoridou, Rowe, & Mohr, 2013), an aspect that is necessary for empathic understanding.

Common to these studies is that they only investigated the effect of OT on the participant's empathy to the distress of a particular *other*, that is, within the context of "other-perspective empathy." The effect of OT on the subjective perception of empathy (i.e., self-perspective empathy) vis-à-vis the other-perspective, however, has not been investigated. To bridge this gap, the current study investigated, in a double-blind placebo-controlled crossover design, the extent to which OT alters the perception of empathy to the pain one imagines from the perspective of oneself versus the pain imagined from the perspective of others in similar painful and nonpainful situations. By contrasting self- versus other-perspective taking, our study can shed light on the potential mechanism by which OT modulates empathetic responses to others in pain, that is, whether OT enhances empathy by blurring the distinction between self and other, or by extenuating the difference between self and other. If the former is correct, then we would expect to find no differences in empathy when taking the self- versus

the other-perspective in the OT condition. Such result would support the share-representations hypothesis (e.g., Decety & Sommerville, 2003; Preston & De Waal, 2002). If the latter is correct, we would expect differences between the self- and the other-perspective during the OT condition, and this would be consistent with the self–other distinctiveness hypothesis of empathy (Batson et al., 1997; Decety, Chen, Harenski, & Kiehl, 2013), positing that empathic concern for others requires an awareness that the self and the other are distinct. Based on earlier studies showing that individuals are more sensitive to pain when imagined from a self-perspective than from another-perspective (Jackson et al., 2006), we predicted that under the placebo condition participants will have higher pain ratings in the imagine-self versus in the imagine-other perspective, but that this bias will be attenuated under the OT condition by increasing the empathic responses during the other-perspective condition. Our prediction is motivated by the role of OT in increasing salience to socially relevant information (Groppe et al., 2013; Heinrichs, Von Dawans, & Domes, 2009; Shamay-Tsoory et al., 2009), and the hypothesis that OT-induced empathy to the distress of others may be mediated by its role in increasing the cognitive availability of such information. Finally, it is noteworthy that the majority of OT studies have been conducted with male participants (Lynn, Hoge, Fischer, Barrett, & Simon, 2014). Since in our sample we included both male and female participants, we analyzed gender as a factor to explore the possibility that the effect of OT on the perception of empathy is gender dependent.

MATERIALS AND METHODS

Participants and protocol

A total of 29 healthy male and female Israeli Jewish adults (10 females, 19 males; mean age = 39.14, SD = 10.91) participated in a double-blind placebo-controlled within-subject crossover design study. All participants gave their written informed consent prior to their participation. Exclusion criteria included the presence of a medical or a psychiatric illness and the use of any substantial medication or other substance (including heavy smoking). All participants were instructed to avoid psychotropic substances, such as caffeine and nicotine, for at least 12 hours prior to the experiment. The study protocol was approved by the Rambam Medical Center Ethics Committee.

Participants were randomly assigned into groups before the experiment for the first administration of either OT or placebo. A single dose of 24 IU of OT or placebo was intranasally administered (three puffs per nostril, each puff containing 4 IU) 45 minutes before the task performance. The placebo contained all inactive ingredients without the neuropeptide. At the second session of the experiment, 7 days later, participants underwent the same procedure with the other substance (i.e., placebo or OT). Sample size, dosage, and waiting time corresponded to those previously used in experiments designed to investigate the effect of the intranasal administration of OT on behavior in humans (Domes et al., 2010; Guastella et al., 2010; Kirsch et al., 2005; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Data collection continued until the target number was satisfied.

Pain evaluation task

In this study, we utilized the pain evaluation task (Jackson, Meltzoff, & Decety, 2005). The task consists of a series of digital color photographs showing right hands and right feet in painful and nonpainful situations. All situations depict familiar events that can happen in everyday life. Various types of pain (mechanical, thermal, and pressure) are represented. For each painful situation, there is a corresponding neutral picture, which involved the same setting without any painful component. Specifically, the task involved stimuli which included (1) right hands in painful situations, (2) right hands in neutral situations, (3) right feet in painful situations, and (4) right feet in neutral situations. The experiment consisted of 40 trials in total (20 painful and 20 nonpainful stimuli) which were presented randomly in one block. Pictures were presented for 750 ms, following a 750-ms presentation of the participant's *own first name* or a *common Israeli Jewish name*, which was preceded by a 67-ms interval (see Figure 1). The selected Jewish names were Moshe, Avi, Yits'hak, Yesrael, and Shimon (see Shamay-Tsoory et al., 2013). In all sessions, the same name was always tagged with the same picture and the combinations of names and pain or no-pain stimuli were randomized between subjects. Following each name and the presentation of a painful or a nonpainful situation, participants were then asked to rate as quickly as possible the degree of pain felt when imagining oneself or imagining another being in a particular situation. The rating was done using a visual analog scale (VAS) using the computer mouse (0—no pain, 10—most painful). The task began with three practice trials, followed by the test

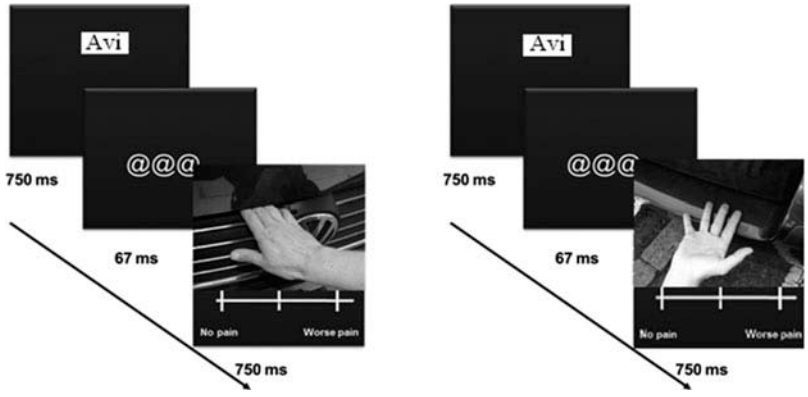

Figure 1. Sample presentation of a right hand in a painful and nonpainful situation.

block. The task was run in E-prime 2.1 (Psychology Software Tools, Pittsburg, PA, USA).

The data were analyzed using a 2 × 2 × 2 × 2 repeated-measures ANOVA where treatment (placebo vs. OT), perspective (self- vs. other-perspective), and stimuli (painful vs. nonpainful) were entered as within-subject factors and sex (male vs. female) as a between-subjects factor. Planned *post hoc* comparisons were Bonferroni corrected, and effect sizes were calculated using Cohen's *d* (1998).

RESULTS

The 2 × 2 × 2 × 2 repeated-measures ANOVA revealed a significant main effect for pain ($F(1,27) = 193.11$, $p < .001$, $\eta_p^2 = .877$) where the participants rated the painful stimuli (mean±SE = 5.90 ± .35) significantly more than the nonpainful stimuli (mean ±SE = .70 ± .32), as well as a significant three-way interaction of treatment × perspective × pain ($F(1,27) = 6.53$, $p = .017$, $\eta_p^2 = .195$). No other significant effects or interactions were discerned. To examine the source of the three-way interaction, we independently examined the interaction between treatment and the type of perspective taken during the pain ratings in the *painful and nonpainful* conditions. In the painful condition, the two-way repeated-measures ANOVA of perspective and treatment revealed nonsignificant main effects for either treatment or perspective. However, there was, as shown in Figure 2, a significant treatment × perspective interaction effect ($F(1,28) = 7.49$, $p = .011$, $\eta_p^2 = .211$), indicating that treatment differently affected the pain ratings during the self- versus the other-perspective. Follow-up paired *t*-tests indicated that following the administration of the placebo, there were no significant differences in the pain ratings given during the imagine-self versus the imagine-other perspectives ($t(28) = -.70$, $p = .49$, $d = .11$). Yet, following the administration of OT, participants rated the pain perceived from the other-perspective significantly higher than the pain perceived from the self-perspective ($t(28) = 2.448$, $p = .021$, $d = .29$). In the *nonpainful* condition, the analysis, as shown in Figure 2, indicated nonsignificant treatment effect, perspective effect, or interaction.

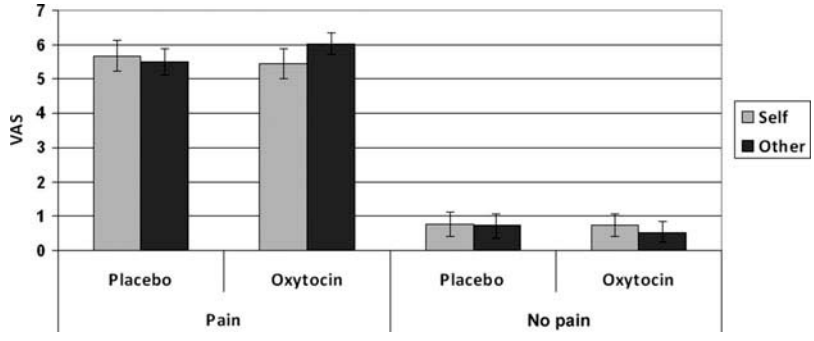

Figure 2. Treatment effect (mean ± SE) on the empathic rating of painful and nonpainful stimuli during the self- versus the other-perspective.

DISCUSSION

The current study was designed to investigate the effect of oxytocin on the participants' empathic responses to the perceived plight of others when viewed from the self- versus the other-perspective in similar painful situations. Our results show that, under OT, participants confer more empathy to the pain perceived from the perspective of others than to the pain perceived from one's own perspective. This is in contrast to the placebo condition where there were no differences between the self- and the other-perspective. This finding, coupled with recent evidence showing a role for OT in enhancing the ability to recognize differences between self and others (Colonnello, Chen, Panksepp, & Heinrichs, 2013), supports the theory positing that empathy to others is motivated, at least in part, by an awareness of self- and other-distinctiveness (Decety & Jackson, 2004; Lamm et al., 2007). While it is obvious that further research is required, it is reasonable to conjecture that the awareness of the emotional and mental states of others, which are known to motivate empathic concern and are themselves modulated by the oxytocinergic system (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Guastella et al., 2010), is mediated by the role of OT in sharpening self–other boundaries.

The increased empathy we observed under the OT condition when taking the other-perspective can also be explained by its role in increasing the salience of socially relevant cues (Groppe et al., 2013; Guastella, Mitchell, & Dadds, 2008; Shamay-Tsoory et al., 2009), an effect that has been shown to improve social cognition such as the recognition of emotions in others (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Guastella et al., 2010), the positive evaluation of others (Colonnello et al., 2013), perspective-taking/mentalizing abilities (Domes et al., 2007; Pedersen et al., 2011), and prosocial behavior more generally (Bethlehem et al., 2013), although this seems to be context dependent (Bartz, Zaki, Bolger, & Ochsner, 2011). In addition, neuroimaging studies of empathic perception when adopting the perspective of another in pain have documented an increase in neuro-hemodynamic response in regions within the mentalizing network including the posterior temporal sulcus (pSTS, AKA TPJ) (Cheng, Chen, Lin, Chou, & Decety, 2010; Jackson et al., 2006; Ruby & Decety, 2004). Activity in this region has been shown (directly or indirectly) to be modulated by intranasal administration of OT (Gordon et al., 2013; Pincus et al., 2010). Crucially, the pSTS has also been shown to play a critical role in self–other distinction (Decety & Lamm, 2007). Thus, the modulation of OT of the pSTS, which is involved in both self–other identification and mentalizing, lends further support for the possible role of OT in extenuating self–other boundaries (Colonnello et al., 2013), which, as pointed above, is an important component of our ability to empathize with others (Lamm et al., 2007).

Our findings are in contrast to a previous study on pain empathy which did not find a significant difference in the pain ratings for others (or the self) in the placebo versus the OT condition (Singer et al., 2008). One potential reason for such a discrepancy may be the use of different experimental paradigms. While in our study, we utilized a picture-based paradigm, allowing direct visual stimulation of painful situations, the other study relied on a cue-based paradigm during which participants were informed via the use of abstract visual symbols who (self or other) and what type of stimulation (painful or nonpainful) would be delivered. In addition, while the Singer et al. study did not find significant differences between the placebo and OT conditions, qualitatively participants gave higher ratings to others during the OT condition. It is also possible that the analysis was underpowered given the smaller sample size of 20 participants. Future OT studies using empathy for pain paradigms could benefit from comparing picture-based versus cue-based paradigms with larger number of participants.

In addition, the lack of difference in the pain ratings during the self- versus the other-perspective under the placebo condition is also in contrast to previous work using a similar experimental paradigm in the context of functional neuroimaging. This research showed that taking a self-perspective was associated with higher pain ratings than when imagining the pain of another (Jackson et al., 2006). A crucial difference between our experiment and Jackson et al. study is that the "others" in the Jackson et al. study were merely strangers, whereas in our study the "others" were Israeli Jews with whom participants share the same religious and national identity primed by the prototypical Jewish Israeli names. While our study was not designed to specifically prime such group membership, previous work has shown that the presentation of prototypical names is sufficient to prime affiliative biases of ingroup and outgroup membership (Bruneau, Dufour, & Saxe, 2012; De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011; Shamay-Tsoory et al., 2013). Therefore, we speculate that the lack of difference between the self-perspective and the other-perspective ratings under the placebo condition is due to

perceived similarities between oneself and others, which is probably motivated by the recognition of a shared affiliative bond (Wright, Aron, & Tropp, 2002). It would be intriguing to uncover in future studies how the perceived nature of the relationship between oneself and others can influence the modulatory effect of OT on empathic perception from the self-perspective versus the other-perspective (see Goubert et al. (2005) for various other contextual factors that may affect perception of empathy including empathy for pain).

Moreover, if under OT administration there is an increased distinctiveness between the self and the other, it would be plausible to have anticipated, contrary to our results, increased empathic responses during the self-perspective rather than during the other-perspective, which would be consistent with studies showing enhanced empathic responses to those who we perceive as similar (Brown et al., 2006). However, it has been shown that taking the perspective of others, which, as mentioned above, can be enhanced with the administration of OT (Domes et al., 2007), substantially reduced racially related biases in the perception and treatment of pain (Drwecki, Moore, Ward, & Prkachin, 2011). In addition, self-perspective empathic responses may not benefit from the administration of OT, since OT may have a saturation point in that it may not make available information that previously (i.e., under the placebo condition) is already salient (Bartz et al., 2010), which, if confirmed, would underscore the selectivity of OT in modulating empathic responses generated from the self- versus other-perspective.

The use of an empathy for pain paradigm may lead to pain-blocking effects of OT rather than its empathy-enhancing effects. While it is true that OT has pain-blocking properties (Juif & Poisbeau, 2013), the administration of OT at the level used in our study is unlikely to have interfered with the empathic perception of others in pain, given evidence showing that the administration of 40IU had no analgesic effect in humans receiving 20-second painful heat stimulation (Kessner, Sprenger, Wrobel, Wiech, & Bingel, 2013). Moreover, it has been shown that patients with congenital insensitivity to pain have normal hemodynamic response to observed pain in the anterior cingulate cortex and the anterior insula (two regions consistently activated by empathy for pain), and that their empathy scores respectively predicted responses in the ventromedial prefrontal cortex and posterior cingulate cortex to somatosensory and emotional representation of others' pain (Danziger, Faillenot, & Peyron, 2009). Altogether, there is reason to believe that the anti-nociceptive effects of OT may not interfere with higher cognitive processing of the perception of others in pain, especially if empathic responses to the pain of others are not necessarily contingent on the ability to experience it.

Our study has a number of limitations. A central limitation is the relatively small sample size, and especially the small number of female and male participants. Gender differences within OT research have received little attention (Lynn et al., 2014). The lack of gender effect in our study should be interpreted with caution, and thus comparing male and female performance in larger samples is needed. In addition, we noted in the introduction that empathy involves a cognitive component and an affective component. Thus, another limitation of our study is that the current paradigm does not differentiate between these two components. It is difficult to speculate which of these components mediated the responses observed here. However, assessing the distress of others using perspective-taking suggests that, under these circumstances, imagining others in pain might be mediated by the cognitive component. This view is consistent with the studies showing that OT increases theory of mind/perspective-taking abilities (Domes et al., 2007; Theodoridou et al., 2013), as well as with the reports showing that imagining others in pain was associated with activations in the precuneus and the pSTS (Jackson et al., 2006), regions that are involved in inferring and representing self and other mental states (Abu-Akel & Shamay-Tsoory, 2011). Accordingly, it would be beneficial for future OT studies utilizing "empathy for pain" paradigms to also include measures assessing mentalizing abilities to explore the extent to which empathic concern for others is mediated by OT-enhanced mentalizing abilities.

Together, our study provides evidence showing that intranasal administration of OT increases empathic responses to pain when taking an other- but not a self-perspective. The emerging picture from these results and other studies (see Olff et al., 2013) suggests that the modulatory effect of OT on empathy is possibly mediated by its role in self- and other-distinctiveness and corollary by its role in increasing salience to social agents. Moreover, the differential effect of OT on self-perspective versus other-perspective empathy further emphasizes the notion that OT does not up-regulate empathic concern in all conditions (Bartz et al., 2011). This is particularly important in the context of research evaluating the therapeutic potential of OT in conditions that are associated with a deficient sense of self such as in individuals with high alexithymia and depression (Luminet, Grynberg, Ruzette, & Mikolajczak, 2011; Olff et al., 2013). Therefore, a full characterization of

the effect of OT in the context of self- and other-perspective taking is needed before widespread clinical application is warranted. Finally, the perception of oneself and other is context dependent whereby the person may opt to act and think egoistically in favor of oneself over others, or empathetically or even altruistically in favor of the others over oneself (Batson, 2009a). Therefore, understanding the mechanism by which OT captures the self–other distinction and the contextual factors that modulate this property will be a key to understanding its role in influencing empathic perception.

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