Oxytocin Increases Attention to the Eyes and Selectively Enhances Self-Reported Affective Empathy for Fear

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Abstract

Oxytocin (OXT) has previously been implicated in a range of prosocial behaviors such as trust and emotion recognition. Nevertheless, recent studies have questioned the evidence for this link. In addition, there has been relatively little conclusive research on the effect of OXT on empathic ability and such studies as there are have not examined the mechanisms through which OXT might affect empathy, or whether OXT selectively facilitates empathy for specific emotions. In the current study, we used eye-tracking to assess attention to socially relevant information while participants viewed dynamic, empathy-inducing video clips, in which protagonists expressed sadness, happiness, pain or fear. In a double-blind, within-subjects, randomized control trial, 40 healthy male participants received 24 IU intranasal OXT or placebo in two identical experimental sessions, separated by a 2-week interval. OXT led to an increase in time spent fixating upon the eye-region of the protagonist's face across emotions. OXT also selectively enhanced self-reported affective empathy for fear, but did not affect cognitive or affective empathy for other emotions. Nevertheless, there was no positive relationship between eye-gaze patterns and affective empathy, suggesting that although OXT influences eye-gaze and may enhance affective empathy for fear, these two systems are independent. Future studies need to further examine the effect of OXT on eye-gaze to fully ascertain whether this can explain the improvements in emotional behavior.

Keywords: Oxytocin, empathy, fear, eye-gaze

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The ability to understand and share another person's emotional state or context, referred to as empathy (Eisenberg & Strayer, 1987), is essential in developing and sustaining successful reciprocal social relationships (Dziobek et al., 2008). Empathy is a broad construct, consisting of both cognitive and affective reactions to others' experiences, and can be split into two components: cognitive empathy and affective empathy. Cognitive empathy is the ability to understand what another person is thinking or feeling, whereas affective empathy involves the vicarious experience of emotions consistent with those of another (Shamay-Tsoory, 2009). In general, empathy is thought to trigger a number of prosocial behaviors intended to benefit others. If the other is perceived to be in a negative state, empathic concern can motivate action and lead to prosocial behavior (de Waal, 2008). Consequently, these abilities facilitate cooperation and helping behaviors and are considered important for appropriate moral development (Hoffman, 2000). Conversely, deficient emotion processing is an important risk factor associated with antisocial behavior and a range of psychiatric and neurodevelopmental conditions including Autism Spectrum Disorders, Conduct Disorder and schizophrenia.

Over the last decade, a plethora of studies have implicated the neuropeptide oxytocin (OXT) in a host of prosocial behaviors, including increased trust (Kosfeld, Heinrichs, Zak, Fischbacher & Fehr, 2005), generosity (Zak, Stanton & Ahmadi, 2007) and facial emotion recognition (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007b). Of particular interest to the current study is the commonly referenced finding concerning the benefits of OXT on mind-reading (Domes et al., 2007a). These findings have spurred interest in the potential of OXT to reduce social deficits associated with disorders.

However, some recent studies (e.g., Nave, Camerer & McCullough, 2015; Lane et al., 2015; Radke & de Bruijn, 2015; Hofmann, Fang & Brager, 2016) have failed to replicate some of the positive effects associated with OXT, raising concerns that previous studies were underpowered and/or that publication bias has resulted in the selective publication of positive findings (Lane, Luminet, Nave, & Mikolajczak, 2016). This, combined with some evidence that OXT can increase negative responses, such as schadenfreude (Shamay-Tsoory, Fischer, Dvash, Harari, Perach-Bloom & Levkovitz, 2009), has cast doubt on the role of OXT in promoting prosocial behaviors. As a result, there is a need for further research on the effects of OXT on prosocial behavior and for closer consideration of the possible mechanisms through which such effects may occur.

Given the important role played by empathy in prosocial behavior, it seems logical to examine whether OXT has an impact on empathy. However, relatively few studies in the OXT literature have examined the role of OXT in empathy, and those that have done so have yielded inconsistent results. Using a between-subjects design with 48 healthy male participants, Hurlemann et al. (2010) examined cognitive and affective empathy using static pictures depicting people in emotionally charged situations. They found that intranasal OXT increased affective, but not cognitive empathy in response to both positively and negatively valenced stimuli. However, Theodoridou, Rowe, and Mohr (2013) found that the self-reported components of affective empathy were unaffected by the administration of OXT, but that performance on a more implicit measure of cognitive empathy was enhanced following OXT. It is worth noting that the findings of Hurlemann and colleagues are also inconsistent with Domes et al.'s (2007) finding that OXT improves cognitive empathy as measured by the Reading the Mind in the Eye task.

Attempts to replicate these findings have proven unsuccessful, raising doubts about the effect of OXT on cognitive empathy (Radke & de Bruijn, 2015). Indeed, a recent meta-analysis of 33 studies found that OXT did not significantly influence emotional theory of mind – a similar construct to cognitive empathy – or the expression of negative emotions in healthy individuals (Leppanen, Ng, Tchanturia & Treasure, 2017). A number of studies have further suggested that OXT only improves cognitive empathy in people who rate themselves as less socially proficient (Bartz et al., 2010), or who display lower baseline trait empathy scores (Feeser et al., 2015). Given the large variations in stimuli and methodology in these studies, it is perhaps not surprising that previous results concerning the effect of OXT on empathy are inconsistent.

Studies investigating the effects of intranasal OXT on affective empathy are scarce. This may be due in part to the difficulty in defining this construct, given that it encompasses both subjective and physiological responses towards other people's internal states. Apart from the aforementioned study by Hurlemann et al. (2010), few studies have directly assessed affective empathy, and those that have done so have tended to focus solely on empathy for pain. For example, two studies using subjective ratings of responses to painful stimuli found that OXT did not have a main effect on pain ratings, but did increase ratings as a function of the perspective (self vs. other) participants were asked to take, or the nationality of the person with whom to empathize (Abu-Akel, Palgi, Klein, Decety & Shamay-Tsoory 2015; Shamay-Tsoory et al., 2013). Similarly, in a within-subjects neuroimaging study examining empathy for a partner's experience of physical pain, Singer and colleagues (2008) found that OXT

neither enhanced subjective empathy nor increased activation in empathy-relevant brain areas such as the anterior insula (AI) and anterior cingulate cortex (ACC). Interestingly, a recent study found that empathy-related activation in the neural circuitry of pain was strongly *reduced* after intranasal OXT, suggesting that OXT might decrease empathy for pain (Bos, Montoya, Hermans, Keysers, & van Honk, 2015). However, because no behavioural data were included in this study, further research incorporating behavioural measures is needed in order to be able to draw firmer conclusions.

One technique that has the potential to explain any beneficial effects of OXT on empathy is to use eye-tracking to provide a measure of visual attention allocation. OXT has been shown to increase gaze toward the eye-region of neutral faces (Guastella, Mitchell, & Dadds, 2008), and also to increase attention to objects that are the gaze targets of static faces (Tollenaar, Chatzimanoli, van der Wee, & Putman, 2013). Such findings have led to the suggestion that OXT might improve prosocial behavior by increasing attention to socially relevant cues (Guastella et al., 2008). If the administration of OXT alters eye-gaze to meaningful social information, it is possible that any improvement in prosocial behavior is via this route. Indeed, within the ASD literature there is evidence that improved facial emotion recognition is due, in part, to participants spending more time looking at the eye area of faces (e.g., Andari et al., 2010). Nevertheless, evidence from healthy participants to support this line of argument is mixed, with one study suggesting that OXT selectively enhances gaze to the eyes (Auyeung et al. 2015), another showing that OXT results in increased gaze to the eye areas for positive faces but decreased gaze to the eyes for negative faces (Domes, Steiner, Porges & Heinrichs, 2013), and others suggesting that improvements in facial emotion recognition are unaffected by eye-gaze (Hubble et al., 2016; Lischke et al., 2012;), but instead are related to pupil dilation (Prehn et al., 2013).

To our knowledge, no study to date has examined the effect of OXT on eye-gaze in relation to empathy. Furthermore, although the use of dynamic stimuli showing characters experiencing emotions and responding to emotional events is generally considered to provide a more realistic context in which to measure emotional reactions (Karrow & Connors, 2003), none of the previous studies examining OXT and empathy used dynamic real-world stimuli. Similarly, to date the effect of OXT on empathy has only been considered for positively or negatively valenced emotion (Hurlemann et al., 2010), with the exception of pain (e.g. Singer et al., 2008). Given that OXT appears to have differential effects in different contexts (e.g., De Dreu et al., 2010), coupled with evidence suggesting that OXT may have a selective effect on the processing of fearful facial expressions (Fischer-Shofty, Shamay-Tsoory, Harari &

Levkovitz, 2010; Leppanen, 2017), it is important to consider the effect of OXT on empathy for different discrete emotions. These issues are taken into account in the present research. A further point is that most OXT studies to date have used between-subjects designs. In response to recent reviews that are critical of the quality and rigor of OXT research (Churchland & Winkielman, 2012; Leng & Ludwig, 2016; Walum, Waldman, & Young, 2016) and in view of evidence of large variations in individual responsivity to OXT across participants (Daughters et al., 2015), we decided to study the effects of OXT using a within-subjects design and to take measures of salivary OXT levels to ensure that the nasal sprays had the intended effect on OXT levels. We also measured eye-gaze during the empathy task, with a view to explaining any observed effects in terms of attention allocation.

To summarize, there is conflicting evidence for beneficial effects of OXT on both cognitive and affective empathy. To address these issues, we aimed to measure cognitive and affective empathy for discrete emotions using a double-blind, within-subjects randomized control trial of intra-nasally administered OXT. We also explored the mechanism by which OXT may affect empathy by measuring eye-gaze. To achieve these aims, participants completed a dynamic empathy task that aimed to evoke empathy experimentally using four short video clips inducing the emotions of pain, sadness, happiness and fear, during which participants' eye-gaze was tracked (van Rijn, Barendse, van Goozen, & Swaab, 2014). After each clip participants were asked to identify (a) the main character's emotions and their intensities, (b) their own emotions and their intensities, and (c) the reasons for the main character's and their own emotions.

Consistent with the previously hypothesized prosocial effects of OXT, we predicted that OXT would enhance both cognitive and affective empathy for all emotions. We also expected OXT to increase attention to the eye-region of faces and that this increased attention would be related to greater empathy.

Method

Participants

Forty healthy male students (M_{age} = 20.98; SD = 4.55) at Cardiff University participated in this experiment in return for course credit or £40. Participants took part in two 3-hour study sessions, with a 2-week interval between each session (for practical reasons seven participants had to be tested at later dates; the longest interval between the two sessions was 35 days). The order in which they received OXT or placebo nasal spray was randomized and counterbalanced, with researchers and participants remaining blind to this order. The decision to examine OXT in male participants was taken for two reasons: (1) the effects of

OXT have been found to differ in males and females, such that collapsing across gender would not be appropriate (Domes et al., 2010; Kirsch et al., 2005); and (2) administering OXT to females entails additional ethical and logistical considerations (e.g., controlling for menstrual cycle phase and/or pregnancy).

Ethical Considerations

The study was approved by both the School of Psychology Ethics Committee at Cardiff University, and by the Research and Development Office at Cardiff and Vale University Health Board. Participants were cleared to participate in the study by a medical professional (co-author AR) and gave written informed consent at each testing session. They were fully debriefed after the second session. They completed medical pre-screening forms and signed statements of health before leaving each testing session. All participants had normal or corrected-to-normal vision, and none of them reported a history of neurological or mental health disorders, or severe allergic reactions. Participants were asked to refrain from consuming alcohol in the 24 hours prior to each study session and from smoking cigarettes or drinking caffeine in the 2 hours prior to each study session.

Measures and Materials

Empathy task: emotion-eliciting video clips. We used eight clips depicting main characters feeling pain/hurt, sad/upset, fearful/scared or happy/cheerful; these will be referred to as the pain, sadness, fear and happiness clips, respectively. The clips were edited from commercially available films or videos and had a duration of approximately 120 seconds. One set of film clips (i.e., those for pain, sadness, fear and happiness) had previously been validated (see van Rijn, Barendse, van Goozen, & Swaab, 2014). The current study used four additional clips, which were selected based on similarity scores from a pilot study to match the previous set of clips with respect to duration, content and emotional intensity. Participants viewed one set of four emotional clips during the first visit and the other four clips on the second visit, and the order of clips was counterbalanced across participants. Clips were shown to participants using Tobii Studio software on a Dell Precision M4700 laptop with a 15.6 inch screen.

Empathy scores. After each clip participants completed two questionnaires, indicating how strongly the main character or they experienced each of 10 emotions (labeled as follows: anger, sad, pain, upset, fearful, happy, scared, cheerful, surprised and hurt). Ratings were made on a 6-point intensity scale, where 0 indicated no emotion and 5 indicated intense emotion. Participants were also asked to explain the reason for the emotion(s) they identified in the main character and in themselves. There were no constraints on the amount

information they provided. These responses were coded for cognitive and affective empathy by research assistants who were blind to the participants' drug condition. Scores took into consideration four important elements of empathy: (1) whether the target emotion was correctly identified; (2) whether another, similar emotion was identified; (3) the intensity of the emotion identified; and (4) the explanation for the causes of the emotion (see van Goozen et al., 2016). Scores for cognitive empathy ranged from 0-9; a maximum of 2 points was awarded for identifying the correct target emotion in the main character at the correct intensity; a maximum of 2 points was also awarded for identifying a relevant similar emotion at the correct intensity, and up to 5 points were awarded for the participant's explanation and understanding of the emotion. For example, an explanation stating "she was scared because she was slipping and she thought she might fall and die" would receive a maximum score of 5. Scores for affective empathy ranged from 0-6, where a maximum of 2 points was awarded for indicating personally feeling the target emotion at a high intensity; another maximum of 2 points was awarded for indicating personally feeling a relevant similar emotion at a high intensity, and up to 2 points were awarded for the participant's explanation and understanding of their own emotion. For example, an explanation stating "I felt sad because I thought about that happening to me" would have scored the maximum of 2. Higher scores on both scales reflect greater empathy. The measures exhibited satisfactory internal consistency (Cronbach's alphas: cognitive empathy = 0.70; affective empathy = 0.83). Inter-rater reliability (Cohen k) between two trained coders on a subset of 10% of the data across clips ranged from .74 to .82)

Eye-tracking. Participants were positioned approximately 60-65 cm from a laptop computer and a 9-point calibration was performed. The quality of calibration was checked; if there were no data for one or more points, or if calibration quality was poor, calibration at those points was repeated. This process was completed for a maximum of three calibration attempts, after which it was unlikely that calibration would improve further. Data from seven participants were excluded due to poor calibration quality. Calibration was followed immediately by the empathy stimuli. Eye movements were recorded with a portable Tobii X2-60 compact eye-tracker sampling at 60Hz with a screen resolution of 1920 x 1080. This equipment is robust to changes in head position, removing the need for a chin rest. An I-VT fixation filter with a minimum fixation criterion of 60 milliseconds sampled the average raw data from both eyes to produce information on eye positions and duration. Eye-gaze validity

was checked using a sample rate percentage that gives an estimate of the quality of the eye-tracking in a recording by providing a percentage score of successfully-recorded data. One participant whose validity fell below 70%, meaning eye-tracking data were not available for more than 30% of the recording, was excluded from the final analysis. For the remaining participants, validity ranged from 70–97%. The seven excluded participants did not differ from those whose eye-tracking data were retained with respect to performance on the empathy task (overall cognitive empathy: $M_{included} = 6.2$, $M_{excluded} = 6.00$, $p > .05$; overall affective empathy: $M_{included} = 3.8$, $M_{excluded} = 3.4$, $p > .05$), age ($M_{included} = 21$, $M_{excluded} = 23$, $p > .05$), or drug order (four of the seven excluded participants received OXT first, the remaining three received PL first).

Saliva Samples

Participants produced four saliva samples during each session: at baseline, and 30, 60, 90 min after OXT/placebo administration. These samples were analyzed to measure salivary OXT at each of these time points. These analyses revealed the OXT nasal sprays were successful in increasing OXT levels: mean saliva oxytocin concentration (in pg/mL) for all participants 60 min after administration (during the empathy task) was 952.0 during OXT and 46.4 during PL (see Daughters et al., 2015). When participants excluded from the eye-tracking analysis were removed, mean salivary OXT concentration after 60 min was 826.8 during OXT and 38.4 during PL. There were no significant differences in OXT concentrations between those included and excluded from the eye-tracking analysis ($p > .05$).

Procedure

Participants self-administered 24 IU (three 4IU puffs per nostril) of synthetic OXT or an independently manufactured placebo nasal spray (PL) that chemically matched the OXT spray for all compounds, except OXT. Both sprays were manufactured by St Mary's Pharmaceutical Unit, Cardiff (http://www.wales.nhs.uk/sites3/home.cfm?orgid=828). A medical doctor was present during administration, and for the subsequent 15 minutes. A 30-min waiting period was used between drug administration and task start in order to allow the drug to take effect. This interval was based on previous studies suggesting that OXT concentrations in both plasma (Gossen et al., 2012) and saliva (Weisman, Zagoory-Sharon & Feldman, 2012) peak at 30 minutes. This waiting time also ensures that saliva measures obtained after this point do not reflect spiking due to direct transfer from nose to saliva (for details, see Martin, Schipper, Verhoef & Merkus, 1998). During the waiting period,

participants completed a set of measures asking for demographics and food and caffeine intake. At the end of the waiting period they completed a 15-minute face processing task (see Hubble et al., 2016), which was followed by the empathy task that started 45 minutes after OXT administration and lasted approximately 30 minutes. Each video clip was followed immediately by the empathy questionnaire. In the second session, participants completed the same empathy task but with different (matched) clip. After completing all tasks, participants were debriefed about the aims of the study and were asked to indicate which spray they thought they had during which session and how confident they were of this. Participants could not accurately report, above chance levels, the session in which they received OXT, (23 guessed correctly) $X^2(1) = 0.9$, $p = .34$. Furthermore, participants who identified the correct spray order indicated that they were less certain of that order than those who reported the incorrect order (Correct $M = 3.8$; Incorrect $M = 5.7$), $t(38) = 2.35$, $p = .024$.

Data Analysis

Tobii analysis software was used to analyze eye movements, which allowed areas of interest (AOI) to be created and a variety of summary reports generated. The eyes were grouped into one area. A second AOI was created around the mouth. A third AOI was around the face as a whole to allow for analysis of when participants were looking at the face. Eye-gaze was analyzed during a 4s segment (equivalent to the time-frame given in static emotion recognition tests) that showed a clear, dynamic development of the emotion. Percentage dwell time (the sum of the duration of all fixations to an AOI divided by the total duration of the segment) for each AOI was calculated. The percentage of time spent looking at the eye and mouth regions was subtracted from that for the whole face to yield a percentage of time spent looking at the other face areas.

Analyses were carried out using SPSS 20 (SPSS Inc., Chicago, IL). The principal analyses reported below are analyses of variance. Where the assumption of sphericity was violated, Greenhouse-Geisser corrections were used. Within each analysis, Bonferroni corrections were applied for all post-hoc comparisons. Effect sizes were calculated as partial eta squared (η_p^2); small ≥ .01, medium ≥ .06, large ≥ .14; Cohen, 1988). Confidence intervals have been calculated at the 95% level for the differences of all key findings (CI_{diff}) and at the 90% level for effect sizes (CI_{es}).

Results

Within-subjects ANOVAs were computed, with Drug (OXT or Placebo [PL]) and Emotion (pain, sadness, fear and happiness) as the within-subject factors. Separate analyses were carried out on the dependent variables of cognitive empathy and affective empathy.

Cognitive Empathy

Mean cognitive empathy scores are shown in Figure 1. Results revealed a significant main effect of Emotion, $F(3, 117) = 12.93$, $p < .001$, $\eta_p^2 = .25$, but no main effect of Drug, $F(1, 39) = 0.04$, $p = .84$, $\eta_p^2 = .00$, and no interaction between Drug and Emotion, $F(3, 117) = 2.14$, $p = .10$, $\eta_p^2 = .05$. Follow-up analyses revealed that cognitive empathy for pain ($M = 6.4$, SD=0.7), and fear ($M = 6.5$, $SD = 0.9$) were similar ($p > .05$) and significantly higher than those for sadness ($M = 5.9$, $SD = 0.7$) and happiness ($M = 5.9$, $SD = 0.8$) (all ps <.05) which did not differ ($p > .05$).

INSERT FIGURE 1 HERE

Affective Empathy

Mean affective empathy scores are shown in Figure 2. There was a main effect of Emotion, $F(3, 117) = 16.03$, $p <.001$, $\eta_p^2 = .29$. Affective empathy was significantly greater for sadness ($M = 4.6$, $SD = 0.9$) compared to pain, happiness and fear (all $ps < .001$), and there were no significant differences in affective empathy between fear ($M = 3.5$, $SD = 1.6$), pain ($M = 3.4$, $SD = 1.3$) and happiness ($M = 3.5$, $SD = 1.0$) (all $ps > .05$). There was no main effect of Drug, $F(1, 39) = 0.13$, $p = .73$, $\eta_p^2 = .00$, but there was a significant interaction between Emotion and Drug, $F(3, 117) = 2.77$, $p = .045$, $\eta_p^2 = .06$, 90% CI_{es} [.001, .13]. Affective empathy for fear was significantly higher ($p = .02$, $\eta_p^2 =.14$, 90% CI_{es} [.02, .31], in the OXT ($M = 3.9$, $SD = 1.7$) than PL ($M = 3.2$, $SD = 1.8$) condition (95% CI_{diff} [0.1, 1.1]). The corresponding differences were not significant for pain ($p = 1.00$), happiness ($p = .25$) or sadness ($p = .35$).

INSERT FIGURE 2 HERE

Eye-gaze Patterns

An ANOVA was conducted with three within-subjects factors: Drug (OXT vs PL), Emotional Clip (Pain, Happiness, Sadness, or Fear) and AOI (Eye, Mouth, or Rest of face). There was a main effect of AOI, $F(1.31, 41.95) = 35.58$, $p < .001$, $\eta_p^2 = .53$, reflecting the fact that percentage dwell time to the eye-region was greatest ($M = 36\%$, $SD = 15.1$), followed by that for the rest of the face ($M = 29\%$, $SD = 7.6$); dwell time to the mouth region was significantly lower than both the eye-region ($p < .001$) and the rest of the face ($p < .001$) ($M =$

11%, *SD* = 8.2). Dwell times for the eye-region and the rest of the face did not significantly differ from each other ($p = .13$).

A significant main effect of Emotion, $F(2.49, 79.6) = 25.81$, $p < .001$, $\eta_p^2 = .45$, showed that participants spent significantly more time looking at the face of the main character during the sadness clip (*M* = 30%, *SD* = 4.3), compared to the happiness (*M* = 26%, *SD* = 4.3) pain (*M* = 24%, *SD* = 5.2) and fear (*M* = 21.2%, *SD* = 5.5) clips (all *p*s < .05). There was no significant difference in dwell time for the face when watching the happiness and pain clips ($p = .33$) but during the fear clip participants spent significantly less time looking at the face compared to the other clips (all *p*s <.05). The main effect of Drug was marginal, $F(1, 32) = 3.76$, $p = .06$, $\eta_p^2 = .11$, and reflected the fact that participants in the PL condition tended to spend more time looking at the face in general (*M* = 26%, *SD* = 3.3) compared to the OXT condition (*M* = 25%, *SD* = 4.4). The Emotion by Drug interaction was not significant, $F(2.29, 73.2) = .05$, $p = .99$, $\eta_p^2 = .00$.

The three-way interaction between Drug, Emotion and AOI was not significant, $F(4.53\ 144.79) = 0.68$, $p = .62$, $\eta_p^2 = .02$, but there were significant interactions between Drug and AOI, $F(2, 64) = 10.71$, $p < .001$, $\eta_p^2 = .25$, 90% CI_{es} [.09, .37] and between Emotion and AOI, $F(3.72, 118.96) = 20.2$, $p < .001$, $\eta_p^2 = .39$, 90% CI_{es} [.26, .47] Means relevant to the Drug by AOI interaction are shown in Figure 3. Follow-up tests revealed that OXT resulted in a greater proportion of time fixating on the eye-region, $F(2, 96) = 11.33$, $p = .002$, $\eta_p^2 = .26$, 90% CI_{es} [.08, .29], 95% CI_{diff} [2.7, 10.9]; given this, it is not surprising that OXT also led to less time spent looking at the mouth, $F(2, 96) = 3.73$, $p = .06$, $\eta_p^2 = .10$, 90% CI_{es} [.004, .15], 95% CI_{diff} [-7.2, 0.2], and the rest of the face, $F(2, 96) = 12.86$, $p = .001$, $\eta_p^2 = .29$, 90% CI_{es} [.09, .30}, 95% CI_{diff} [-11.8, -3.2].

INSERT FIGURE 3 HERE

Means relevant to the Emotion by AOI interaction are shown in Figure 4. Follow-up tests revealed that there were significant differences between the clips in the proportion of time spent fixating upon the eyes, $F(4, 119) = 34.05$, $p < .001$, $\eta_p^2 = .77$, and mouth, $F(4, 119) = 21.29$, $p < .001$, $\eta_p^2 = .68$. Further analyses revealed that participants spent a significantly greater proportion of time fixating on the eyes during the sadness clip compared to the happiness, fear and pain clips (all *p*s < .05), whereas a significantly greater proportion of time was spent looking at the mouth during the pain clip compared to the happiness, sadness and

fear clips (all *p*s < .05). There were no differences between clips with respect to the amount of time spent fixating upon the rest of the face, $F(4, 119) = 0.98$, $p = .41$, $\eta_p^2 = .09$.

INSERT FIGURE 4 HERE

Comparing Empathy and AOI

To examine the relationship between eye-gaze and empathy, we calculated Spearman's rhos to assess the association between changes in cognitive empathy and affective empathy scores from PL to OXT for each emotional clip and the change in dwell time to the eye-region from PL to OXT for the same clip (difference scores were calculated as OXT – PL for each variable). As can be seen in Table 1, there was a significant inverse correlation between affective empathy for fear and dwell time to the eye-region ($p < .05$).

INSERT TABLE 1 HERE

Discussion

We set out to establish whether OXT affects self-reported empathy and whether any changes in empathy are associated with altered eye-gaze to socially relevant stimuli. In contrast to our hypothesis, which predicted that OXT would result in enhanced cognitive and affective empathy across all emotions, our results demonstrate that a single dose of OXT administered to healthy male subjects enhanced their ability to empathize affectively with a fearful protagonist, but not with a protagonist displaying pain, sadness or happiness. This is inconsistent with the findings from Domes et al. (2007) who found that OXT improved cognitive empathy. However, our findings are partly consistent with evidence from Hurlemann et al. (2010), who found that OXT increased affective but not cognitive empathy, although these authors found increased affective empathy for both positively and negatively valenced stimuli. A possible reason for this discrepancy in findings is that the empathy-inducing stimuli differed between the two studies. Hurlemann et al. used static photos, whereas we used dynamic clips. Dynamic clips are arguably of greater ecological validity, in that they reflect more closely the kind of everyday interpersonal interaction in which an empathic response could be aroused (Karrow & Connors, 2003). An additional strength of the present study is the use of a within-subjects design, which controls for the sizeable individual differences that arise in response to intranasally administered OXT (Daughters et al., 2015).

The selective effect of OXT on fear observed in the present study is consistent with findings from research exploring the effect of OXT on facial emotion recognition. Fischer-Shofty et al. (2010), also employing dynamic video clips of emotional facial expressions,

found that OXT selectively enhanced recognition only for fearful faces. In a recent meta-analysis of 9 studies investigating the effects of intranasal OXT on the recognition of fear (two of which included people with schizophrenia and borderline personality disorder), Leppanen et al. (2017) concluded that OXT significantly improved the recognition of basic emotions, albeit with a small effect size, and that the effect is robust, with no evidence of publication bias. However, it was only reliable for healthy individuals. OXT has also been found to increase attention and approach towards fearful facial expressions (Clark-Elford et al., 2015; Tollenaar et al., 2013). In a further meta-analysis, Leppanen, Ng, Kim, Tchanturia, and Treasure, (2018) found that OXT significantly increased the physiological startle response to threat in healthy participants, but did not increase fixations to threatening stimuli. Thus the present findings are consistent with evidence that OXT influences the salience of threatening stimuli.

Interestingly, neuroimaging evidence suggests that the administration of OXT inhibits amygdala activation (Domes et al., 2007b; Kirsch et al., 2005; Singer et al., 2008), thereby dampening the fear response, which appears to be inconsistent with the improvement in fear recognition observed by Fischer-Shofty et al. (2010) and with the greater affective empathy for fear responses observed in the present research. Given that there are a number of brain areas associated with the processing of fearful stimuli and affective empathy, and that OXT binding sites have been observed in different areas of the rats brain that are involved in emotion processing (Febo, Numan & Ferris, 2005; Ferris, 2008; Smeltzer, Cutis, Aragona & Wang, 2006), it is possible that OXT modulates different cortical regions that are important for processing threatening stimuli, and thereby improves affective empathy for fear (Fischer-Shofty et al., 2010).

A strength of the present study is the use of eye-tracking technology to investigate whether any improvement in empathy resulting from OXT was matched by increased attention to socially relevant stimuli. We found that OXT led to a general increase in the amount of time participants fixated on the eye-region of the face for four different types of emotion. These results contrast with those reported by Lischke et al. (2012), who found no evidence that OXT altered eye-gaze in healthy participants. Nevertheless, our results are consistent with evidence from ASD literature suggesting that OXT increases attention to socially relevant stimuli, and specifically for the eye-region (e.g., Andari et al., 2010).

ASD researchers have argued that improvements in facial emotion recognition associated with OXT administration result from increased attention to the eye-region, although few studies have empirically tested this notion. With respect to empathy research,

no prior study has examined eye-gaze as a possible mediator of enhanced empathy. We found no evidence that changes in eye-gaze resulting from OXT were related to greater empathy. Thus the observed increase in affective empathy for fear did not result from increased attention to socially relevant stimuli. Indeed, improved empathy for fear was associated with a *reduced* time looking at the eye region, a pattern that was also evident for other emotions, albeit to a lesser extent. Given the relatively small sample size in this study, further research is needed to establish the reliability of this finding. If replicated, it may reflect an attempt by participants who are empathizing more strongly with the protagonist's fear to regulate their own emotions by looking less at the protagonist's eyes.

A possible explanation for absence of a strong link between emotional responding and eye gaze concerns the stimuli used. Evidence for a link between emotion recognition and eye-gaze has typically been found in studies using images where the only basis for judgments is provided by facial features. The emotional stimuli used in the current study depicted protagonists experiencing emotions in arousing situations. Participants therefore had access to non-facial cues, such as tone of voice, gestures and contextual information. This may have rendered information from the face less important. However, we do not regard this as a limitation, because dynamic stimuli showing people responding to emotional situations is more reflective of everyday occurrences; instead, the results suggest that eye-gaze may be less important in everyday interactions than it is in studies simply investigating responses to facial images. It is worth noting that in a separate task, using the same group of participants but static facial expressions, OXT did not result in significant changes in eye-gaze (Hubble et al., 2016), which also suggests that the dynamic nature of the stimulus was important in the current finding.

Another possible reason for the absence of a strong relationship between eye-gaze and empathy concerns the timing of the measures. Affective empathy was measured after each clip, requiring participants to integrate their emotional experiences during the 2-min stimulus into a single score, whereas the eye-gaze data were collected during a 4-sec segment of each clip that showed a clear, dynamic development of the emotion. Comparing strictly contemporaneous eye-gaze and empathy data might reveal a stronger relationship between them, although this would be very difficult to implement, given that providing continuous ratings of emotions (one's own or another's) would likely interfere with eye-tracking analysis. Physiological measures therefore offer a better way of comparing eye-gaze and empathy continuously, although but they are affected by other issues (e.g., they reflect arousal but are relatively insensitive to valence; see Lang, Greenwald, Bradley & Hamm,

1993). Given the evidence that OXT may be especially involved in the initial allocation of attentional resources (Gamer, Zurowski & Buchel, 2010), future studies could consider whether monitoring early fixations would result in a stronger relation between eye-gaze and empathy.

Limitations

Our conclusions concerning the possible role of OXT on affective empathy for fear and eye-gaze derive from an exogenous administration study, in which participants received intranasal OXT or a matching PL. This method has the advantage of being able to draw conclusions about cause and effect relationships, which would not be possible if one were correlating endogenous oxytocin with empathy or eye-gaze. The disadvantage of this method, however, is that the pathways through which intranasal OXT affects brain activity and behavioral responses are not fully understood (e.g., McCullough, Churchland, & Mendez, 2013). Although there is good evidence that intranasal OXT increases the concentration of endogenous OXT found in blood plasma and saliva (Daughters et al., 2015; Gossen et al., 2012; Weisman et al., 2012), doubt has been cast on the extent to which intranasal OXT crosses the blood-brain barrier (Neumann et al., 2013; Paloyelis et al., 2014; Striepens et al., 2013). Walum et al. (2016) also raised concerns about the power of OXT studies, suggesting that a sample size of more than 300 participants is needed to achieve sufficient power, compared to the average of 49 participants (between-subjects) used in previous studies. Although nowhere near the size proposed by Walum et al., our study represents an improvement on many previous studies, especially given that it benefitted from the use of a within-subject design. We were also able to confirm that OXT levels were higher in the OXT condition, thereby mitigating some of the concerns associated with exogenous administration of OXT. Nevertheless, we acknowledge that the results from this study would benefit from replication with larger samples.

A further limitation of the present study stems from the fact that our measure of affective empathy depended on self-reports of emotion. Self-reported emotional states can be confounded by conscious awareness of the response or even the willingness to report this response. They are also vulnerable to demand characteristics and social desirability (e.g., Eisenberg-Berg & Hand, 1979). Consequently, self-reports might not necessarily reflect how the individual actually felt, but rather indicate perceptions of how other people expect one to feel. Physiological measurements, such as skin conductance or facial responsivity can help to overcome some of these pitfalls. For example, Korb et al. (2016), used facial EMG to show that facial mimicry increased during OXT, particularly in response to angry infant faces.

Nevertheless, physiological measures also have limitations; for example, they do not distinguish between empathy, sympathy and personal distress (Zhou, Valiente & Eisenberg, 2003).

The limitations associated with particular measures of affective empathy suggest that no single measurement is perfect. Studies examining the convergence between different measures of affective empathy show that some measurements, such as self-report measures and facial responsiveness, correlate with each other (Anastassiou-Hadjicharalambous & Warden, 2007), suggesting there is a common construct that is tapped by each measure. This points to the importance of measuring affective empathy using a multi-method approach to examine whether OXT enhances different components of affective empathy. Indeed, evidence from studies examining the effect of OXT on facial emotion recognition (Prehn et al., 2015) suggests examining pupil dilation in response to empathy could be a worthwhile next step.

A final limitation is that we examined the effects of OXT in a male-only sample. This arose from the practical and ethical complications entailed in administering OXT to women. Evidence suggests that there are sex differences in empathic abilities (e.g., Baron-Cohen & Wheelwright, 2004) and that OXT differentially modulates the neural circuitry involved in face processing in men and women. For example, while it has been demonstrated that OXT decreases amygdala activity in response to fear in men (Kirsch et al., 2005), it appears to increase amygdala activity to similar stimuli in women (Domes et al., 2010). Additionally, women typically report higher levels of affective empathy than men (Hurlemann et al., 2010; Theodoridou et al., 2013). Our results may therefore not be generalizable to women. In addition, given that our sample were all undergraduates who tend to perform reasonably well in these types of tasks, it is possible that our results may not be generalizable to populations who might find these tasks more challenging. It is worth noting that OXT has been found to have stronger effects when task difficulty is higher (Domes et al., 2007a; Feeser et al., 2015), suggesting the effect of OXT on empathy may be greater in populations showing empathy deficits (Feeser et al., 2015).

Conclusion

The present results suggest that the administration of OXT selectively enhances affective empathy for fear, whilst leaving cognitive empathy and affective empathy for sadness, happiness and pain unaffected. Furthermore, we show for the first time using an emotion-inducing film clip paradigm that OXT significantly increased gaze towards the eye-region of faces across the four emotions studied here. However, increased dwell time for the eyes was

not positively related to affective empathy for fear, suggesting that the widely held, but rarely tested, notion that OXT-induced effects on emotional responding result from increased attention to socially relevant stimuli is in need of closer scrutiny.

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Table 1

Intercorrelations (Spearman's rho) between the difference in affective and cognitive empathy scores between OXT and PL conditions for each clip and the difference in eye-region dwell times for OXT and PL conditions for each clip

Affective Empathy	**Eye-region dwell time N=33**	**Cognitive Empathy**	**Eye-region dwell time N=33**
Pain	-.06	Pain	-.29
Happiness	.06	Happiness	.002
Sadness	.16	Sadness	.13
Fear	-.43*	Fear	-.33^{+}

* = p <.05, $^{+}$ = .058

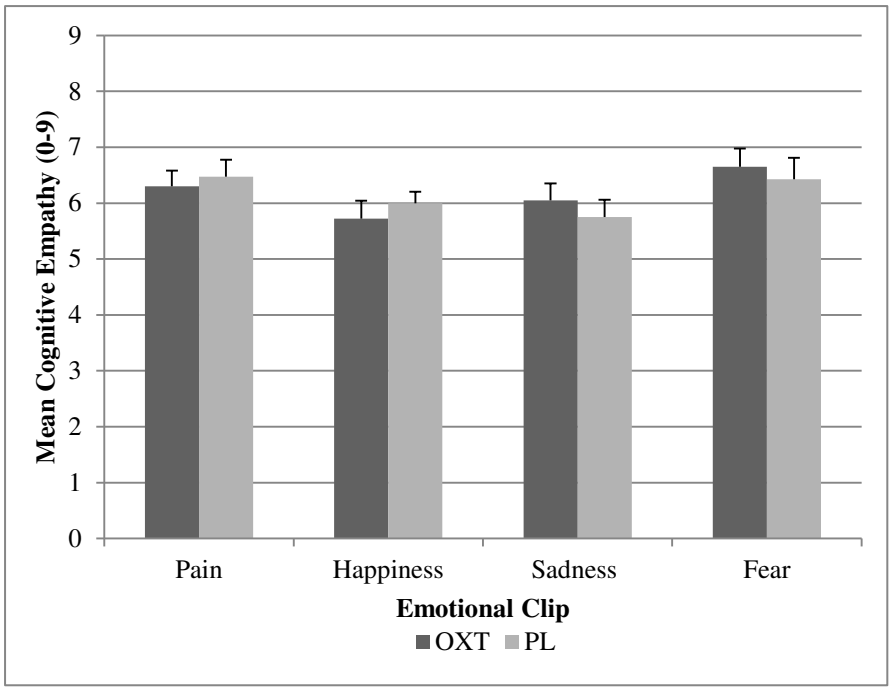

Figure 1: Cognitive empathy as a function of emotional clip and drug. Error bars show +2 SE

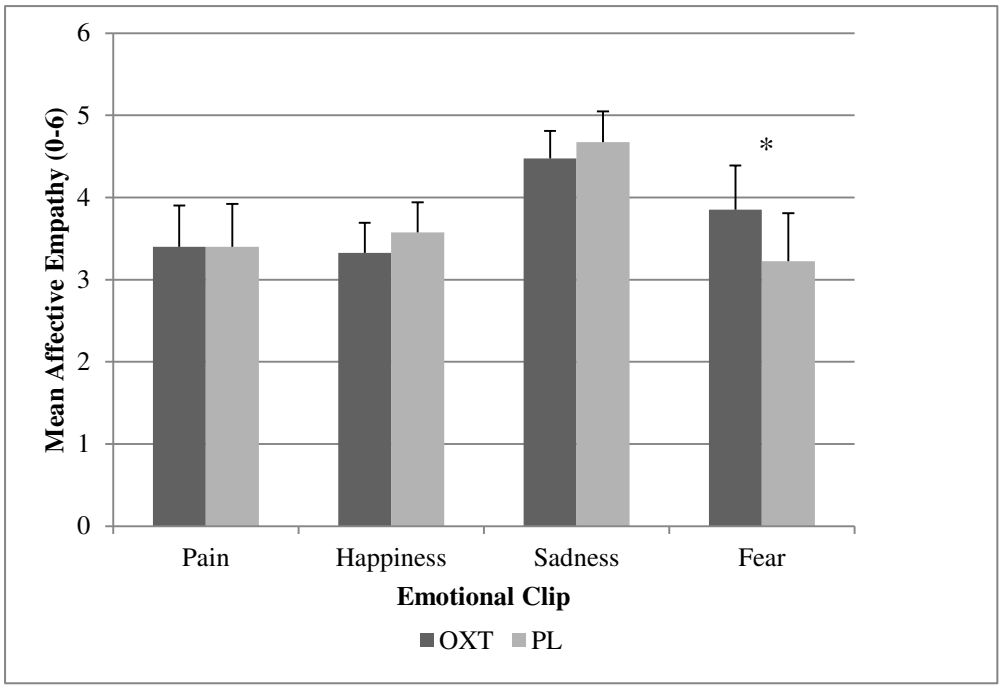

Figure 2. Affective empathy as a function of emotional clip and drug. Error bars show +2 SE. *$p < .05$

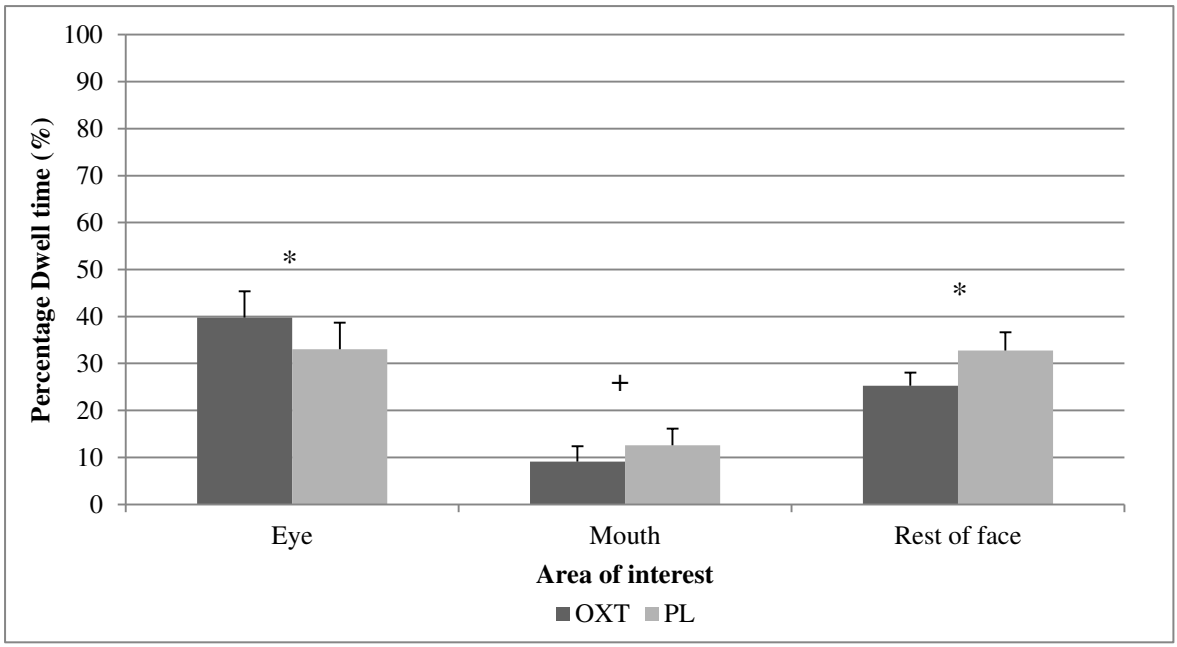

Figure 3: Percentage dwell time as a function of area of interest and drug. Error bars show +2 SE. +$p < .10$, *$p < .05$

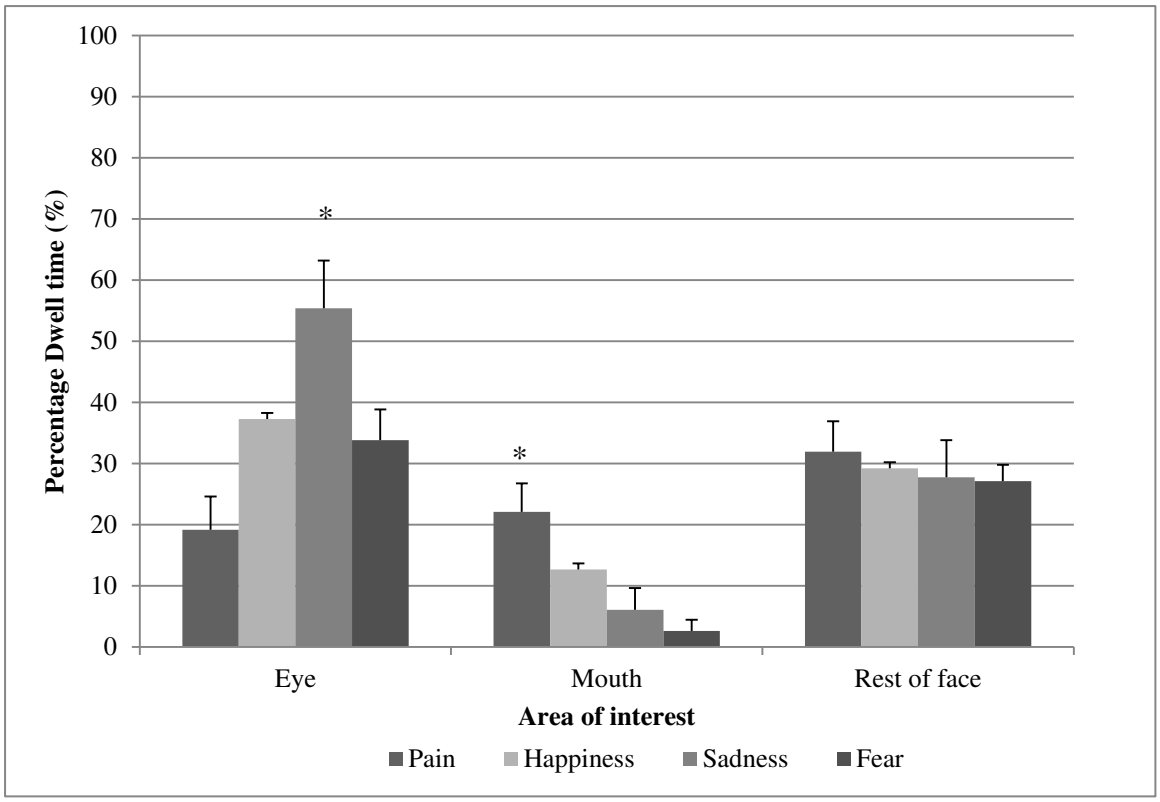

Figure 4: Percentage dwell time as a function of area of interest and emotion. Error bars show +2 SE. *$p < .05$