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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.

1. Introduction

The ability to understand and share another person's emotional state or context, referred to as empathy (Eisenberg and 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, 2009a). 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 et al., 2005), generosity (Zak et al., 2007) and facial emotion recognition (Domes et al., 2007a). Of particular interest to the current study is the commonly referenced finding concerning the benefits of OXT on mind-reading (Domes et al., 2007b). These findings have spurred interest in the potential of OXT to reduce social deficits associated with disorders.

However, some recent studies (e.g., Nave et al., 2015; Lane et al., 2015; Radke and de Bruijn, 2015; Hofmann, Fang and 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

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findings (Lane et al., 2016). This, combined with some evidence that OXT can increase negative responses, such as schadenfreude (Shamay-Tsoory et al., 2009b), 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 et al. (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 (2007b) 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 and 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 et al., 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 et al., 2015; Shamay-Tsoory et al., 2013). Similarly, in a within-subjects neuroimaging study examining empathy for a partner's experience of physical pain, Singer et al. (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 et al., 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 et al., 2008), and also to increase attention to objects that are the gaze targets of static faces (Tollenaar et al., 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 et al., 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 (Karow and 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 et al., 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 and Winkielman, 2012; Leng and Ludwig, 2016; Walum et al., 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 et al., 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.

2. Method

2.1. 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-h 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