Oxytocin, Stress Reactivity, and Emotional Information Processing: Investigating Two Potential Mechanisms Mediating Oxytocin's Pro-Social Effects

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ABSTRACT

Oxytocin, Stress Reactivity, and Emotional Information Processing: Investigating Two Potential Mechanisms Mediating Oxytocin's Pro-Social Effects

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The nonapeptide oxytocin promotes social affiliation in both human and non-human animals. However, the mechanisms underlying this phenomenon require further elucidation. There is increasing evidence that oxytocin is facilitating pro-social behaviour by modulating stress reactivity and social cognitive processes. Two double-blind placebo controlled studies were conducted to further test this theory. Study 1 examined the influence of intranasal oxytocin on the affective and cortisol response to the Yale Interpersonal Stressor (YIPS), a live social-rejection paradigm. Ninety-Six undergraduate students underwent the YIPS, where participants are excluded from two separate conversations by two same-sex confederates. Salivary cortisol levels and mood were repeatedly measured throughout the study. Participants were administered a single dose of intranasal oxytocin (24 I.U.) or placebo prior to beginning the YIPS. The YIPS elicited a significant negative mood response that was more pronounced in females than males. However, no significant cortisol response to the stressor and no sex difference in cortisol reactivity were observed. A significant effect of drug condition on cortisol levels was observed. Participants who were administered oxytocin, relative to placebo, exhibited a decrease in cortisol levels during the YIPS. The study ultimately revealed that oxytocin was effective at reducing cortisol concentrations during an interpersonal challenge.

The aim of study 2 was to investigate the relationship between oxytocin and basic emotional information processing in men and women. Eighty-four participants self-administered 24 I.U. intranasal oxytocin or saline and later completed an assessment of the acoustic startle reflex with varying emotional foregrounds. Oxytocin had no impact on the affective modulation of the startle eyeblink response. Rather, oxytocin significantly diminished the acoustic startle response irrespective of the emotional foreground of pictorial stimuli. The results are consistent with studies showing a dampening effect of intranasal oxytocin on the activation of the amygdala in response to emotional stimuli, and further support oxytocin's anxiolytic effects on physiological arousal.

Overall, both studies demonstrate that oxytocin modulates the HPA axis during interpersonal challenge, and also the basic startle reflex. It is possible that by dampening these physiological systems, oxytocin is serving to facilitate social approach behaviour.

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Anne-Marie Linnen was involved in developing the experimental design and testing participants (data collection). She performed the statistical analyses and wrote the first draft of the manuscript. Mark Ellenbogen edited subsequent versions of the manuscript. All authors contributed to and approved the final version of the manuscript.

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Chapter 2

1. INTRODUCTION

George Sand once wrote: "There is only one happiness in life, to love and be loved" (Sand, 1862). Although a ubiquitous human experience, love remains an elusive phenomenon. It is best understood through the relationships that are created when people get married, have children, make new friends etc… Although social relationships are often taken for granted in daily life, in the realm of psychology they are studied extensively. Most notably, researchers have discovered that positive social relationships confer important health benefits. For example, an abundant number of studies have demonstrated that social support increases resiliency to physical illness (Stewart & Yuen, 2011) and represents a protective factor against the development of mental illness (Cohen, Hammen, Henry, & Daley, 2004; Korol, 2008). Conversely, the absence of positive relationships has been identified as an important factor in the pathogenesis of mental illness (Cohen et al., 2004; Hammen, 2003b; Hirschfeld et al., 2000; Yan, Hammen, Cohen, Daley, & Henry, 2004) and has been shown to have a negative impact on cardiovascular health (O. Evans & Steptoe, 2001; Roy, Steptoe, & Kirschbaum, 1998; Steptoe, 2000) as well as on health behaviours i.e. exercise, smoking, alcohol consumption (Allgower, Wardle, & Steptoe, 2001; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996). In short, low social support has been linked to negative health outcomes (House, 2001).

Considering the impact of positive social relationships on physical and mental health, significant research has been conducted to identify the neurobiological mechanisms regulating social affiliation (Insel, 1997). Of interest, there has been

overwhelming evidence implicating oxytocin (a peptide hormone) in the development of social behaviour across a number of different animal species (Carter, 1998). The effects of oxytocin on human behaviour have received considerably less attention. Measuring oxytocin in blood plasma is impractical because it degrades rapidly (half-life of 3 min.) The systematic administration of oxytocin in periphery, via oral ingestion or intraveniously, is also impractical because oxytocin does not readily cross the blood brain barrier.

Born (2002) conducted a study that revolutionized oxytocin research in humans. The study examined whether intranasal peptide administration would penetrate the central nervous system (CNS) in healthy human males and females. One of the three peptides examined was vasopressin, a neuropeptide which closely resembles oxytocin in structure (Barberis & Tribollet, 1996). The intranasal administration of vasopressin resulted in a significant increase in cerebrospinal fluid (CSF) concentrations, which began to rise after 10 minutes, peaked at 80 minutes, and remained elevated up to 120 minutes after administration. Considering the structural similarity between vasopressin and oxytocin, intranasal oxytocin has since been purported to penetrate the CNS and along the same time frame as intranasal vasopressin (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). As a result of the experiment performed by Born (2002), the number of studies examining the influence of intranasal oxytocin on human behaviour has risen drastically in the last decade.

Congruent with animal research, it has been fairly well established that oxytocin promotes social affiliation in humans (Campbell, 2010). However, the mechanisms underlying this relationship remain unknown. As such, the present dissertation was not

intended to further investigate *if* oxytocin modulates pro-social behaviour but was rather conceived to examine *how* the hormone exerts its pro-social effects. Before describing the two studies that were undertaken to address this question, we will begin by reviewing the existing research literature on oxytocin. More specifically, we will provide background information on oxytocin and will review its effects on social affiliation, social cognition, and stress reactivity. Despite the presence of an extensive animal literature on the effects oxytocin on pair bonding and maternal behavior (Insel, 2010; Insel, Gingrich, & Young, 2001) the present review of the literature places greater emphasis on research performed on humans, which we have largely drawn upon to conduct our own studies.

1.1 Oxytocin Background

1.1.2 Structure and Synthesis

Oxytocin is a peptide hormone that consists of a sequence of 9 amino acids. It is highly similar in structure to vasopressin, a peptide hormone differing in only two amino acids (Barberis & Tribollet, 1996). It is speculated that oxytocin and vasopressin evolved from a common ancestral peptide called vasotocin, which controls courting sounds, sexual behaviour, and birthing in reptiles (Macdonald & Macdonald, 2010). Oxytocin and vasopressin are typically referred to as mammalian hormones and are both involved in the regulation of social behaviours (Heinrichs, von Dawans, & Domes, 2009).

Oxytocin is stored in large magnocellular cells in the supraoptic nucleus and parventricular nucleus of the hypothalamus. From there, oxytocin is transported to the

posterior pituitary where it is released peripherally into the bloodstream. Oxytocin is also synthesized and stored in smaller parvocellular cells in the paraventricular nucleus of the hypothalamus where it is released directly in the CNS to act on receptors in the brain and spinal cord regions (Carter, 1998). It is dubious to what extent the peripheral and central release of oxytocin is coordinated (Campbell, 2010). As such, studies of endogenous OT measured in blood plasma do not necessarily inform us about its central activity or release.

1.1.3 Oxytcocin Receptors in the CNS

Oxytocin's behavioural functions depend on its ability to bind to specific receptors. Within the CNS, oxytocin receptors are mostly distributed in the olfactory system, limbic-hypothalamic system, amygdala, brainstem, and spinal cord areas that regulate reproductive and autonomic functions (Carter, 1998). The location and density of these receptors vary across species and stage of development and mediate the effects of oxytocin on behaviour (Insel, 1997). Variations in oxytocin receptor distribution appear to be associated with both transient (i.e. hormone related) and static (i.e. genetically determined) influences (Furman, Chen, & Gotlib, 2011; Gimpl & Fahrenholz, 2001). Gonadal hormones (particularly estrogen) play an important role in modulating oxytocin receptor expression, density, and affinity (Gimpl, Wiegand, Burger, & Fahrenholz, 2002; Young, Lim, Gingrich, & Insel, 2001). In female rats for example, estrogen regulates the expression and binding of oxytocin receptors in the ventromedial nucleus of the hypothalamus, which is essential for sex behaviours (Bale, Davis, Auger, Dorsa, &

McCarthy, 2001). Although up-regulated by estrogen, it is important to note that oxytocin receptors are found in both sexes. That being said, the distribution of oxytocin receptors can vary between sexes, thereby contributing to sexually dimorphic hormonal effects on behaviour (Campbell, 2008). Identifying the mechanisms through which oxytocin impacts behaviour is further complicated by the fact that it and vasopressin are capable of binding to each others' receptors (Barberis & Tribollet, 1996).

1.1.4 Classic Functions of Oxytocin

Oxytocin is well known for its reproductive functions. Oxytocin is released from the posterior pituitary in pulses that trigger uterine contractions during labour. During lactation, oxytocin contracts the myoepithelial cells surrounding the mammary glands of the breasts in order to produce milk letdown upon nipple stimulation. Oxytocin also modulates certain sexual functions. For instance, oxytocin facilitates lordosis behaviour in female rats and penile erection in male rats (Pfaus, 2009). In humans, plasma oxytocin levels have been associated with sexual arousal and have been shown to spike after orgasm in both men and women (Carmichael et al., 1987). However, the role of oxytocin on human sexual functioning requires further investigation. Apart from its role in reproductive functions, oxytocin is also directly involved in promoting social affiliation, including attachment formation and trust.

1.2 Oxytocin and Social Affiliation

1.2.1 Oxytocin and Attachment

There is extensive research implicating oxytocin in the neurobiology underlying attachment formation, including mother-infant bonding (Insel et al., 2001). The central administration of oxytocin has been found to stimulate maternal behaviours in rats (Pedersen, Caldwell, Peterson, Walker, & Mason, 1992; Pedersen, Caldwell, Walker, Ayers, & Mason, 1994), ewes (Kendrick, Keverne, & Baldwin, 1987) and in non-human primates (Holman & Goy, 1995).

There is now evidence which corroborates these findings in humans. In a seminal study conducted in women, plasma oxytocin levels across pregnancy and in the post-partum period predicted maternal behaviours (i.e. affectionate touch, "motherese", gazing at infants) and mothers' attachment representations (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). These results have since been replicated and extended to fathers (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010a). Plasma oxytocin levels measured in fathers 6 months postpartum have been associated with paternal behaviours (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010b). As described previously, peripheral oxytocin is a poor measure of oxytocin in the CNS. The influence of intranasal oxytocin, which has direct effects in the CNS, was also examined on fathers' parental behaviours. Intranasal oxytocin increased fathers' observed responsiveness to their children and decreased fathers' hostility during a laboratory play session (Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010). As such, it would appear that oxytocin is facilitating positive parenting behaviours behaviour postpartum in humans (Feldman, Gordon, & Zagoory-Sharon, 2011).

Oxytocinegic activity appears to also be implicated in attachment bonds to parents (Gordon et al., 2008). Animal research indicates that oxytocin is important in the formation of attachment bonds in monogamous relationships. Oxytocin has been implicated in a gender specific mechanism for the development of pair bonding in female prairie voles (Cho, DeVries, Williams, & Carter, 1999). Oxytocin is released during copulation and interacts in specific brain regions (i.e. Nucleus Accumbens and Prelimbic Cortex) to facilitate partner preferences and ultimately, long lasting pair bonds (Insel & Hulihan, 1995; Williams, Catania, & Carter, 1992; Young et al., 2001).

In human research, intranasal oxytocin has been observed to enhance the experience of attachment security among insecurely attached adults (Buchheim et al., 2009). However, intranasal oxytocin has also been shown to negatively bias recollections of maternal care and closeness among anxiously attached individuals but to positively bias these recollections among less anxiously attached individuals (Bartz et al., 2010). It is therefore questionable to what extent oxytocin would enhance attachment security in persons with a history of unhealthy parent-child relationships. Nevertheless, oxytocin is released peripherally in response to "warm touch" among married couples (Holt-Lunstad, Birmingham, & Light, 2008). In addition, intranasal oxytocin increases positive communication and decreases cortisol levels during couple conflict (Ditzen et al., 2009). Oxytocin has further been shown to enhance perceived facial attractiveness, which could help to facilitate partner preferences (Theodoridou, Rowe, Penton-Voak, & Rogers, 2009). Based on these findings, it is possible that oxytocin is involved in the formation and maintenance of monogamous bonds and attachment in humans. However, more research is needed to better identify the mechanisms involved in this process, and to

determine the situations and individual dispositions that alter these relationships. The pro-social behavioural effects of oxytocin are not limited to social attachment. For example, researchers have devoted significant attention towards examining the effect of oxytocin on trusting behaviours in humans.

1.2.2 Oxytocin and Trust

There is increasing evidence that oxytocin is associated with human trustworthiness (Zak, Kurzban, & Matzner, 2005). Participants administered intranasal oxytocin are significantly more likely to entrust others with money than control participants (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Kosfeld et al., 2005) and to trust others even when their confidential information is at stake (Mikolajczak, Pinon, Lane, de Timary, & Luminet, 2010). Oxytocin appears to be increasing trust by reducing fear of betrayal as opposed to increasing a general propensity to take risks (Baumgartner et al., 2008; Theodoridou et al., 2009). Baumgartner et al., (2008) have found that the amygdala plays an important role in modulating oxytocin's effect on trust. They observed that during a monetary trust game, oxytocin diminished fear responses associated with betrayal by reducing amygdala activation and connected brainstem effector sites. Although oxytocin increases trust, it does not necessarily increase gullibility. In a recent study, oxytocin failed to increase trust in others when they were perceived to be unreliable (Mikolajczak, Gross, et al., 2010). Oxytocin has also been observed to increase trust within participants' own "in-groups" but not towards competing "out-groups" (De Dreu et al., 2010). As such, oxytocin appears to foster trust

in contexts that are socially adaptive and that are less likely to result in aversive outcomes.

In view of research highlighting the pro-social effects of oxytocin in humans, the mechanisms mediating these effects have been increasingly questioned. In particular, oxytocin has been investigated within the areas of social cognition and stress reactivity. It has been purported that oxytocin is promoting social affiliation by modulating how individuals process social information and respond to stress.

1.3 Oxytocin and Social Cognition

1.3.1 Oxytocin, Social Recognition, and Memory

In non-human animals, oxytocin has been shown to impact social cognition by altering social memory processes and social recognition. For example, oxytocin is crucial for social recognition in mice (Ferguson, Aldag, Insel, & Young, 2001). In fact, oxytocin knockout mice fail to recognize familiar conspecifics after repeated social encounters (Winslow & Insel, 2002). Oxytocin appears to regulate social recognition in other species such as ewes (Kendrick, Keverne, Chapman, & Baldwin, 1988), prairie voles (Insel & Hulihan, 1995), and rats (Popik, Vetulani, & van Ree, 1992).

Although oxytocin appears to play an important role in learning and memory in humans, studies have demonstrated inconsistent effects on human memory function. Earlier studies have reported amnesic effects of oxytocin on verbal memory processing, with oxytocin impairing initial storage and rate of storage (Bruins, Hijman, & Van Ree, 1992; Fehm-Wolfsdorf, Born, Voigt, & Fehm, 1984). More recently,oxytocin was

observed to hinder word recall performance during an explicit memory test irrespective of the meaning of the word, and it selectively impaired performance during an implicit conceptual test by impairing the generation of associated target words for words associated with themes of reproduction relative to neutral meanings (Heinrichs, Meinlschmidt, Wippich, Ehlert, & Hellhammer, 2004).

Opposite results have been reported with respect to emotional stimuli. Oxytocin was reported to improve the recognition of memory for faces, but not for non-social stimuli (Rimmele, Hediger, Heinrichs, & Klaver, 2009). The administration of oxytocin improved memory performance for facial identity (Savaskan, Ehrhardt, Schulz, Walter, & Schachinger, 2008), and enhanced the encoding of positive social memories (Guastella, Mitchell, & Mathews, 2008). It has been purported that the influence of oxytocin on human memory function might vary according to the memory test and the psychobiological relevance of the stimuli employed.

1.3.2 Oxytocin and Emotional Processing

Oxytocin in humans has consistently been shown to enhance emotional recognition (Schulze et al., 2011). However, while some studies have found that oxytocin enhances recognition of positive relative to negative emotional stimuli (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Marsh, Yu, Pine, & Blair, 2010; Unkelbach, Guastella, & Forgas, 2008), others have reported that oxytocin increases recognition of negative relative to positive emotional stimuli (Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010; Guastella, Carson, Dadds, Mitchell, & Cox, 2009). Discrepancies in

findings may be partly attributable to methodological differences between studies. Some studies have examined the effect of oxytocin at a more elaborative and conceptually driven (i.e. top down) stage of information processing (Di Simplicio et al., 2009; Unkelbach et al., 2008) whereas others have examined the effects of oxytocin at a perceptual (i.e. bottom-up) level (Guastella, Carson, et al., 2009; Schulze et al., 2011). Using an attentional shifting paradigm, oxytocin was recently found to decrease effortful processing of emotional faces (sad, angry) but to have no impact on automatic processing of emotional faces (Ellenbogen, Linnen, Grumet, Cardoso, & Joober, in press). As such, the effects of oxytocin on emotional recognition may vary according to the cognitive task being examined and to the stage of information processing it is acting at (S. Evans, Shergill, & Averbeck, 2010).

Moreover, studies within this research area have employed different types of emotional stimuli within their paradigms (i.e. words, schematic faces, photographs of human faces), which further complicates comparisons between results. For instance, considering that oxytocin increases gaze to the eye region of human faces (Guastella, Mitchell, & Dadds, 2008), it is feasible that oxytocin would impact the recognition of human faces differently from schematic faces. In short, the effects of oxytocin on emotion recognition appear to be paradoxical in that it directs attention to emotional cues that can either signal threat or that can foster pro-social behaviour. It is possible that oxytocin reduces the processing of threatening social cues after the initial threat has been detected.

Oxytocin appears to play a specific role in modulating fear. It has been reported to dampen a variety of fear responses in rodents (Windle, Shanks, Lightman, & Ingram,

1997) and to impact fear conditioning and extinction (McCarthy, McDonald, Brooks, & Goldman, 1996). Research on rats has revealed that oxytocin is gating fear responses through distinct neuronal outputs in the central amygdala (Viviani et al., 2011). Studies conducted on human males have demonstrated that oxytocin attenuates amygdala activation in response to emotional stimuli (Domes, Heinrichs, Glascher, et al., 2007; Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008). On the other hand, oxytocin has been reported to enhance amygdala activation to fearful stimuli in female participants (Domes et al., 2010).

The fact that oxytocin both enhances the processing of emotional stimuli and dampens brain activity in response to emotional stimuli presents an inherent contradiction. These differential effects appear to be mediated by different subregions of the amygdala (Gamer, Zurowski, & Buchel, 2010). The administration of intranasal oxytocin increases amygdala activation in areas, such as the basal nucleus and superior colliculi, that regulate the shift of attention towards the eyes. Oxytocin decreases amygdala activity in nuclei (i.e. lateral amygdaloid nucleus) important for the fear and stress response (Gamer et al., 2010). More research is needed to examine how these differential effects are manifested in both males and females.

1.4 Oxytocin and Stress Reactivity

It has long been established that positive social interactions play a pre-eminent role in the behavioural and neuroendocrine response to stress (Thorsteinsson & James, 1999). In particular, positive relationships appear to attenuate the neuroendocrine stress response

associated with interpersonal challenge. For instance, among juvenile rhesus macaques, having a companion buffers the cortisol response that is associated with new group formation (Gust, Gordon, Brodie, & McClure, 1996). In humans, positive couple interactions diminishes the cortisol and heart rate responses to a public speech task (Ditzen et al., 2007), and spousal support satisfaction attenuates the cortisol response elicited during couple conflict (Heffner, Kiecolt-Glaser, Loving, Glaser, & Malarkey, 2004). Although there is substantive evidence to uphold the positive effects of social support on stress reactivity, it is not fully understood how positive social interactions suppress stress-responsive physiologic systems. Because oxytocin is responsive to social support (Grewen, Girdler, Amico, & Light, 2005; Light, Grewen, & Amico, 2005) and promotes social affiliation (Carter, 1998), it has been proposed as a regulatory mechanism of stress reactivity (Ozbay, Fitterling, Charney, & Southwick, 2008).

Support for this theory can be derived from research on animal models. Emotional stress triggers both the central and peripheral release of oxytocin in rats, suggesting that endogenous oxytocin might play a role in modulating stress reactivity (Engelmann, Ebner, Landgraf, Holsboer, & Wotjak, 1999; Windle et al., 1997). Accordingly, the central administration oxytocin in male rats attenuates the basal secretion of adrenocorticotropic releasing hormone (ACTH) and stress-induced ACTH through its actions in the paraventricular nucleus of the hypothalamus and the medio-lateral septum (Neumann, Kromer, Toschi, & Ebner, 2000; Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000). Moreover, exogenous oxytocin appears to modulate the cardiovascular system (Petersson, 2002). The central administration of oxytocin in both male and female rats decreases blood pressure up to 10 days later (Petersson, Alster, Lundeberg, & Uvnas-

Moberg, 1996). In addition, post-natal rats treated with exogenous oxytocin display lower blood pressure in adulthood (Holst, Uvnas-Moberg, & Petersson, 2002), which seems to indicate that oxytocin has long-term effects on cardiovascular health.

Similar findings have been reported with respect to other species. In prairie voles, the central administration of oxytocin antagonists has been shown to increase basal cortisol (Kramer, Cushing, & Carter, 2003) whereas exogenous oxytocin has been shown to reduce heart rate and increase vagal regulation of the heart in response to prolonged social isolation (Grippo, Trahanas, Zimmerman, Porges, & Carter, 2009). Furthermore, exogenous oxytocin has been reported to attenuate reactivity of the HPA axis to prolonged social isolation in both steers and squirrel monkeys (Parker, Buckmaster, Schatzberg, & Lyons, 2005; Yayou et al., 2008).

Research examining the relationship between endogenous oxytocin and stress reactivity in humans has yielded inconsistent results. In a study conducted by Light, Grewen, and Amico (2005) plasma oxytocin levels in women undergoing estrogen replacement therapy were positively associated with lower sympathetic activity, blood pressure, and vascular resistance, during a series of behavioural stressors. However, in a comparable sample of women, Taylor, Gonzaga, and Gian (2006) reported no relationship between plasma oxytocin and blood pressure in response to the same behavioural stressors. Moreover, plasma oxytocin levels were positively associated with relationship distress and elevated basal cortisol levels (Taylor et al., 2006; Taylor, Saphire-Bernstein, & Seeman, 2010). In accordance with these findings, elevated plasma oxytocin levels have been associated with anxiety over relationships (Turner, Altemus, Enos, Cooper, & McGuinness, 1999).

The contradictory findings have led to the conjecture that endogenous oxytocin levels might relate to stress in a bidirectional manner: oxytocin exerts stress-buffering effects, but is also released in response to psychosocial stressors (Tops, van Peer, Korf, Wijers, & Tucker, 2007). However the central mechanisms involved in such a bi-directional relationship remain unknown.

Several studies have examined the effect of intranasal oxytocin on measures of biological stress reactivity and have reported discordant findings. Oxytocin has been observed to increase positive communication and decrease cortisol levels during a couple conflict (Ditzen et al., 2009). Although these findings support the stress-buffering effects of oxytocin, it is important to underscore that the conflict was not considered to be subjectively stressful to the participants and that the task failed to elicit a significant cortisol response. Heinrichs, Baumgartner, Kirschbaum and Ehlert (2003) examined the effect of intranasal oxytocin and social support on the cortisol response to the Trier Social Stress Test (TSST); an achievement-related stressor consisting of a public speech task and mental arithmetic. Participants were randomly assigned to receive intranasal oxytocin or a placebo before the TSST, and either social support from their best friend during the speech preparation period or no social support. Oxytocin had no main effect on cortisol reactivity but interacted with social support to attenuate the cortisol response to the TSST.

Quirin, Kuhl, and Dusing (2011) examined the influence of oxytocin on cortisol reactivity to a similar public speech task in individuals low and high in emotional regulation abilities. Oxytocin attenuated cortisol reactivity to the public speech task but only in participants low in emotional regulation abilities. Oxytocin alone failed to

modulate the cortisol response to the stressor. The effects of oxytocin were also assessed on other measures of stress reactivity during a public speech task, which included skin conductance, heart rate and blood pressure (de Oliveira, Zuardi, Graeff, Queiroz, & Crippa, 2011). Although oxytocin diminished skin conductance and subjective ratings of anxiety, it had no effect on heart rate and blood pressure during the task.

Overall, it is possible that the effects of oxytocin on stress-responsive physiological systems vary depending on environmental cues and personality variables (Bartz, Zaki, Bolger, & Ochsner, 2011). For example, it is possible that individuals who have difficulty regulating their emotions during stressful situations benefit most from the stress-buffering effects of oxytocin (Quirin et al., 2011). It is also possible that oxytocin attenuates stress reactivity in certain environmental contexts but not others. The effect of oxytocin on stress reactivity has generally been assessed in the context of a public speech task, considered to be an achievement-oriented stressor. This type of psychosocial stressor is useful because salivary levels reliably show a 2 to 4-fold elevation in cortisol above baseline within 30 minutes of the stressor (Dickerson & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993). However, the public speech task frequently involves highly structured interactions with a panel of "judges" who only communicate according to specific directives (i.e. to keep the speech going, to start over after errors in mental arithmetic). Another version of the task has been employed, which simply involves giving a public speech in front of a video camera (de Oliveira et al., 2011; Quirin et al., 2011). Because oxytocin is responsive to social interactions, it is feasible that it would exert greater stress-reducing effects in response to an interpersonal challenge. This hypothesis was investigated within our first study.

1.5 Research Goals

As aforementioned, it has been stipulated that oxytocin is facilitating pro-social behaviour by modulating social cognition and stress reactivity. More specifically, it is believed that oxytocin is promoting social affiliation in part by altering how social information is processed and in part by dampening stress reactivity associated with social-approach behaviour. We conducted two separate studies to further test the theory. The aim of the first study was to assess the effects of oxytocin on the affective and cortisol response to the "Yale Interpersonal Stressor, a validated social rejection paradigm (Stroud, Salovey, & Epel, 2002; Stroud, Tanofsky-Kraff, Wilfley, & Salovey, 2000)." Considering that oxytocin has been found to facilitate desire for social engagement in response to social rejection (Alvares, Hickie, & Guastella, 2010), it was expected that oxytocin would attenuate cortisol reactivity within the context of a similar interpersonal challenge.

The aim of the second study was to examine the effect of oxytocin on emotional information processing, or more specifically, on the emotion modulated startle response. The emotion modulated startle response (described in greater detail on page 45) was examined because it both reliably and effectively assesses the automatic processing of emotional information. Most studies have investigated oxytocin's role in the effortful processing of emotional information and have yielded conflicting results. For example, oxytocin has been reported to enhance recognition of fearful faces (Fischer-Shofty et al., 2010) as well as to attenuate amygdala activation in response to fearful and fear-conditioned stimuli (Kirsch et al., 2005; Petrovic et al., 2008). It is possible that different

findings would emerge with respect to the early automatic processing of emotional information. In the emotion modulated startle response paradigm, the magnitude of the eyeblink startle reflex, in response to acoustic probes, is potentiated during the viewing of negatively valenced emotional stimuli and attenuated during the viewing of positively valenced emotional stimuli. We examined if oxytocin would selectively attenuate the eyeblink startle response during the viewing of negative, relative to positive and neutral emotional stimuli.

In contrast to previous studies that have mostly relied on male samples, both studies were conducted in males and females. Each study was developed to offer its own unique contribution to the research literature.

2. STUDY 1: INTRANASAL OXYTOCIN DECREASES CORTISOL LEVELS DURING SOCIAL REJECTION IN UNIVERSITY STUDENTS

2.1 Introduction

It is well established that chronic interpersonal stress contributes to the development of mental disorders (Daley, Hammen, Davila, & Burge, 1998) as well as physical illness (Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1994). Interpersonal stress, for example, is central to current conceptualizations of major depression (Hammen, 2003a). Moreover, the health disadvantages associated with interpersonal stress are often greater than of those related to non-interpersonal stress (Orth-Gomer & Leineweber, 2005). The relationship between interpersonal stress and disease may be partly mediated through the activation of the hypothalamic-pituitary-adrenal axis (HPA), as there is evidence that poor interpersonal functioning is associated with elevated cortisol levels (Decker, 2000; Steptoe, 1991). Chronically elevated levels of basal cortisol have negative health consequences, such as suppressed immunological functioning (Sapolsky, 2004). Thus, understanding the neurobiological regulation of interpersonal stress has important implications for mental and physical health. The aim of the current study was to investigate the role that oxytocin might play in modulating the cortisol response to interpersonal stress.

Oxytocin is a mammalian hormone that also acts as a neuromodulator in the central nervous system. Although well-known for its peripheral functions, which include stimulating uterine contractions during labour as well as milk-let down during lactation, oxytocin is directly involved in promoting social affiliation. In non-human mammals,

oxytocin has been shown to play an important role in pair-bond formation (Insel & Hulihan, 1995; Williams, Catania, et al., 1992; Young et al., 2001) maternal behaviour (Pedersen, 1997; Pedersen et al., 1994), and social recognition (Winslow & Insel, 2004). Studies in humans have demonstrated that intranasal oxytocin increases interpersonal trust (Baumgartner et al., 2008; Kosfeld et al., 2005; Theodoridou et al., 2009) and increases positive communication during couple conflict (Ditzen et al., 2009). Moreover, oxytocin has been reported to enhance the encoding of positive social memories (Guastella, Mitchell, & Mathews, 2008; Unkelbach et al., 2008), facilitate the recognition of positive facial expressions (Marsh et al., 2010), and to improve the ability to infer the mental states of others (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). These lines of research underscore the importance of oxytocinergic activity in promoting pro-social behaviour.

Considering that positive social interactions attenuate physiological responses to interpersonal stress (Ditzen et al., 2007; Heffner et al., 2004), oxytocin has been proposed as the regulatory mechanism of this effect. In support of this theory, oxytocin has been observed to impact on fear conditioning and extinction in rodents (McCarthy et al., 1996) and to attenuate HPA reactivity to prolonged social isolation in squirrel monkeys (Parker et al., 2005). Oxytocin has also been recognized to exert anxiolytic effects in humans, by dampening activation of the amygdala in response to both threatening and positive facial stimuli, (Domes, Heinrichs, Glascher, et al., 2007; Kirsch et al., 2005) as well as to aversely conditioned emotional responses to social stimuli (Petrovic et al., 2008). Few studies have examined the effects of oxytocin on the physiological stress response to interpersonal challenge. Heinrichs and colleagues (2003) examined the effect of

intranasal oxytocin on the cortisol response to the Trier Social Stress Test (TSST), an achievement-related stressor consisting of a public speech task and mental arithmetic (Heinrichs et al., 2003). Male participants were randomly assigned to receive intranasal oxytocin or a placebo before the TSST, and either social support from their best friend during the speech preparation period or no social support. Results of the study revealed that social support and oxytocin interacted to suppress the cortisol response to the TSST. Interestingly, the direct effect of oxytocin (i.e. in the absence of social support) on cortisol reactivity was marginal, which may be related to the fact that the study was conducted solely in male participants using a social-evaluative paradigm characterized by highly structured interactions. Recently, intranasal oxytocin was found to increase positive communication and reduce cortisol levels during a couple conflict task (Ditzen et al., 2009). Although these findings provide evidence that oxytocin may attenuate the biological response to interpersonal stress the conflict was not considered to be subjectively stressful to the participants and there were no changes in cortisol in response to the task.

The aim of the present study was to assess the effect of oxytocin on the cortisol and affective response to a validated interpersonal stressor in both male and female participants. Because most oxytocin administration studies have been conducted on male samples, it is imperative that similar research be conducted in women, especially in light of recent evidence suggesting that the effects of oxytocin on fear-related information processing may differ in women relative to men (Domes et al., 2010). We used the Yale Interpersonal Stressor (YIPS), a live social rejection paradigm known to stimulate negative mood change and activate the HPA axis (Stroud et al., 2000). The YIPS

involves two interactions with two same-sexed confederates posed as undergraduate students, in which the participant is made to feel excluded and isolated. In contrast to the TSST, the cortisol response to the YIPS has been reported to be greater in female than male participants, suggesting that women are more biologically reactive to interpersonal stress than men (Stroud et al., 2002). To the author's knowledge, the reported sex difference in the cortisol response to interpersonal stress has never been replicated. Therefore, a second goal of the present study aimed to replicate this important finding.

In line with the studies conducted by Stroud et al. (2000; 2002) we predicted that the YIPS would induce significant negative mood change and increased cortisol levels relative to baseline, and that these changes would be greater among female than male participants. However, we hypothesized that the participants randomly assigned to receive oxytocin would report significantly less negative mood change and have significantly lower mean cortisol levels following the YIPS than participants in the placebo group. Given the paucity of oxytocin administration studies in women, we had no specific hypotheses regarding sex differences in oxytocin's effects on stress reactivity.

2.2 Methodology

Participants

One hundred undergraduate students, between the ages of 18 and 35, were recruited to participate in the study. To recruit students, advertisements were placed in the classified ads of McGill and Concordia Universities (Montreal, Canada) and flyers were posted on both campuses. Students were also recruited through classroom visits at both universities.

Students were excluded from participation if they smoked, consumed legal or illegal drugs, were not fluent English speakers, were currently ill, were suffering from either a chronic medical condition or major sensory impairment, or if they were ever diagnosed with a mental disorder. Females were excluded from participation if they were pregnant or believed they could be pregnant.

Of the 100 students who participated in the study, one provided incomplete mood ratings during the study, and three had missing cortisol data. As such, the final sample consisted of 96 participants. Forty-seven participants (24 Females/23 Males) were administered oxytocin and 49 were administered the placebo (24 Females/25 Males).

Yale Interpersonal Stressor

In accordance with the paradigm, students were informed that they were participating in a study assessing communication skills and were asked to engage in two separate conversations with two same-sexed confederates posed as fellow undergraduate students. The confederates then proceeded to gradually exclude the participant from each conversation through a series of verbal techniques and non-verbal cues. In the present study, confederates excluded participants in two 10 minute conversations. Both conversations were video-recorded and observed through a one way mirror.

In the first conversation, participants and confederates were asked to introduce themselves and then to discuss "the advantages and disadvantages of living in Montreal". In the first two minutes, confederates were polite in their conversation with the participant. However, as the conversation progressed, confederates began to engage with

one another more than with the participant. At minutes three to five, confederates would ask each other more questions and would verbally agree with each other more than with the participant. They would also make greater eye contact with each other and smile and nod at one another more than at the participant. At minutes six to eight, confederates behaved in a dismissive manner towards the participant. They would interrupt the participant, disagree with him/her, and/or respond indifferently before resuming their own conversation. Confederates continued to interact positively with one another, using both verbal and non-verbal positive cues. For example, if the participant reported that she "really liked the parks in Montreal", the confederate would reply "that's nice" in an uninterested tone, and then continue conversing with the other confederate. In the last two minutes of the conversation, confederates ignored the participant completely. For the second conversation, participants and confederates discussed their hobbies.

Confederates were undergraduate volunteers in the laboratory and were previously unknown to participants. Twelve confederates (3 males and 9 females) were used in the study. All confederates took part in 6 hours of training (3 sessions) on the YIPS procedures. Each experimental session was observed by one of the investigators (via a one-way mirror), and confederates received feedback on their performance immediately after each session. One –hour review sessions were also performed throughout the study to maintain adherence to the YIPS protocol.

Materials

Medical History Questionnaire. An in-house self-report questionnaire on participants' medical history was developed to assess past and current drug use, present medical

problems, current medications, significant past illnesses, and drug reactions/allergies. In females, the questionnaire was also used to assess phase of menstrual cycle, oral contraceptive use, and possible pregnancy.

Profile of Mood States (POMS). The bipolar form of the POMS is a 72 item, self-report questionnaire that was designed to measure six bipolar mood states. Each mood state corresponds to a scale composed of 12 adjectives. Participants rate how they currently feel on a 4 point Likert scale ranging from "much unlike this" to "very much like this." The POMS-bi scales are: composed-anxious, agreeable-hostile, elated-depressed; confident-unsure; energetic-tired; clearheaded-confused. For each scale, a low score reflects high ratings of negative affect and low ratings of positive affect. A high score reflects the opposite. The POMS takes approximately 10-15 minutes to complete. The authors report good test-retest reliability and construct validity (Lorr & McNair, 1988; Lorr & Wunderlich, 1988) and it is sensitive to mild changes in mood state (Ellenbogen, Young, Dean, Palmour, & Benkelfat, 1996).

Bogus Social Perceptions Questionnaire (BSPQ). The BSPQ is a 12 item in-house inventory to assess participants' perceptions of the two confederates they interacted with. It was based on the inventory used by Stroud et al. (2000). Nine items were measured on a five point Likert scale (i.e. this person seems friendly, this person is interesting to talk to, this person seems extraverted). Three items required a yes or no response (i.e. I would prefer to keep this person as an acquaintance, as opposed to a friend, I would like to know this person better, this is the type of person I might include within my social circle).

Participants completed the BSPQ after each conversation and for each of the two confederates. The use of the BSPQ helped maintain the deception of participants, who believed they were assessing the communication skills of fellow participants. Moreover, it was used as a manipulation check to ascertain that the participants felt excluded by the confederates.

Cortisol Sampling

Saliva was expressed directly into polypropylene 6 ml vials. Samples were frozen at minus 20 ˚C until assayed for cortisol using a sensitive commercial enzyme immunoassay kit from *Salimetrics* (State College, Pensylvania; Schwartz et al., 1998). The sensitivity of the assay was set at 0.012 µg/dl. The inter- and intra-assay coefficient of variation for the assays were 2.8 % and 4.6 % (on a range of 0.01-10 µg/dl dose), respectively. Samples were centrifuged at 3000 RPM for 10 minutes to separate debris from saliva. Assays were conducted in the laboratory of Dr. C.-D. Walker at the Douglas Hospital Research Centre (Montreal, Canada).

Procedure

Undergraduate students interested in participating in a study on "communication skills" were initially screened by telephone or by e-mail. Individuals meeting inclusion criteria were scheduled to arrive at the laboratory at either 1200h or 1445h to control for diurnal variations in cortisol. Participants were asked to refrain from eating, drinking (except

water), or exercising one hour prior to arrival at the laboratory. Upon arrival, one confederate was already in the laboratory and the other was cued (by cellular phone) to arrive several minutes after the participant. The participant and confederates were informed that they would be placed in separate rooms to complete questionnaires and undergo a relaxation phase. Each participant provided written informed consent and completed a Medical History Questionnaire. Eligible participants provided a first saliva sample and completed the bipolar form of the POMS questionnaire. In a double-blind randomized controlled design, each participant was administered either a single intranasal dose of 24 I.U. oxytocin (3 puffs per nostril; Syntocinon Spray, Novartis, Switzerland) or placebo (saline), via a nasal spray. Each participant then underwent a 45 minute relaxation phase, which involved sitting on a reclining chair and reading magazines or books not part of coursework and/or listening to music. A second POMS questionnaire was completed following the relaxation phase. Afterwards, the participant was brought to a common room and underwent the YIPS (see above). The experimenter informed the participant and confederates that they would be engaging in the first of two 10-minute conversations aimed at assessing communication skills in small groups. They were informed that their conversations would be recorded and observed live through a one-way mirror. At the end of the first conversation, the participant and confederates were returned to separate rooms and the participant provided a second saliva sample and completed a third POMS questionnaire as well as the BSPQ for each of the two confederates. Next, participants took part in the second conversation, provided a third saliva sample, and completed the POMS and BSPQ. Afterwards, participants provided saliva samples every 10 minutes during a 30-minute recovery period, for a total of six samples. Participants

were fully debriefed and remunerated $50 for the time spent at the laboratory. All procedures were approved by Concordia University's Human Research Ethic Committee.

2.3 Data Analyses

On the bipolar form of the POMS questionnaire, data from the six scales were summed to create a score for total mood change for each participant. A lower total mood score reflected higher ratings of negative affect and lower ratings of positive affect. Cronhbach alphas for the total mood scale were the following at each time point throughout the YIPS: α =0.83 (arrival at laboratory), α =0.85 (after relaxation phase), α =0.86 (Post-1st YIPS conversation), α = 087 (Post 2nd YIPS conversation).To assess changes in mood over time, a 2 (sex) X 2 (drug condition) X 4 (time) repeated measures analysis of variance (ANOVA) was conducted on total mood scores. Chi square analyses were performed on the following three items of the BSPQ: "I would prefer to keep this person as an acquaintance, as opposed to a friend", "I would like to know this person better", "This is the type of person I might include within my social circle", and were used to determine if the frequency of participants, who reported negative perceptions of the confederates, differed significantly from what was expected by chance. In order to determine if perceptions of confederates varied by sex and/or drug condition, both variables were entered in the chi square analysis.

For the cortisol data, a paired sample t-test revealed that cortisol concentrations were significantly higher upon laboratory arrival than after the first YIPS conversation, $t(95) = 4.56$, $p < 0.05$. Because the first sample tends to be subject to outside influences

(i.e. driving, public transport, novelty of the situation), it was excluded from the data analyses. Cortisol changes over time were analyzed with a 2 (sex) X 2 (drug condition) X 5 (time) repeated measures analysis of covariance (ANCOVA), controlling for time of testing (1200h or 1445h). All within-subject effects were Greenhouse-Geisser corrected for violations of sphericity.

2.4 Results

Validity of the interpersonal stressor

The BSPQ was administered to assess the effectiveness of the interpersonal manipulation. Following the first (second) conversation, 73% (76%) of participants reported that they had no interest in getting to know at least one of the confederates better, $X^2(1, N = 96) = 20.17$, $p < 0.05$ (first conversation); $X^2(1, N = 96) = 26.04$, $p < 0.05$ (second conversation), for both confederates pooled. Eighty-six percent (90%) reported that they would rather keep at least one of the confederates as an acquaintance as opposed to a friend, $X^2(1, N = 96) = 51.04$, $p < 0.05$ (first conversation); $X^2(1, N = 96) = 60.17$, $p < 0.05$ (second conversation), and 82% (83%) indicated that they would not include at least one of the confederates in their social circle, $X^2(1, N = 96) = 40.04$ (first conversation), $p < 0.05$; $X^2(1, N = 96) = 42.67$, $p < 0.05$ (second conversation). As expected, participants did not relate well to the confederates and were reluctant in getting to know them better. These data support the effectiveness of the YIPS in eliciting mild social rejection. Following the first conversation, males (98%), relative to females (76%), were significantly more likely to report that they had no interest in getting to know at least one

of the confederates better $X^2(1, N = 96) = 10.25$, $p < 0.05$. No other sex differences were observed and there were no significant differences by drug condition. In short, the drug manipulation did not alter how participants perceived the confederates following both YIPS conversation.

The Affective Response to the YIPS

The Sex X Drug X Time repeated measures ANOVA revealed that mood ratings varied significantly across time, $F(3, 276) = 21.23$, $p < 0.05$, $\eta^2 = 0.19$ and that sex was a significant predictor of total mood ratings across time, $F(3, 276) = 6.66$, $p < 0.05$, $\eta^2 = 0.07$ (see Figure I). No significant main effect of drug condition, or Sex X Drug interaction, was found. Irrespective of sex, participants who were administered oxytocin reported comparable mood ratings following the YIPS as participants who were administered the placebo.

To follow up the main effect of time, Bonferonni-corrected paired-sample t-tests, using an adjusted p-value less than 0.013, were performed between the two baseline measures and the two post-YIPS measures. Relative to baseline, mood ratings decreased significantly following the first, $t(95) = 4.42$, $p < 0.013$, d = 0.47, and second YIPS conversation, $t(95) = 5.31$, $p < 0.013$, d = 0.60. The decrease in mood ratings following each conversation was also observed with respect to mood ratings reported after the 50 minute relaxation period, $t(95) = 4.92$, $p < 0.013$, d = 0.54 (first conversation); $t(95) = 5.41$, $p < 0.013$, d = 0.58 (second conversation). No other significant differences were obtained.

Secondary analyses were conducted to identify the individual mood scales that were most sensitive to the YIPS. A Sex X Drug X Time Mood repeated Measures ANOVA was performed on individual mood scales of the POMS. Mood ratings varied significantly across time on all scales including, in the order of effect size, the agreeable-hostile scale, F (2.07, 190.11) = 44.96, $p < 0.05$, $\eta^2 = 0.33$, elated-depressed scale, F (2.40, 219.90) = 34.01, $p < 0.05$, $\eta^2 = 0.27$, composed-anxiety scale, F (2.33, 217.00) = 26.47, $p < 0.05$, $\eta^2 = 0.22$, energetic-tired scale, F (2.35, 216.13) = 6.55, $p < 0.05$, $\eta^2 = 0.07$, confident-unsure scale, F (2.40, 221.00) = 6.17, $p < 0.05$, $\eta^2 = 0.06$, and clearheaded-confused scale F (2.40, 220.93) = 3.86, $p < 0.05$, $\eta^2 = 0.04$. For all scales, mood ratings become more negative following the first and second conversations relative to baseline (data not shown). Thus, mood change during the YIPS occurred across all POMS scales.

The main effect of sex was followed-up with a one way ANOVA on total mood ratings at each individual time point. Females reported significantly lower mood ratings than males after the first YIPS conversation, F (1, 94) = 5.93, $p < 0.05$, d = 0.50, and marginally lower mood ratings than males after the second YIPS conversation, F (1, 94) = 3.57, $p > 0.05$, d = 0.39, although the latter fell short of statistical significance. There were no significant sex differences in the mood ratings at either of the first two time points.

Sex differences in mood ratings across time were found on the following individual scales, in the order of effect size: energetic-tired scale F (2.35, 216.13) = 5.51, $p < 0.05$, $\eta^2 = 0.06$, composed-anxiety scale F (2.33, 217.00) = 4.64, $p < 0.05$, $\eta^2 = 0.05$, confident-unsure scale F (2.40, 221.00) = 4.53, $p < 0.05$, $\eta^2 = 0.05$, and elated-depressed

scale F (2.40, 219.90) = 3.63, $p < 0.05$, $\eta^2 = 0.04$ (data not shown). Drug condition did not significantly predict mood ratings across time on any of the POMS scales. Thus, sex differences in the mood response during the YIPS occurred primarily for anxious, depressed, tired, and unsure mood states.

In sum, the YIPS elicited robust negative mood change following both conversations and across all POMS scales, and mood change was more pronounced among females than males. Contrary to expectation, oxytocin did not modulate the mood response to the YIPS, in either males or females.

The Cortisol Response to the YIPS

Time of day (1200h versus 1445h start time) effects on drug administration and cortisol levels were examined, but none were found (data not shown). The Sex X Drug X Time repeated measures ANCOVA, controlling for time of testing, revealed that cortisol concentrations did not vary significantly across time, F (4, 364) = 0.63, $p > 0.64$, $\eta^2 = 0.01$ and there were no significant main effect of sex, F (1, 91) = 2.97, $p > 0.05$, $\eta^2 = 0.03$ or sex X time interaction, F (4, 364) = 0.72, $p > 0.05$, $\eta^2 = 0.01$ (Table I). In short, the YIPS failed to elicit a significant cortisol response, regardless of sex.

The repeated measures ANCOVA revealed a significant Drug X Time interaction, F (4, 364) = 2.70, $p < 0.05$, $\eta^2 = 0.03$. Because participants receiving oxytocin unexpectedly displayed higher cortisol concentrations at baseline (following first YIPS conversation; M = 0.1724, SD = 0.129) than participants receiving the placebo (M = 0.148, SD = 0.10), $t(95) = 1.20$, $p > 0.05$), baseline cortisol concentrations were added as

an additional covariate in these analyses. The Drug X Time interaction remained statistically significant after controlling for baseline cortisol, F (3, 273 = 3.15, $p < 0.05$, $\eta^2 = 0.03$, (see Figure II). A follow up repeated measures ANOVA was performed to assess variations in cortisol over time in each separate drug condition. Participants in the oxytocin condition displayed a statistically significant decrease in cortisol concentrations over time, F (4, 184) = 4.50, $p < 0.05$, $\eta^2 = 0.09$ whereas participants in the placebo condition exhibited no change in cortisol over time, F (4, 192) = 0.29, $p > 0.05$, $\eta^2 = 0.00$ (see Figure II). In sum, cortisol concentrations did not increase in response to the YIPS, neither in male or female participants. Participants administered oxytocin, relative to placebo, displayed a significant decrease in cortisol concentrations throughout the YIPS. On the other hand, participants administered placebo, relative to oxytocin, displayed cortisol levels following the YIPS that were virtually unchanged from baseline.

Secondary Analyses Controlling for Phase of Menstrual Cycle and Oral Contraceptive Use

In female participants, self-reported phase of menstrual cycle (luteal, and follicular) and oral contraceptive use (yes/no) were entered as covariates in Drug X Time repeated measures ANCOVAS conducted separately for mood ratings and cortisol concentrations. Because three females failed to report information on their menstruation cycle or oral contraceptive use on the Medical History Questionnaire, these data were performed on 45 females. Twenty-two females were in the follicular phase, and 23 were in the luteal phase. Fifteen females reported using the oral contraceptive pill relative to 30 females

who reported that they did not. Neither phase of menstrual cycle nor oral contraceptive use was significantly associated with mood ratings or cortisol variations over time (data not shown).

2.5 Discussion

The present study examined the effect of intranasal oxytocin on the affective and cortisol response to the Yale Interpersonal Stressor (YIPS), a social rejection paradigm aimed at eliciting interpersonal stress. As expected, the YIPS elicited a robust lowering of mood in the full study sample, and the negative mood response was greater in women than in men. Moreover, we assessed the validity of the social rejection manipulation by having participants rate the likeableness of the study confederates. As expected, 80% or more of the study participants reported negative ratings of the confederates. Both of these findings attest to the effectiveness of the interpersonal stress manipulation. In contrast to its robust effects on social and emotional measures, the YIPS did not elicit an increase in cortisol concentrations

We had hypothesized that the participants receiving oxytocin would report significantly less negative mood change and have significantly lower mean cortisol levels following the YIPS than participants in the placebo group. Contrary to the hypothesis, oxytocin did not influence the mood response on the POMS or any of its subscales. With one exception (Heinrichs et al., 2003), most studies have failed to find an effect of oxytocin on self-report ratings of emotion (Buchheim et al., 2009; Di Simplicio et al., 2009; Kosfeld et al., 2005). Each of the above studies investigated a single dose of 24

I.U. of oxytocin, indicating that dosage effects cannot account for the inconsistencies between studies. Despite the negative findings in this study, it is possible that the effects of oxytocin on mood are limited to participants who are vulnerable to mood change (Buchheim et al., 2009). These types of interactions have rarely been assessed in studies of exogenous oxytocin, and therefore warrant further research.

In accordance with our hypothesis on HPA functioning, intranasal oxytocin induced decreasing cortisol concentrations during the YIPS as compared to the placebo. The findings are consistent with other laboratory stress inductions (Heinrichs et al., 2003) and suggest that oxytocin dampens the functioning of the HPA axis during different kinds of psychological challenge. The stress-attenuating effects of oxytocin may serve as a mechanism to facilitate pro-social behaviour (Heinrichs et al., 2009; Taylor, 2006). It will be important to determine if oxytocin attenuates HPA reactivity to non-psychological challenges (i.e. corticotrophin-releasing hormone and physical stress), and how oxytocin reaches the CNS. Although passage of oxytocin from nose to brain is likely thorough extraneuronal intercellular clefts in the olfactory epithelium, the exact process is not well delineated (Born et al., 2002).

A second goal of the current study was to replicate previous findings reported by Stroud et al. (2000; 2002), which demonstrated that the YIPS induced higher cortisol concentrations among female compared to male participants. This finding was particularly influential in the literature, as it suggested that women were biologically more sensitive to interpersonal stress than men, with implications for understanding the sex difference in prevalence rates of depression (Hyde, Mezulis, & Abramson, 2008; Young & Korszum, 1999). The present study failed to replicate the sex difference in the

cortisol response to interpersonal stress. To our knowledge, no published study has directly replicated the result. In a study conducted by Zwolinski (2008) only females in the luteal phase of their menstrual cycle, and with a history of high relational victimization, displayed a significant cortisol response to a modified version of the YIPS. The lack of observed sex differences in HPA axis reactivity to laboratory stress is consistent with several previous studies that used other types of stress inductions (Kelly, Tyrka, Anderson, Price, & Carpenter, 2008; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Stoney, Davis, & Matthews, 1987).

Although no sex difference in cortisol concentrations was found, female participants reported greater negative mood change in response to the YIPS than male participants. These findings are consistent with research demonstrating that females display more negative emotional reactions to interpersonal stress in the natural environment than males (Hankin, Mermelstein, & Roesch, 2007; Rudolph, 2002). Interestingly, Stroud et al. (2000; 2002) observed no sex differences in affect ratings over time. The discrepancy in findings may be due to the fact that Stroud et al. (2000; 2002) employed visual analog scales to measure affect whereas the present study relied on the POMS. The original POMS questionnaire has been identified as a more sensitive measure of mood change than visual analog scales (Little & Penman, 1989). Alternatively, the sample size in the present study (n =96) was larger than the samples in the studies by Stroud et al. (2000; 2002; n =25; n =50 respectively), allowing for more power to detect group differences. It is possible that this sex difference was related to perceptions of confederates. Male and female participants were exposed to different sets of same-sex confederates, which may have contributed to sex differences in the mood response to the

YIPS. Males reported a greater disinterest in the confederates than females. Perhaps, males engaged in external attributions of confederates (i.e. the confederates are jerks), whereas females engaged in internal attributions of confederates (i.e. the confederates don't like me). If so, females would be expected to be more sensitive to the rejection of confederates and to report a greater negative mood response to the YIPS.

A number of study limitations warrant discussion. First, the YIPS failed to elicit a significant cortisol response, and therefore the present study may relate to daytime *cortisol levels* but cannot readily be interpreted as demonstrating an effect of oxytocin on biological *stress reactivity* per se. Second, although participants were randomly assigned to receive oxytocin or placebo, a non-significant group difference in cortisol was observed at baseline. Therefore, it is possible that the observed decrease in cortisol over time, in participants who were administered oxytocin, reflected a regression towards the mean as opposed to an actual attenuation of the HPA axis. We addressed this possibility by statistically controlling for the first cortisol measure and found that the drug X time interaction remained statistically significant. Third, the HPA axis was the only physiological system that was investigated in the present study, and it is possible that the YIPS activated other stress-related physiological systems. Stroud (2000) had observed a significant increase in systolic and diastolic blood pressure in response to the YIPS. Although oxytocin has previously been shown to dampen the sympathetic nervous system in rats (Holst et al., 2002), it was recently found to have no effect on blood pressure or heart rate measures during a public speech task (de Oliveira et al., 2011).

Fourth, our failure to replicate the biological sex difference in cortisol reactivity to interpersonal stress reported by Stroud et al. (2000; 2002) may be attributed to

methodological differences between studies, such as the administration of oxytocin. Because oxytocin attenuated the cortisol levels, separate analyses were performed in the placebo group (n=49) and revealed no significant sex differences in cortisol reactivity to the YIPS. Several procedures were implemented to replicate the YIPS, as reported by Stroud et al. (2000; 2002). Confederates received extensive training on the YIPS. The vast majority of participants (93%) reported that the confederates had deceived them. Because each conversation was observed live through a one-way mirror, confederates were given regular feedback on their performance during and after sessions to prevent deviations from the YIPS protocol over time. Overall, the ratings on the BSPQ were comparable to those reported by Stroud et al. (2000; 20002) and supported the efficacy of the paradigm in eliciting mild social rejection.

Fifth, the phase of menstrual cycle varied among female participants, and participants using oral contraceptives were included in the study. Statistical analyses revealed that they had no significant influence on mood ratings or cortisol concentrations over time. However, menstrual cycle phase data were based on self-report and may have been inaccurate. It is possible that levels of circulating estrogen modulate the effects of oxytocin on behaviour and physiology (Gimpl & Fahrenholz, 2001). Finally, the placebo nasal spray used in the control condition contained a saline solution without the inactive compounds present in the oxytocin solution. Thus, it is possible that some of the findings observed in the present study could be due to the effects of a non-active compound administered with oxytocin.

In conclusion, women reported a greater increase in negative affect in response to an interpersonal stressor than men. Although women may be more emotionally

responsive to interpersonal rejection than men, they exhibited no evidence of heightened adrenocortical reactivity to interpersonal stress, as reported previously (Stroud et al, 2002). In addition, the results of the present study indicate that oxytocin attenuates HPA axis functioning during an interpersonal challenge. These results support the mediating role of oxytocin in the stress-protective effects of positive social interactions. In view of the fact that positive social relationships protect against stress-related disease (Uchino et al., 1999), results of the study reveal important implications for better understanding the neurobiology that regulates this phenomenon.

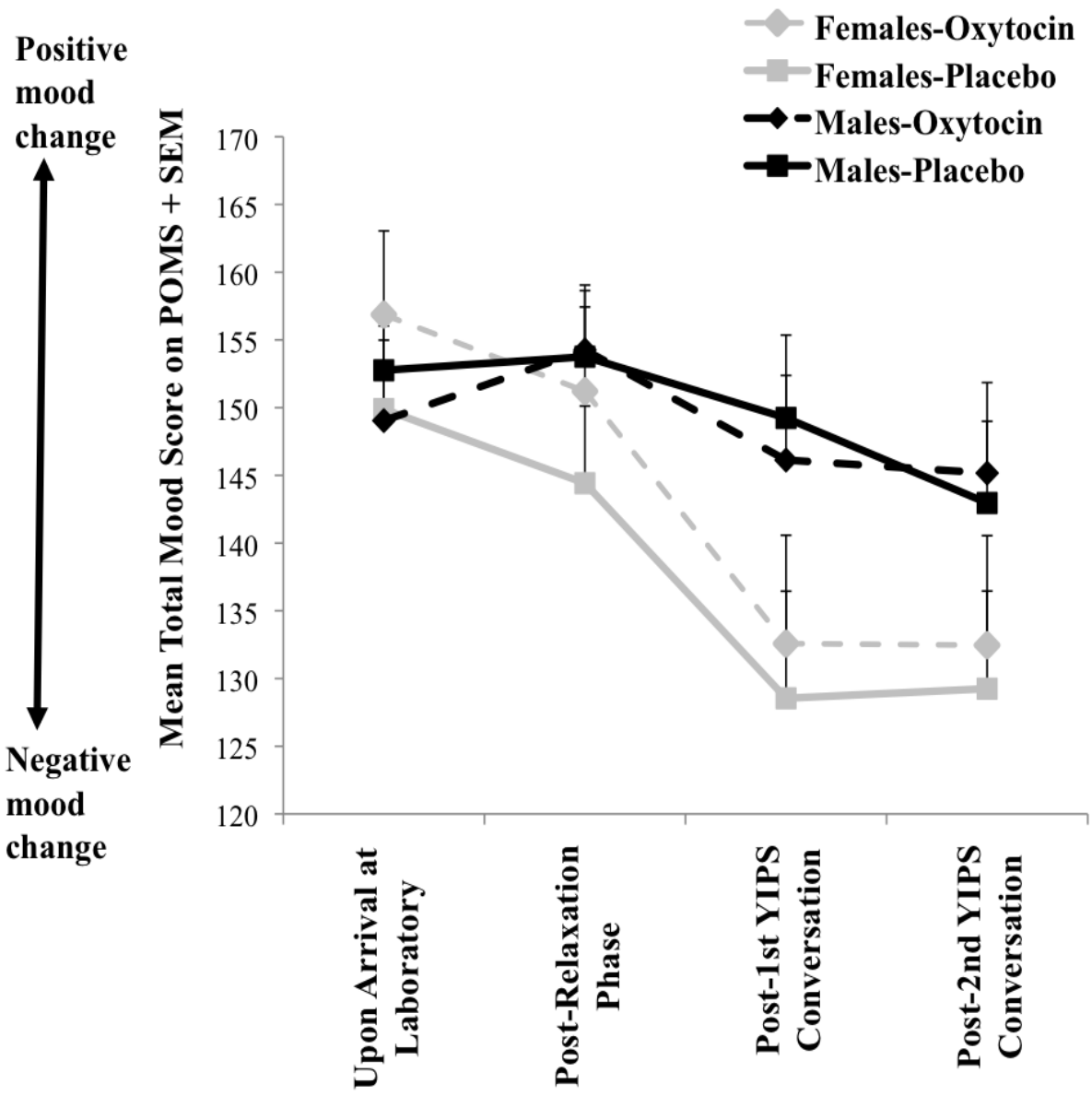
Table 1.

Mean cortisol levels (μg/dl), by gender and drug condition, across 5 time points throughout the Yale Interpersonal Stressor (YIPS).

	Oxytocin (n = 47)		Placebo (n = 49)	
	Males	Females	Males	Females
Cortisol Sampling Times	M *(SD)*	M *(SD)*	M *(SD)*	M *(SD)*
Post 1st YIPS Conversation	.19 (.16)	.14 (.08)	.16 (.14)	.11 (.05)
Post 2nd YIPS Conversation	.19 (.14)	.14 (.08)	.16 (.10)	.12 (.08)
10 min. post 2nd YIPS Conversation	.16 (.11)	.14 (.07)	.15 (.11)	.13 (.10)
	84.21%	*100%*	*93.75%*	*118.18%*
20 min. post 2nd YIPS Conversation	.15 (.09)	.13 (.07)	.16 (.15)	.12 (.09)
	79.95%	*92.85%*	*100%*	*109.09%*
30 min. post 2nd YIPS Conversation	.13 (.06)	.13 (.07)	.18 (.18)	.13 (.09)
	68.42%	*92.85%*	*112.5%*	*118.18%*

Note. Percentages in italics are the proportions of cortisol concentrations from baseline (following first YIPS conversation).

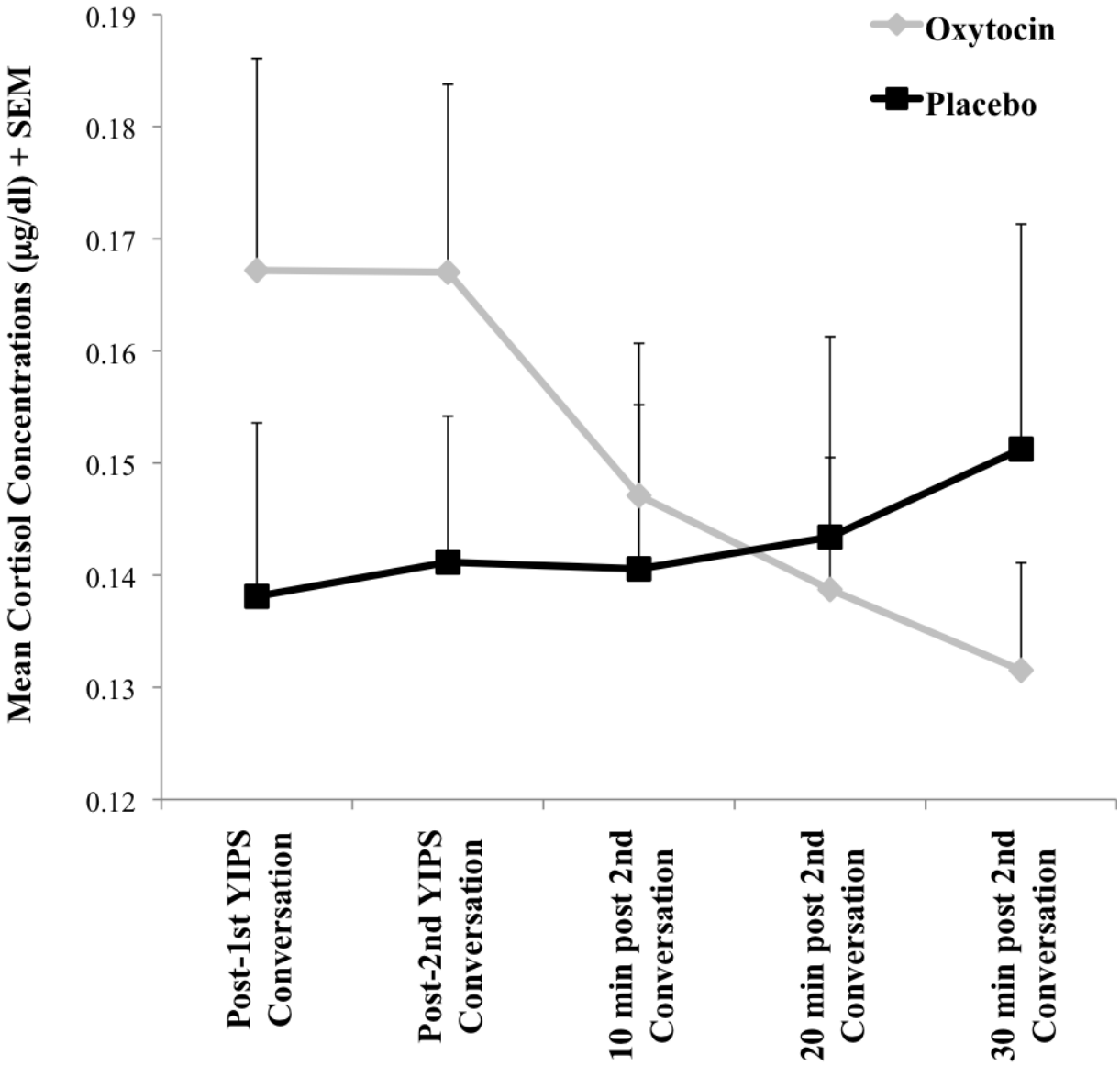
Figure 1. Variations in Mood across the Yale Interpersonal Stressor (YIPS), Depicted by Gender and Drug Condition



Mean total mood ratings + SEM, in participants administered either oxytocin (24 females/ 23 males) or placebo (24 females/ 25 males) at 4 separate intervals throughout YIPS. Total mood ratings were calculated by summing the scores on each composite scale of the bipolar form of the Profile of Mood States (POMS) questionnaire. Relative to

baseline, participants exhibited a statistically significant decrease in total mood ratings following the two YIPS conversations $F(3, 276) = 21.23$, $p < 0.05$, $\eta^2 = 0.19$, which was more pronounced in females than males $F(3, 276) = 6.66$, $p < 0.05$, $\eta^2 = 0.07$. Drug did not significantly predict mood ratings across time.

Figure 2. Variations in Cortisol Concentrations across the Yale Interpersonal Stressor (YIPS), Depicted by Drug Condition



Mean cortisol levels (µg/dl) + SEM, in participants receiving oxytocin (n = 47) or placebo (n = 49), and across 5 time points throughout the Yale Interpersonal Stressor (YIPS). Participants in the oxytocin condition displayed a significant decrease in cortisol over time, whereas participants in the placebo condition exhibited no change in cortisol

concentrations over time F (4, 364) = 2.70, $p < 0.05$, $\eta^2 = 0.03$, even after statistically controlling for the first baseline measure.

3. TRANSITION TO STUDY 2

The present dissertation was undertaken to investigate the mechanisms underlying oxytocin's pro-social effects on human behaviour. As described previously, oxytocin's effects on behaviour may occur, in part, through changes in stress reactivity and how social information are processed in the environment. Thus, the objective of study 2 was to assess its effects on emotional information processing. The specific question being addressed was whether oxytocin would modulate the automatic processing of negative emotional stimuli. As previously mentioned, the emotion modulated startle response was employed as our experimental paradigm because it measures basic underlying emotional processes on information processing.

3.1 Emotion Modulated Startle Response

The startle response is a brainstem reflex that is intended to protect the back of the neck (whole body startle) or the eye (eyeblink) in response to sudden stimuli (Grillon & Baas, 2003). The eyeblink startle response is typically measured using electromyography, which records electrical activity of the orbicularis occuli (muscle below the eye) in response to an acoustic probe (Blumenthal et al., 2005). Interestingly, the magnitude of the eyeblink startle response can be manipulated experimentally through exposure to affectively valenced pictorial stimuli. Startle amplitude is highest when viewing negatively valenced emotional stimuli and lowest when viewing positively valenced emotional stimuli (Lang, Bradley, & Cuthbert, 1990; Vrana, Spence, & Lang, 1988).

Affective modulation of the startle response is believed to reflect aversive and appetitive motivational systems in the brain. Lang and Bradley (2010) have argued that the startle response represents a defensive system, which is enhanced during the viewing of negative emotional stimuli because the aversive nature of the reflex is *congruent* with the affective state, and which is attenuated during the viewing of positive emotional stimuli because the aversive nature of the reflex is *incongruent* with the affective state.

The emotion modulated startle response has been replicated using various stimulus modalities such as pictures (Vrana et al., 1988), odors (Miltner, Matjak, Braun, Diekmann, & Brody, 1994), mental imagery (Cook, Hawk, Davis, & Stevenson, 1991), as well as classically-conditioned threat cues (Grillon, Chavis, Covington, & Pine, 2009). The emotion modulated startle response has further been found to yield moderate temporal stability (Larson, Ruffalo, Nietert, & Davidson, 2000). Although a validated and reliable measure of emotional processing, no known human study has examined the effects of oxytocin on the emotion modulated startle response, or even still, on the basic startle reflex. Oxytocin's influence on the startle response has received significantly more attention in non-human animals.

3.2 Oxytocin and the Startle Response in Non-Human Animals

Studies performed in non-human animals have examined the effects of oxytocin on the basic startle reflex and have yielded inconsistent findings. Oxytocin receptor knockout mice, for example, have been reported to display normal acoustic startle responses (Caldwell, Stephens, & Young, 2009). In rats, high doses of oxytocin have been shown to

have no impact on (Feifel & Reza, 1999) or to increase the startle response (King, Brown, & Kusnecov, 1985). In a more recent study, oxytocin, administered subcutaneously in rats, decreased the basic startle reflex during a fear conditioned startle response paradigm, but was shown to have no impact on contextually conditioned or cue conditioned fear (Missig, Ayers, Schulkin, & Rosen, 2010). A follow up study demonstrated that this effect was specific to the peripheral administration of exogenous oxytocin. When administered in the cerebroventricular system, oxytocin had no impact on the acoustic startle response (Ayers, Missig, Schulkin, & Rosen, 2011). The impact of oxytocin on the startle response therefore requires further elucidation in both human and non-human animals.

4. STUDY 2: INTRANASAL OXYTOCIN ATTENUATES THE HUMAN ACOUSTIC STARTLE RESPONSE INDEPENDENT OF EMOTIONAL MODULATION

4.1 Introduction

Oxytocin is a nonapeptide that is produced and stored in the hypothalamus and released peripherally in the bloodstream as well as into the central nervous system. Within the central nervous system, oxytocin acts in the olfactory system, limbic-hypothalamic system, amygdala, brainstem, and in spinal cord areas that regulate reproductive and autonomic functions (Carter, 1998). Although well known for its role in parturition and lactation, oxytocin has also been identified as an important modulator of social behaviour (Williams, Carter, & Insel, 1992; Young et al., 2001). For example, oxytocin has been implicated in the development of pair bond formation in female prairie voles (Insel & Hulihan, 1995; Williams, Catania, et al., 1992) and has further been shown to activate the postpartum onset of maternal behaviour in rats (Pedersen, 1997), and to mediate social recognition in mice (Winslow & Insel, 2002). Over the past decade, oxytocin has been shown to promote social affiliation in humans as well. Oxytocin has been observed to increase trust (Baumgartner et al., 2008; Kosfeld et al., 2005; Mikolajczak, Pinon, et al., 2010) positive communication during couple conflict (Ditzen et al., 2009) supportive parenting behaviours during father-infant interactions (Naber et al., 2010) and perceived attractiveness (Theodoridou et al., 2009) as well as to enhance the perception and memory encoding of positive social stimuli (Guastella, Mitchell, & Mathews, 2008).

Oxytocin appears to facilitate social approach behaviour in part by reducing anxiety and neuroendocrine stress responses. Exogenously administered oxytocin has

been reported to exert anxiolytic effects on behaviour in rodents (Insel & Winslow, 1991; McCarthy et al., 1996; Windle et al., 1997). Oxytocin has also been shown to decrease hypothalamic-pituitary-adrenal (HPA) activity in response to social stressors (Grippo et al., 2009; Parker et al., 2005); an effect which has been corroborated in humans (Ditzen et al., 2009; Heinrichs et al., 2003; Linnen, Ellenbogen, Cardoso, & Joober, in press).

Evidence from neuroimaging studies in humans indicates that oxytocin may be acting on the amygdala to impact fear processing. However, conflicting results have been reported. Although oxytocin has been shown to reduce amygadala activation in response to both fearful and fear-conditioned stimuli in male participants (Kirsch et al., 2005; Petrovic et al., 2008), it has also been found to attenuate amygdala responses to emotional faces, regardless of valence (Domes, Heinrichs, Glascher, et al., 2007). It is therefore unclear whether oxytocin is modulating fear processing per se or is simply dampening amygdala activation indiscriminately in response to social stimuli. Moreover, a study in female participants demonstrated that oxytocin actually enhanced amygdala activity in response to fearful facial expressions relative to neutral facial expressions (Domes et al., 2010). The discrepancies in the literature may be explained in part through oxytocin having opposite effects in different subregions of the amygdala (Gamer et al., 2010). Studies of information processing have largely produced equivocal results with respect to the early processing of fear-related stimuli (Di Simplicio et al., 2009; Ellenbogen et al., in press; Guastella, Carson, et al., 2009). As such, the relationship between oxytocin and emotional processing appears to require further elucidation in both males and females.

The aim of the present study was to examine the effect of intranasal oxytocin on emotional information processing in both males and females by measuring affective modulation of the acoustic startle response. The acoustic startle response refers to the orienting of attention to a novel stimulus, such as a loud and unexpected noise. This response, which is automatic and involuntary, has been demonstrated across species and contexts (Grillon & Baas, 2003). In recent years, researchers have used an "emotion-modulated startle response" paradigm as a means of objectively measuring emotional information processing (Lang et al., 1990). The paradigm consists of the presentation of an emotional stimulus (i.e. an angry face, or a threatening scene), which is followed by the presentation of a startling stimulus, such as a loud tone. Using this simple procedure, the electromyographic (EMG) response in muscle below the eye (obicularis oculi) has been consistently shown to change in magnitude across varying emotional foregrounds (Vrana et al., 1988) making it an especially attractive tool with which to measure basic underlying emotional processes on information processing. The modulation of the startle response reflects the activation of defensive or appetitive brain pathways, showing potentiation in relation to negative, arousing environmental stimuli and attenuation in relation to positive, arousing emotional stimuli (Bradley, Codispoti, & Lang, 2006). As such, the emotional modulation of this response can give us information about individual differences in processing of threatening information in the environment (Yiend et al., 2008).

The amygdala appears to have an important role in the neural circuitry underlying the emotion modulated startle response. Animal models indicate three sets of neurons comprising startle circuitry, with one of these, the nucleus reticularis pontalis caudalis,

receiving excitatory projections from nuclei in the amygdala (Lee & Davis, 1997). In rodents, electrical stimulation of the amygdala significantly enhances the acoustic startle reflex (Rosen & Davis, 1988). Lesion studies have also revealed that the amygdala is essential for fear potentiation of the startle response (Antoniadis, Winslow, Davis, & Amaral, 2009; Hitchcock & Davis, 1986). Similarly, work in humans indicates that the amygdala is involved in fear-potentiated and affectively modulated startle (Angrilli et al., 1996; Pissiota et al., 2003). Consequently, the emotion-modulated startle response appears to provide an indirect measure of amygdala modulation.

The present study examined the effect of intranasal oxytocin on the emotion modulated startle response using unpleasant, pleasant, and neutral stimuli selected from the International Affective Picture System (IAPS; Lang & Greenwald, 1988). Compared with pleasant and neutral stimuli, unpleasant emotional stimuli were expected to elicit the largest startle response. However, oyxtocin, relative to placebo, was expected to induce a significant decrease in startle response during the viewing of unpleasant emotional stimuli. No significant group differences were expected in the pleasant and neutral conditions. The present study further examined the interaction between drug and gender on startle amplitude. However, considering the dearth of previous research examining the effects of oxytocin in women, no a priori hypotheses were put forth.

4.2 Methodology

Participants

One hundred and two undergraduate students, between the ages of 18 and 30, were recruited to participate in the study. To recruit students, advertisements were placed in the classified ads of McGill University and Concordia University (Montreal, Canada) and flyers were posted on McGill and Concordia campuses. Students were excluded from participation if they smoked, were taking legal or illegal drugs, were not fluent English speakers, were currently ill, were suffering from either a chronic medical condition or major sensory impairment, or if they were ever diagnosed with a mental disorder. Females were excluded from participation if they were pregnant or believed they could be pregnant.

Of the 102 students who participated in the study, data from 4 participants were excluded because of equipment failure, and 14 participants were excluded because they did not exhibit a measurable startle response, exhibiting mean startle amplitude lower than 10 μV (Blumenthal et al., 2005). As such, the final sample consisted of 84 participants. Forty-one participants were administered oxytocin (19 males/ 22 females) and 43 were administered the placebo (19 males/ 24 females).

Materials and Design

Medical History Questionnaire. An in-house medical history questionnaire was used to assess past and current drug use, present medical problems, current medications, significant past illnesses, and drug reactions/allergies. Female participants provided information about their menstrual cycle (to determine their current phase), and reported if

they were taking oral contraceptives or if they were pregnant or believed that they could possibly be pregnant.

Pictorial Stimuli & Acoustic Probe

Thirty-six pictorial stimuli were selected from the IAPS[1] (Lang & Greenwald, 1988) and normative ratings from the system were used to define affective categories. Of the 36 pictures, 12 included negative content (i.e. mutilation, violence, tragedy, threat), 12 included neutral content (i.e. people, common scenes, household objects) and 12 included positive content (nature scenes, couples, families, wealth). Visual stimuli, 1024 x 768 pixels, were presented on a 19-in. color monitor, using the STIM visual presentation software (*James Long Company*, Caroga Lake, NY). Participants were positioned on a chin rest to ensure a 57 cm viewing distance. The 36 pictures were presented twice in a randomized order.

The emotion-modulated startle probe protocol was administered using an integrated stimulus presentation and physiology recording system from the *James Long Company* (Caroga Lake, NY). Acoustic startle stimuli were presented binaurally through Telephonics high-impedance headphones. The acoustic startle probes were 50 ms pulses of 110 dB sound pressure level white noise (limited to below 4 kHz) with 0 ms rise and fall times.

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[1] IAPS pictures used in this study were: **Negative:** 2205, 2683, 3005.1, 3530, 6312, 6313, 6230, 9140, 9265, 9433, 9571; **Neutral:** 2038, 2102, 2435, 2485, 2580, 2593, 2594, 2595, 2597, 7190, 7207, 7546; **Positive:** 2091, 2154, 4599, 4626, 4641, 5260, 5270, 5480, 5551, 5594, 5831, 8502

The acoustic probe was presented at 0.5 seconds, 2.5 seconds, and 4.5 seconds after picture onset. To reduce predictability and conditioning effects, one in four pictures was presented without a startle probe.

Startle EMG Data Collection and Data Reduction

We followed published guidelines for human startle blink studies, including subject presentation, electrode placement, amplification and filtering, response quantification, and artifact analysis and removal (Blumenthal et al., 2005). Prior to the placement of electrodes, the skin was prepared with an abrasive solution (NuPrep) to keep impedances under 10,000 Ω. Electromyographic (EMG) activity from the orbicularis oculi muscles were measured from the right eye, using two Electro-Cap International Inc. (Eaton, OH) E21-6S 6 mm tin cup electrodes, one under the pupil and the other 2 cm lateral to the first, as close to the margin of the lower lid as possible (as described by Blumenthal el al., 2005). A ground electrode was placed behind the right ear, on the mastoid. Electrodes were filled with high-conductivity electrode gel and affixed with adhesive collars.

The raw EMG signal was amplified and filtered using a custom-built electrically-isolated bioamplifiers (SA Instrumentation, San Diego, California). The raw EMG signal was bandpass filtered (highpass filter set at 10 Hz, low-pass filter set at 250 Hz), amplified (gain 4K), and were digitized on-line at a sampling rate of 1024 Hz and stored on hard disk for later analysis. The digitized EMG was digitally filtered off-line to highlight signals between 80 and 240 Hz. The data were analyzed in 75 percent overlapping 8 ms windows, yielding a time resolution of 2 ms. Natural blink artifacts

were detected using EMGART software from the James Long Company. Baseline EMG activity was sampled 50 ms before stimulus onset to 20 ms after stimulus onset and aggregated across all trials. This aggregated baseline was used to detect confounding natural blinks exceeding baseline. Trials with baseline periods in which the threshold was exceeded (greater than 2 SD above aggregate baseline mean EMG) were rejected from the analysis. After the deletion of trials with artefacts (less than 1.0% of the trials), the EMG peak amplitude between 20 ms and 200 ms post startle probe was analyzed. Latency from probe onset to peak EMG for each trial was also recorded, but is not presented here. We averaged amplitude measures across each of the nine levels of the valence (positive, neutral, negative) and probe presentations (0.5 s, 2.5 s, and 4.5 s) for each participant.

Procedure

Following a telephone or electronic mail screening, individuals meeting inclusion criteria were scheduled for testing. Upon arrival at the laboratory, participants provided informed consent and completed a medical history questionnaire to confirm the absence of medical or psychiatric disorders and other exclusion criteria. Eligible participants were then administered either a single intranasal dose of 24 I.U. oxytocin (3 puffs per nostril; Syntocinon Spray, Novartis, Basel, Switzerland) or placebo (saline), via a nasal spray. Drug condition was randomized across participants in a double-blind placebo-controlled design. Participants were instructed to clear their nostrils, and to spray three times in each

nostril, while sitting down. Each participant then underwent a 35-minute relaxation phase on a reclining chair.

Once terminated, electrodes were affixed and participants began the EMG emotion-modulated startle protocol (described above). The participant was instructed to focus his/her attention on each picture during the entire viewing period. They were informed that they would hear occasional noises but were told not to pay attention to them. Participants viewed the 72 pictures for 6 s each with a fixed inter-trial interval of either 12 or 18 s. After viewing all the pictures, the electrodes were removed and participants performed a modified spatial cueing task and a negative priming task, which are presented elsewhere (Ellenbogen et al., in press) . They were then remunerated $60 CAD for their participation.

Data Analyses

All data were analyzed using Predictive Analytics Software (PASW) version 18. Startle magnitude represented the primary dependent variable. Startle EMG data were collapsed across probe presentation latency and were z transformed within subjects in order to decrease between-subject variability and skew. This transformation conserved participants' response patterns while ensuring that each participant contributed equally to the group mean, thus minimizing the influence of outliers (Patrick, Bradley, & Lang, 1993). Standardized startle data were subject to a Drug X Sex X Picture Valence mixed design ANOVA. Picture valence (pleasant, neutral, unpleasant) was a within-subject factor. Drug condition (oxytocin, placebo) and sex were between-subject factors. Simple

contrasts were applied to follow up any significant within-subject effect of picture valence on startle amplitude.

Because standardized data were centered on each participant's mean (averaged across the 3 valence conditions), the influence of drug and sex on overall startle amplitude, irrespective of valence, could not be discerned from standardized data. As such, separate data analyses were conducted on the raw data to specifically examine main effects of drug and sex on startle amplitude, irrespective of stimuli valence. Data were subjected to a multivariate ANOVA (MANOVA). Mean startle responses, within each valence condition, were entered as dependent variables. Drug and sex were entered as independent variables.

4.3 Results

Did emotional foreground alter the amplitude of the startle response?

The Drug X Sex X Picture Valence mixed design ANOVA revealed a significant effect of picture valence on startle amplitude, $F(2, 160) = 3.03$, $p < .05$, $\eta^2 = 0.04$ (see Figure 1). According to the simple contrasts, participants exhibited significantly lower startle responses when viewing pleasant pictorial stimuli as opposed to both neutral $F(1, 80) = 6.68$, $p < .05$, $\eta^2 = 0.08$ and unpleasant pictorial stimuli $F(1, 80) = 4.89$, $p < .05$, $\eta^2 = 0.05$. There was no significant difference in startle amplitude during the viewing of unpleasant relative to neutral pictorial stimuli $F(1, 80) = 0.01$, $p > .05$, $\eta^2 = 0.00$. Thus, evidence of emotional modulation of the startle response was observed with positive

pictures, but no evidence of modulation was found, surprisingly, for the negative pictures when compared to the neutral ones.

Did drug or sex alter the emotion-modulated eye blink startle response*?*

The Drug X Sex X Picture Valence ANOVA revealed no significant effects of drug condition, sex, or any interactions on startle amplitude. Thus, there was no evidence of that oxytocin, relative to placebo, changed the emotion- modulated startle response.

Did drug or sex alter the amplitude of the eye blink startle response, irrespective of picture valence?

Using the raw data, a Drug X Sex MANOVA revealed a main effect of drug on the mean amplitude of the acoustic startle response $F(3, 78) = 4.26$, $p < .05$, $\eta^2 = 0.14$. The main effect of sex and the Drug X Sex interaction were not significant. Relative to placebo, participants who were administered oxytocin displayed significantly lower startle responses when viewing pleasant $F(1, 80) = 9.79$, $p < .05$, $\eta^2 = 0.11$, neutral $F(1, 80) = 11.79$, $p < .05$, $\eta^2 = 0.13$, and unpleasant emotional stimuli $F(1, 80) = 8.28$, $p < .05$, $\eta^2 = 0.09$ (see Figure 2). In other words, participants who were administered oxytocin displayed an attenuation of the acoustic startle response irrespective of the emotional foreground of stimuli.

Secondary Analyses Controlling for Phase of Menstrual Cycle and Oral Contraceptive Use

Because five female participants failed to report information on their menstruation cycle or oral contraceptive use on the medical history questionnaire, data analyses controlling for both variables were performed on a total of 41 female participants. Nineteen female participants were in the follicular phase of their menstrual cycle whereas 22 were in the luteal phase. Fifteen female participants reported using oral contraceptives.

Self-reported phase of menstrual cycle (follicular, luteal) and oral contraceptive use (yes/no) were entered as covariates in a Drug x Picture Valence mixed design ANCOVA performed on standardized startle data. Both variables were also entered as covariates in a MANCOVA conducted on raw startle data, assessing the effect of drug on the amplitude of the startle response irrespective of the emotional foreground of stimuli. Neither phase of the menstrual cycle nor oral contraceptive use was associated with variations in startle amplitude for both the standardized and raw data set.

However, when controlling for phase of menstrual cycle and oral contraceptive use, the main effect of drug on startle amplitude, irrespective of picture valence, fell short of statistical significance $F(3, 35) = 2.69$, $p = .06$, $\eta^2 = 0.18$. However, the magnitude of the effect was larger than in previous analyses conducted on the full sample. The absence of a significant effect was most likely related to the loss in degrees of freedom, which resulted in lower statistical power.

4.4 Discussion

The aim of the present study was to examine the effect of oxytocin on the emotion-modulated acoustic startle response; a methodology aimed at tapping into the activation defensive and appetitive motivational circuits that influence early sensory processing and mobilize the organism for action (Lang & Bradley, 2010). The present study had two main hypotheses. First, the eye blink startle response was hypothesized to be significantly smaller when evoked during the viewing of affectively pleasant slides and significantly larger when evoked during the viewing of negative slides (Bradley, Cuthbert, & Lang, 1990; Vrana et al., 1988). Congruent with this hypothesis, pleasant emotional stimuli evoked significantly smaller startle responses than both neutral and unpleasant emotional stimuli. Contrary to the hypothesis, there was no significant difference between startle responses evoked during the viewing of negative and neutral stimuli. It is unclear why startle responses were not greater during the viewing of negative stimuli, which is in contrast to numerous past finding (Bradley et al., 1990; Vrana et al., 1988). It may be that the negative pictures, despite having robust negative ratings of valence, were not arousing enough to elicit activation of negative motivational brain circuits (i.e. amygdala). We did not include pictures of mutilation, which have among the highest ratings of arousal in IAPS.

The second hypothesis stipulated that oxytocin, relative to placebo, would attenuate the acoustic startle response evoked during the viewing of unpleasant emotional stimuli but not during the viewing of neutral or pleasant emotional stimuli. This hypothesis was only partially supported. Relative to placebo, oxytocin significantly

decreased startle amplitude to an acoustic probe regardless of the affective content of the foreground slide presentation. That is, oxytocin dampened the actual startle reflex, but did not influence the affective foreground modulation of the response. In accordance with our finding, a recent study demonstrated that fear conditioned rats exhibited diminished startle under the influence of oxytocin in both the presence and absence of the fear-conditioned stimulus. Oxytocin had no impact on fear-potentiated startle but diminished background anxiety during the startle paradigm (Missig et al., 2010).

Our finding is consistent with a number of studies in humans showing a dampening effect of intranasal oxytocin on the activation of the amygdala in response to emotional stimuli (Domes, Heinrichs, Glascher, et al., 2007; Gamer et al., 2010; Kirsch et al., 2005; Petrovic et al., 2008). By dampening amygdala activation, oxytocin has been purported to reduce uncertainty about the predictive value of a social stimulus in order to facilitate social approach behaviour (Domes, Heinrichs, Glascher, et al., 2007). The amygdala has been shown to play an important role in the neural circuitry underlying the emotion modulated startle response (Angrilli et al., 1996; Pissiota et al., 2003) and to be directly involved in modulating the basic startle reflex in rodents (Rosen & Davis, 1988). It is therefore quite probable that oxytocin dampened startle amplitude by attenuating amygdala activation irrespective of the emotional stimuli presented. The fact that amygdala activation has not only been observed in response to negative emotional stimuli but to positive emotional stimuli as well further supports this interpretation (Yang et al., 2007). Moreover, this explanation is consistent with findings reported by Domes et al. (2007) demonstrating that oxytocin attenuated right-sided amygdala responses to

emotional faces irrespective of the stimuli valence. Attenuation of the amygdala was not restricted to negative emotions but was also observed when happy faces were presented.

Although the amygdala represents a possible mechanism through which oxytocin impacted the acoustic startle response, amygdala activation was not measured in the present study. Consequently, we do not know if oxytocin acted on receptors in the amygdala to attenuate the acoustic startle response. Oxytocin may have affected other components of the neural circuit underlying the acoustic startle. This neural circuit is well documented in animals and involves three synapses located on 1) the cochler root neurons; 2) neurons in the nucleus reticularis pontis; 3) spinal motoneurons (Koch, 1999). Although there appears to be some overlap in humans, the neural pathways underlying the startle response in humans are not well established (Pissiota et al., 2003). As such, it is difficult to specify where and how oxytocin would affect these pathways. On the other hand, we know that the amygdala is involved in the modulation of the acoustic startle response (Lee & Davis, 1997) and that it contains dense concentrations of oxytocin receptors, which regulate its activity (Huber, Veinante, & Stoop, 2005). Using functional magnetic resonance imaging, future research would be required to examine if oxytocin, relative to placebo, reduces amygdala activation to emotional stimuli during the acoustic startle response.

Alternate explanations of oxytocin's attenuation of the acoustic startle reflex include possible changes in auditory sensory processing or changes in other neuropeptide systems that modulate the reflex (i.e. corticotropin-releasing hormone, for example). With respect to the former, there is animal research suggesting that oxytocin could modulate auditory sensory processing (Kanwal & Rao, 2002) but this effect has not been

observed in human research using auditory evoked potentials (Fehm-Wolfsdorf, Bachholz, Born, Voigt, & Fehm, 1988; Pietrowsky, Braun, Fehm, Pauschinger, & Born, 1991). Because high levels of exogenous glucocorticoids also attenuate the acoustic startle reflex (Buchanan, Brechtel, Sollers, & Lovallo, 2001) possibly through a negative feedback-induced decrease in the production of corticotropin-releasing hormone, it is possible that oxytocin is acting through interactions with this neuropeptide (Keck, Welt, Muller, Landgraf, & Holsboer, 2003). Future work should address these relationships further, particularly the interactions between oxytocin and other neuropeptide systems.

Results of the present study lend further credence to the stress-reducing effects of oxytocin that have been previously reported in the hypothalalmic-pituitary-adrenal axis (Ditzen et al., 2009; Heinrichs et al., 2003; Linnen et al., in press; Quirin et al., 2011). In congruence with our findings, intranasal oxytocin selectively increased sympathetic and parasympathetic indices of autonomic cardiac control during laboratory testing (Norman et al., 2011). Similar beneficial effects of exogenous oxytocin administration on the sympathetic nervous system have been reported in rats (Holst et al., 2002). Oxytocin was shown to induce a long term decrease of blood pressure in rats (Petersson et al., 1996). Oxytocin appears to modify blood pressure and heart rate in rodents both through effects in the central nervous system and through its effects in other organs such as the heart, blood vessels, and kidneys (Petersson, 2002). Oxytocin receptor genetic variation has been observed to influence heart rate responses during a startle anticipation task (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Compared with individuals homozygous for the G allele of rs53576 (GG) gene, individuals with one or two copies of the A allele (AG/AA) exhibited greater cardiovascular activity during the startle

anticipation task. Taken together, these results suggest that the oxytocinergic system is involved in the modulation of basic physiological arousal and support the notion that oxytocinergic activity facilitates and maintains social contacts by modulating the biological stress response that is associated with social-approach behaviour (Taylor, 2006).

With a few exceptions (Ditzen et al., 2009; Norman et al., 2011), most studies examining the effects of intranasal oxytocin on human behaviour have relied on male samples exclusively The present study is unique for having administered intranasal oxytocin to both male and female participants. However, gender did not moderate the effect of oxytocin on the acoustic startle response. Discordant with our findings, the administration of intranasal oxytocin in women induced enhanced, rather than decreased, amygdala reactivity to fearful faces (Domes et al., 2010). In view of this finding, women would be expected to display a higher startle response when viewing unpleasant emotional stimuli, which was not observed in the present study. As such, the relationship between sex, oxytocin, and changes in physiological activation is more complex than expected. Discrepancies between studies may be due to the fact that oxytocin stimulates receptors in different subregions of the amygdala which has different effects on neural activity and behavior (Gamer et al., 2010). Oxytocin decreases activation of the lateral and dorsal regions of the anterior amygdala, but increases activation in posterior amygdala. The former is believed to be related to decreases in fear arousal, while the latter is associated with reflexive shifts of attention to the eye region of the face. Thus, our results are interpreted as providing further evidence that oxytocin plays a role in

decreasing physiological arousal in both men and women (Ditzen et al., 2009), which is likely related to specific regions of the amygdala and their associated neural circuits.

The present study has several limitations, which warrant discussion. First, because oxytocin dampened the startle response independent of emotion modulation, oxytocin appeared to have decreased startle responses to affective stimuli in general. However, within our paradigm, there were no instances in which the acoustic probe was not preceded by a picture. It is therefore not known whether oxytocin would have attenuated the acoustic startle reflex in the absence of foreground pictures. There is evidence to suggest that oxytocin exerts differential effects on amygdala reactivity depending on the stimuli presented. For example, a greater reduction of amygdala activation has been reported when socially relevant stimuli are presented (Petrovic et al., 2008). However, the attenuation of the startle reflex following oxytocin administration was equally strong during neutral foreground trials as it was during the emotional foreground trials. Moreover, Buchanan and colleagues (2001) have reported equivalent attenuation of the acoustic startle reflex after the administration of 20 mg of hydrocortisone during the presentation of startle probes with (experiment 2) and without (experiment 1) an emotional foreground. Still, future work in this area should include trials where an acoustic probe is presented in the absence of foreground emotional stimuli.

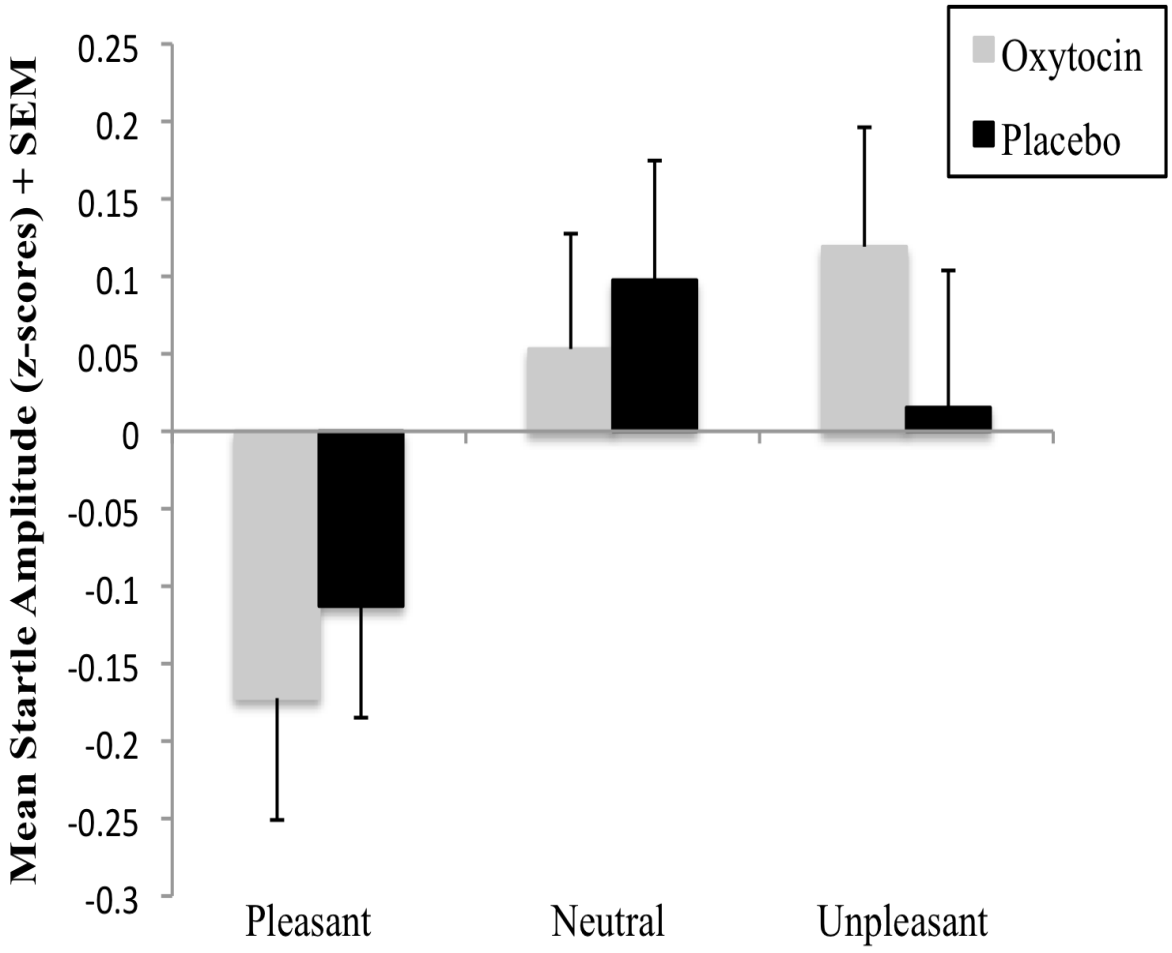
Second, phase of menstrual cycle varied among female participants, and participants using oral contraceptives were included in the study. Considering that gonadal hormones influence the oxytocinergic system (Gimpl et al., 2002; Ochedalski, Subburaju, Wynn, & Aguilera, 2007), it is possible that they moderated the effect of oxytocin on the startle response in women. However, we conducted data analyses

controlling for the effects of self-reported phase of menstrual cycle and oral contraceptive use and observed that they had no impact on our findings. Subsequent studies could assess levels of gonadal hormones to better examine the nature of the interaction. It is conceivable that gonadal hormones may have the dual function of interacting with exogenous oxytocin to either increase threat perception (Domes et al., 2010) or decrease physiological arousal (Ditzen et al., 2009).

Third, our placebo was comprised of saline. It would have been preferable to employ a placebo containing all inactive ingredients of synthetic oxytocin (syntocinon) in order to further isolate the effects of the oxytocin molecule.

In sum, the present study demonstrated that intranasal oxytocin attenuated the acoustic startle response, independent of emotion modulation. The acoustic startle reflex is construed as a defensive response, associated with neuropsychological components of avoidance and escape behaviour. By dampening the acoustic startle response, oxytocin appears to be reducing physiological arousal associated with threat perception, which might serve as an impetus to initiate social approach behaviour.

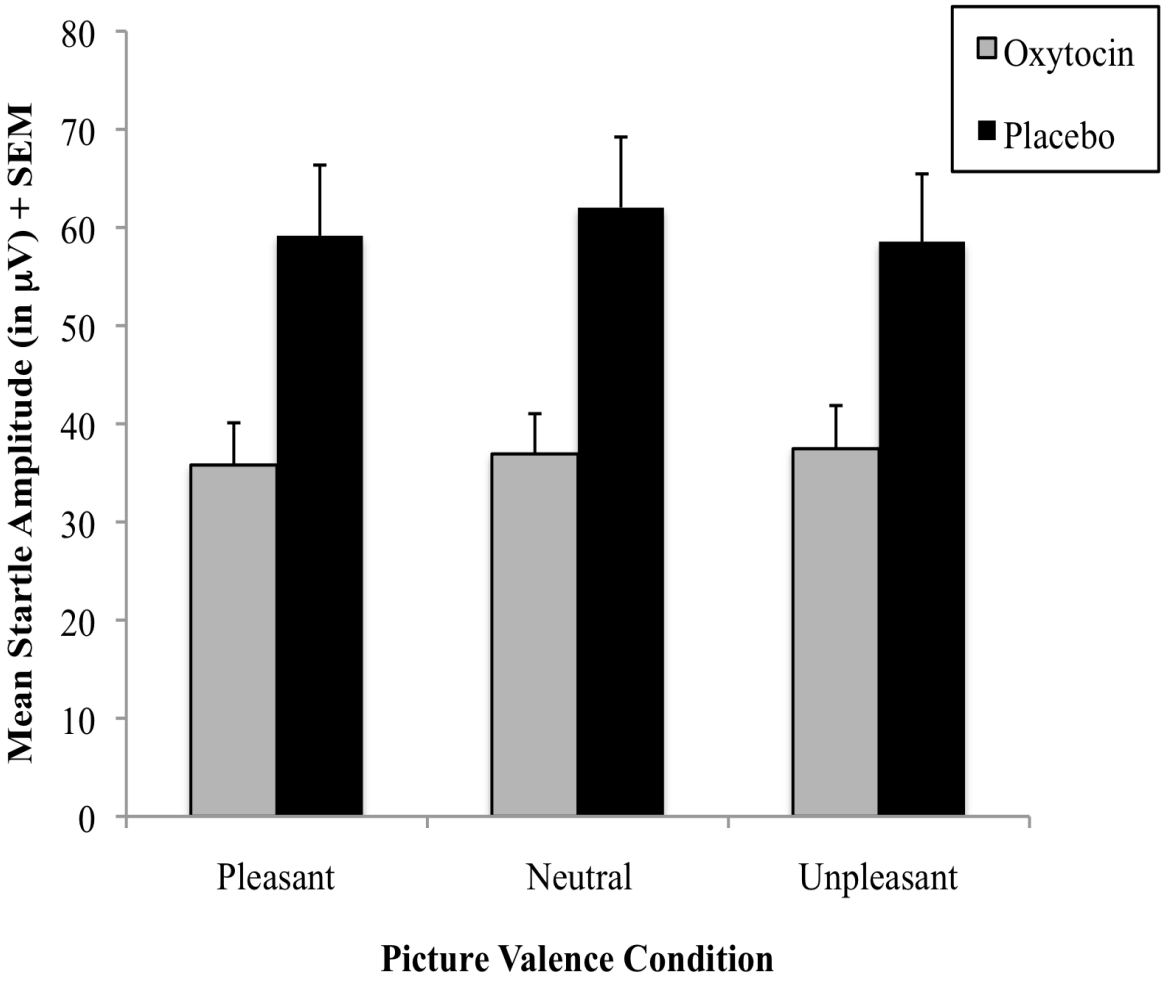
Figure 1. Mean Startle Amplitude (Z-Transformed Data) during Exposure to Affectively Valenced Stimuli



Mean startle amplitude + SEM (z-transformed data) evoked during the viewing of pleasant, neutral, and unpleasant emotional stimuli in healthy male (n = 36) and female participants (n = 46). Within the overall sample, startle amplitude was significantly lower during the viewing of pleasant relative to both neutral $F(1, 80) = 6.68$, $p < .05$, $\eta^2 = 0.08$ and negative pictorial stimuli $F(1, 80) = 4.89$, $p < .05$, $\eta^2 = 0.05$. There was no

significant difference in startle amplitude during the viewing of negative relative to neutral pictorial stimuli. Drug condition had no significant effect on the modulation of the startle reflex by the emotional foreground.

Figure 2. Mean Startle Amplitude During Exposure to Affectively Valenced Stimuli, Depicted by Drug Condition



Mean startle responses (in μV) + SEM evoked during the viewing of pleasant, neutral, and unpleasant pictorial stimuli in healthy male and female participants. Relative to placebo, intranasal oxytocin induced a significantly lower startle response during the viewing of all pictorial stimuli $F(3, 78) = 4.26$, $p < .05$, $\eta^2 = 0.14$ in both males and females.

5. GENERAL DISCUSSION

Oxytocin is a hormone that promotes social affiliation across various species, including humans (Campbell, 2010). The aim of the present dissertation was to investigate the mechanisms underlying oxytocin's pro-social effects in humans. More specifically, we investigated the role that oxytocin plays in regulating stress reactivity and rudimentary emotional information processing in healthy male and female participants. In study 1, we examined the effects of oxytocin on the cortisol and mood response to the YIPS, a social rejection paradigm. In study 2, we examined oxytocin's influence on the emotion modulated acoustic startle response. Several key findings emerged from these studies. Results of study 1 revealed that oxytocin decreased cortisol levels during the YIPS, even though the YIPS failed to elicit a significant cortisol response. The YIPS did elicit a negative mood response, that was more pronounced in females than males, and that was unaltered by intranasal oxytocin. Results of study 2 revealed that oxytocin attenuated participants' acoustic startle responses independent of emotion modulation. That is, oxytocin did not have an influence on the defensive orienting reflex activated when viewing aversive stimuli. Rather, oxytocin attenuated the basic orienting reflex to an acoustic probe, regardless of pictures presented in the foreground.

These findings are congruent with research demonstrating that oxytocin dampens stress-responsive physiological systems (Holst et al., 2002; Parker et al., 2005; Petersson et al., 1996; Yayou et al., 2008), attenuates amygdala activation (Domes, Heinrichs, Glascher, et al., 2007; Kirsch et al., 2005; Petrovic et al., 2008), and exerts anxiolytic effects on behavior in animal studies (Grippo et al., 2009; McCarthy et al., 1996; Windle

et al., 1997). In other words, results of both studies further support the role of the oxytocinergic system in the modulation of neural pathways associated with fear, stress, and anxiety.

From an evolutionary perspective, oxytocin may serve an adaptive function by inhibiting threat perception and basic physiological arousal associated with social approach behaviour. Evolutionary theory suggests that the oxytocinergic system was originally developed to help motivate maternal care crucial for the survival of altricial species (Pedersen, 2004). In these species, infants are helpless at birth; they depend on their mothers' milk and bodily warmth. To ensure survival, a new motivational system in the brain was needed to incite sustained maternal care (Seltzer, Ziegler, & Pollak, 2010). In order to foster pro-social behaviour, evolution had to offset asocial inclinations associated with an older defence system relying on sympathetic fight or flight circuits (Macdonald & Macdonald, 2010). This defence system was developed to increase fear, risk aversion, and distrust. The oxytocinergic system was evolutionarily conserved, in part, because it helped to induce a state of calm and security within the context of social relationships. A dynamic interplay evolved between both systems, thereby ensuring greater safety and providing homeostasis to the organism.

Conceptualized somewhat differently, Taylor (2006) contended that humans evolved a stress response not only dependant on fight or flight mechanisms, but also on the tendency to affiliate- that is to come together in groups to provide and receive joint protection from potential threat. Taylor (2006) referred to this process as "tend and befriend." From Taylor's standpoint, endogenous oxytocin is released in response to stressors and serves as an impetus to develop positive social relationships. These

relationships are associated with increases in oxytocinergic activity and attenuated stress/fear responses. Although perhaps too simplistic a theory, it is plausible that oxytocin's stress buffering/anxiolytic effects represent one mechanism through which the hormone modulates social behaviour. The evolutionary upshot of this system appears to have been the development of social relationships that are integral for survival.

The function of oxytocin in human behaviour, however, may be more complex than originally thought. The oxytocinergic system is not immutable with fixed functions. Rather, the system is adaptable and is influenced by individual characteristics and environmental factors (Bartz, Zaki, et al., 2011). In fact, oxytocin's actions largely depend on the individual and/or context. For example, although several studies have demonstrated that oxytocin increases trust in humans (Baumgartner et al., 2008; Kosfeld et al., 2005; Mikolajczak, Pinon, et al., 2010), this effect is negated when the person potentially being trusted is perceived as untrustworthy (Mikolajczak, Gross, et al., 2010) or is part of a competing social "outgroup"(De Dreu et al., 2010). Moreover, oxytocin has actually been shown to decrease trust in participants diagnosed with borderline personality disorder (Bartz, Simeon, et al., 2011) a disorder characterized by interpersonal difficulties often related to trust. It is therefore probable that oxytocin's pro-social effects cannot be generalized to everyone or to every situation.

Bartz, Zaki, Bolger and Ochsner (2011) have argued that an interactionist approach could further our understanding of oxytocin's behavioural effects. They have contended that many of the discordant findings reported in the human literature could result from the fact that situational factors and/or individual variables are frequently ignored. For instance, we know that oxytocin both enhances emotion recognition (Di

Simplicio et al., 2009; Guastella, Carson, et al., 2009) and dampens amygdala activation in response to emotional stimuli (Domes, Heinrichs, Glascher, et al., 2007; Kirsch et al., 2005; Petrovic et al., 2008). These contradicting effects appear to be mediated by different subregions in the amygdala (Gamer et al., 2010). However, little is known about the conditions that facilitate oxytocin's effects in one subregion relative to another. It is feasible that oxytocin's actions are responsive to environmental cues, as suggested by Taylor (2006). Oxytocin might feasibly attenuate amygdala activation in a non-threatening situation but enhance recognition of negative emotions in a more dangerous context (Fischer-Shofty et al., 2010).

Individual moderators could also influence the effects of oxytocin on fear and anxiety. For example, although we demonstrated that oxytocin attenuated the acoustic startle response independent of emotion modulation, individual factors (i.e. personality traits, affect, genes) may have moderated the magnitude of this effect across participants. Accordingly, genetic variance in the oxytocin receptor has been associated with heart rate responses to a startle anticipation task (Rodrigues et al., 2009) and with amygdala volume (Furman et al., 2011). It is therefore conceivable that polymorphisms in the oxytocin receptor gene could alter the impact of the hormone on physiological arousal, (i.e. startle reflex), and on fear responses.

Research examining oxytocin's effects on stress reactivity also supports an interactionist approach. Heinrichs, Baumgartner, Kirschbaum and Ehlert (2003) observed that oxytocin decreased the cortisol response to the TSST, but only in individuals receiving social support from a friend. Moreover, Quirin, Kuhl, and Dusing (2011) reported that oxytocin decreased the cortisol response to a public speech task but only in

individuals with low emotional regulation abilities. It is possible that individuals with a greater vulnerability to stress benefit more from the stress-reducing effects of oxytocin. In support of this theory, oxytocin was reported to reduce subjective ratings of anxiety during the YIPS but only in females with maladaptive coping abilities (Cardoso, Linnen, Ellenbogen, & Joober, in press). Oxytocin was also found to exert a more robust dampening effect on the cortisol response to the TSST in participants diagnosed with borderline personality disorder relative to control participants (Simeon et al., 2011).

Given the attenuating effects of oxytocin on amygdala activation and on stress-responsive physiological systems, oxytocin has been examined as a potential therapeutic agent for the treatment of anxiety disorders. Research that has been undertaken to examine a biological basis for oxytocin in relation to anxiety disorders has yielded equivocal results. Studies have shown that patients diagnosed with obsessive-compulsive disorder (OCD) show no improvement in compulsive, depressive, or anxiety symptoms when administered intranasal oxytocin over several weeks (den Boer & Westenberg, 1992; Epperson, McDougle, & Price, 1996). In patients diagnosed with social anxiety disorder, intranasal oxytocin administered weekly, as an adjunct to exposure therapy, had no impact on either the short or long term clinical outcomes (Guastella, Howard, Dadds, Mitchell, & Carson, 2009). However, intranasal oxytocin was shown to attenuate amygdala activation to fearful stimuli in patients diagnosed with generalized anxiety disorder (Labuschagne et al., 2010). In view of these findings, it would appear that oxytocin does not play a global role in the treatment of anxiety disorders (Striepens, Kendrick, Maier, & Hurlemann, 2011) but that it could be employed to mitigate fear responses.

Our research suggests that oxytocin might play a more relevant role in the treatment posttraumatic stress disorder (PTSD). PTSD is a mental disorder with a lifetime prevalence of approximately 8% (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). PTSD is developed following a traumatic event and is characterized by a pervasive difficulty regulating stress/anxiety, particularly in situations reminiscent of the trauma. Studies have shown that individuals diagnosed with PTSD exhibit exaggerated physiological reactivity when exposed to cues associated with the trauma. In particular, they display enhanced sympathetic arousal (Bedi & Arora, 2007), amygdala hyperactivity (Francati, Vermetten, & Bremner, 2007; Koenigs & Grafman, 2009), and heightened startle responses (Jovanovic et al., 2010). Moreover, the HPA axis is deregulated in PTSD. Patients exhibit low basal cortisol levels and a heightened cortisol response to psychosocial stress (Bremner, Vermetten, & Kelley, 2007; Gola et al., in press). Because of their difficulty regulating stress/anxiety, individuals suffering from PTSD actively avoid both external and internal cues associated with the trauma.

Olff, Langeland, Witteveen, and Denys (2010) put forth a psychobiological rationale for oxytocin as an adjunct to cognitive behavioural therapy in the treatment of PTSD. Cognitive behavioural interventions are presently geared towards extinguishing fear responses to the trauma through exposure to fear conditioned stimuli. Because oxytocin has been shown to attenuate sympathetic arousal, amygdala activation, and HPA reactivity, the authors theorized that it could facilitate treatment by reducing fear and stress responses during both cognitive and behavioural exposure. The fact that oxytocin decreased the acoustic startle response in our study provides further evidence that it could dampen physiological arousal during an exposure-based treatment.

Providing empirical support for this theory is a study conducted in male Vietnam veterans diagnosed with PTSD (Pitman, Orr, & Lasko, 1993). Participants receiving intranasal oxytocin, relative to vasopressin and placebo, displayed reduced physiological responses (blood pressure, heart rate, skin conductance) during the viewing of personal combat imagery. Oxytocin, however, had no influence on emotional reactions to the combat imagery. This finding is not surprising when considering that intranasal oxytocin has rarely been found to influence mood in healthy participants (Ditzen et al., 2009; Kirsch et al., 2005). Rather than alter maladaptive emotional responses associated with PTSD, oxytocin may simply be more effective at targeting specific symptoms of the disorder, those that are perhaps more physiologically related.

Ultimately, more research is needed to assess oxytocin's therapeutic effects in the treatment of PTSD. Considering that PTSD is 2-3 times more likely to afflict women than men (Olff, Langeland, Draijer, & Gersons, 2007), clinical trials would need to be conducted in both genders. In our own research, sex did not moderate the effects of oxytocin on cortisol levels or the acoustic startle response. As such it is possible that females diagnosed with PTSD would benefit from the hormone's anxiolytic properties. However, we can only speculate as to how females would respond to the hormone in view of the fact that human studies on oxytocin have mostly been conducted in male participants only.

Females have largely been excluded from human studies on oxytocin because female sex hormones (i.e. estrogen and progesterone) are known to influence the oxytocinergic system. (Gimpl et al., 2002). Sexually dimorphic effects of oxytocin have been reported in the animal literature. In prairie voles for example, the hormonal

mechanisms regulating pair bond formation are sexually dimorphic. Partner preference formation is facilitated by oxytocin in females and by vasopressin in males (Insel & Hulihan, 1995). Sexually dimorphic effects of oxytocin are largely steroid dependent and/or mediated by reproductive and somatosensory interactions (Witt, 1997).

Sex differences represent a research area that warrants further research in humans as well. It is possible that sexually dimorphic effects would emerge with respect to certain behavioural outcomes but not with others. For example, oxytocin exerts sexually dimorphic effects on reproductive behaviours in rats (Bale et al., 2001) but has similar anxiolytic effects in both sexes (Neumann, Wigger, et al., 2000; Petersson et al., 1996).

Considering that gonadal hormones play an important role in modulating oxytocin receptor expression, density, and affinity (Gimpl & Fahrenholz, 2001), the relationship between gonadal hormones and oxytocin requires further investigation in human females. Plasma oxytocin levels have been observed to vary throughout the menstrual cycle with oxytocin levels peaking during ovulation and remaining elevated until menstruation (Mitchell, Haynes, Anderson, & Turnbull, 1981). In our own studies, we statistically controlled for phase of menstrual cycle and our results remained unchanged. However, it would be interesting to examine if the effects of oxytocin on female behaviour are potentiated during ovulation or are more pronounced in the luteal relative to the follicular phase. For greater accuracy, circulating levels of gonadal hormones would need to be measured rather than relying on females' self-reported phase of menstrual cycle. Better understanding these interactions would serve to explain sex differences as opposed to continuously avoiding them with studies consisting solely of male samples.

By and large, the brain mechanisms underlying oxytocin's behavioural/physiological effects require further investigation in humans. For one, more neuroimaging studies are needed to assess how oxytocin receptors are mapped in the human brain. Oxytocinergic brain pathways have been better identified in rodents (Onaka, 2004). The expression of oxytocin receptors in specific regions of the CNS regulate different behaviours in rodents. In female rats, for example, estrogen-dependent expression of oxytocin receptors in the ventromedial nucleus of the hypothalamus regulates sex behaviours whereas dopamine controlled expression of oxytocin receptors in the central nucleus of the amygdala regulates anxiety-related behaviours (Bale et al., 2001). However, the physiological mechanisms regulating these behaviours may differ in humans. Differences between the human brain and that of other animal species need to be considered when translating findings from animal models to humans.

Furthermore, there is a need to evaluate how the oxytocinergic system interacts with other physiological systems (i.e. neurotransmitters, corticosteroids, endogenous opioids) to regulate human behaviour. These interactions have received greater attention in non-human animals. In female prairie voles, the dopaminergic system is believed to interact with oxytocin in the nucleus accumbens to facilitate pair-bond formation (Young et al., 2001) whereas the serotenergic system is purported to influence central oxytocin neurotransmission at ejaculation in male rats (de Jong, Veening, Olivier, & Waldinger, 2007). It is posited that oxytocin's effects on stress reactivity may also be mediated by complex physiological interactions. In rats, noradrenergic neurons appear to play an important role in modulating endogenous oxytocin responses to fear-related stressors (Onaka, 2004). Research in rats has further shown that exogenous oxytocin attenuates the

HPA axis in response to acute and chronic stressors by inhibiting mRNA expression of corticotropin releasing factor via gamma- aminobutyric acid receptors in the parventricular nucleus of the hypothalamus (Bulbul et al., 2011; Zheng et al., 2010). Of course, these types of interactions are difficult to study in humans due to methodological limitations. Unravelling these brain mechanisms in humans is therefore a feat for future research.

Future research is also needed to evaluate the relationship between endogenous and exogenous oxytocin. It is unknown if the behavioural effects generated by exogenous oxytocin are the same as those produced by endogenous oxytocin. It is also unclear to what extent the effects of intranasal oxytocin on human behaviour are dose-dependent. A dose of 24 I.U. oxytocin was employed in both of our studies, which has been the most extensively examined in the human literature (Ditzen et al., 2009; Heinrichs et al., 2003; Kosfeld et al., 2005). Although smaller and larger doses of intranasal oxytocin have been investigated, no known study has directly examined whether behavioural effects vary as a function of dose.

Dose-dependent behavioural effects of oxytocin have frequently been reported in animals. For instance, in female prairie voles, the administration of a low neonatal dose oxytocin will facilitate pair bonding in adult life whereas a high neonatal dose will inhibit pair bonding in adult life (Carter, Boone, Pournajafi-Nazarloo, & Bales, 2009). Rather than form partner preferences and long lasting pair bonds, females will avoid familiar partners. In male rats, low acute doses of oxytocin facilitate copulatory performance whereas high doses attenuate male sexual responses (Stoneham, Everitt, Hansen, Lightman, & Todd, 1985). Oxytocin's impact on stress reactivity and physiological

arousal also appears to be dose-dependent. Windle et al. (1997) demonstrated that a low dose of centrally infused oxytocin had no impact on the corticosterone response to the stressor whereas both a moderate and high dose attenuated the response. Furthermore, in a fear potentiated startle paradigm, only a high dose of centrally administered oxytocin attenuated the startle response in rats (Ayers et al., 2011).

Although well established in the animal literature, interpreting these dose-dependent effects can be challenging. There is little consistency in the doses employed between studies and there are no standard criteria to delineate low, moderate, and high doses. As such, these categories are arbitrary to each study. Based on reported findings, it would appear that central oxytocin has no impact on the HPA axis or the acoustic startle response at low doses; findings that would need to be replicated in humans. Moreover, it is unclear whether the effects of oxytocin on a given behavior would vary linearly or non-linearly in the form, for example, of an inverted "U" shape curve as observed in the relationship between glucocorticoids and cognition in humans (Lupien & McEwen, 1997). Studies in animals indicate that oxytocin's effects are frequently reversed when the dose exceeds a certain threshold. If representative of our own findings, high doses of exogenous oxytocin would be expected to increase cortisol levels and to heighten the startle response.

It also remains uncertain how long the effects from exogenous oxytocin can be sustained. Does oxytocin induce long-lasting effects or are these present only under drug administration? Addressing this question is key in determining how effective oxytocin can be in the treatment of mental disorders. It is dubious whether intranasal oxytocin can be safely and effectively administered at high doses over long periods of time. Prolonged

oxytocin exposure in male rats has been shown to result in a 50% decrease in oxytocin receptor density in areas throughout the brain (Witt, 1997). Very few human studies have examined the effects of long-term oxytocin administration. Epperson et al. (1996) administered intranasal oxytocin over several weeks in participants diagnosed with OCD and reported no adverse effects associated with long-term administration and no positive effects on treatment outcomes either. In a case study performed in a man diagnosed with OCD, exogenous oxytocin, administered daily over a 4 week period appeared to alleviate OCD symptoms, but was also associated with severe memory disturbances (Ansseau et al., 1987). This study highlights the need for caution in the chronic administration of exogenous oxytocin. In the end, higher oxytocin doses or longer exposures to the hormone may not necessarily lead to greater benefits.

In conclusion, the last decade has been privy to a dramatic increase in the number of studies examining the behavioural effects of oxytocin in humans. Its pro-social effects have generated so much interest and excitement that oxtocin has been described as a "love hormone" in the media (O'Callaghan, 2010). Albeit popular, this representation of oxytocin is grossly oversimplified. The oxytocinergic system is complex and branches into many different aspects of human functioning. It can modulate stress-responsive physiological systems as well as social cognitive processes (i.e. learning, memory, empathy, emotional processing). One could argue that these functions are all intended for the attainment of pro-social outcomes, but this does not always appear to be the case. The hormone does not promote affiliative behaviours when it is maladaptive to the individual. As such, oxytocin might serve a greater purpose of ensuring the well-being and safety of humans.

We have demonstrated that oxytocin impacts the HPA axis during interpersonal challenge and attenuates the basic startle reflex. By dampening these physiological systems, oxytocin could be serving to facilitate social approach behaviour. However, it is also possible that oxytocin is providing homeostasis by regulating sympathetic fight or flight circuits. We know that the stress response is adaptive when triggered by acute stressors but that it has deleterious health outcomes when over-stimulated for prolonged periods of time (Sapolsky, 2004). By restoring a sense of calm and safety, oxytocin could be mediating the beneficial effects that positive social relationships have on physical and mental health.

This is one hypothesis that requires future investigation. Considering that this area of research is relatively new, many avenues are open for future directions. We can only hope that our contribution to the research literature has opened a door to some of these possibilities!

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