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Oxytocin selectively moderates negative cognitive appraisals in high trait anxious males

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Summary The mammalian neuropeptide oxytocin has well-characterized effects in facilitating prosocial and affiliative behavior. Additionally, oxytocin decreases physiological and behavioral responses to social stress. In the present study we investigated the effects of oxytocin on cognitive appraisals after a naturalistic social stress task in healthy male students. In a randomized, double-blind, placebo-controlled trial, 48 participants self-administered either an oxytocin or placebo nasal spray and, following a wait period, completed an impromptu speech task. Eye gaze to a pre-recorded video of an audience displayed during the task was simultaneously collected. After the speech, participants completed questionnaires assessing negative cognitive beliefs about speech performance. Whilst there was no overall effect of oxytocin compared to placebo on either eye gaze or questionnaire measures, there were significant positive correlations between trait levels of anxiety and negative self-appraisals following the speech. Exploratory analyses revealed that whilst higher trait anxiety was associated with increasingly poorer perceptions of speech performance in the placebo group, this relationship was not found in participants administered oxytocin. These results provide preliminary evidence to suggest that oxytocin may reduce negative cognitive self-appraisals in high trait anxious males. It adds to a growing body of evidence that oxytocin seems to attenuate negative cognitive responses to stress in anxious individuals.
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1. Introduction

The neuropeptide oxytocin has garnered increasing interest over the last decade as a critical mediator of mammalian social behavior. Oxytocin is well-known for its peripheral effects; after release into the bloodstream during birth, it plays a crucial role in regulating uterine contractions and promoting lactation. Released centrally, oxytocin has a fundamental role in a range of affiliative and prosocial behaviors, including the onset and maintenance of maternal behavior, formation of adult bonds, and social recognition (reviewed recently in Meyer-Lindenberg et al., 2011). Of particular interest, receptors for this hypothalamic hormone are found in a number of neural regions associated with the control of social behavior, as

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well as reward, stress-responsivity, and the processing of emotional information (Landgraf and Neumann, 2004).

Exogenous oxytocin, administered as a nasal spray, facilitates the perception and interpretation of social information. For example, oxytocin increases trusting behavior (Kosfeld et al., 2005) and decreases fear of social betrayal (Baumgartner et al., 2008). Oxytocin also modulates aspects of social cognition, including emotion understanding (Domes et al., 2007b; Guastella et al., 2010) and recognition (Domes et al., 2007a; Marsh et al., 2010), and attention to socially relevant information of human faces (Guastella et al., 2008a; Gamer et al., 2010). These effects are thought to be mediated by modulation of amygdala activity and associated cortical and subcortical areas in both humans (Kirsch et al., 2005; Domes et al., 2007a; Baumgartner et al., 2008) and rodents (Ferguson et al., 2001; Lee et al., 2007).

Endogenous oxytocin additionally functions as an anxiolytic, acting to increase release of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the central amygdala (Viviani and Stoop, 2008) and attenuate hypothalamic–pituitary–adrenal (HPA) axis activity (Neumann, 2002) in response to fearful stimuli. Cumulative evidence from rodent models suggests that both acute and chronic administration of oxytocin reduces physiological and behavioral stress responsivity (Windle et al., 1997; Slattery and Neumann, 2010; Lukas et al., 2011). Homologous evidence exists in humans; Heinrichs et al. (2003) first demonstrated that intranasal oxytocin attenuated cortisol levels and subjective reports after psychosocial stress induction, an effect which was augmented by the addition of social support. Similar results have recently been reported, with reduced anticipatory anxiety (de Oliveira et al., 2012) and attenuated cortisol responses to public speaking tasks in individuals with impaired emotional regulation abilities (Quirin et al., 2011) after oxytocin administration. Evidence is also starting to emerge that oxytocin may have therapeutic potential for psychiatric illnesses, especially those characterized by anxiety, stress, or social deficits. For example, individuals diagnosed with social anxiety disorder (SAD), who were given oxytocin as an adjunct to cognitive behavior therapy (CBT), exhibited reduced negative cognitive beliefs about their perceived performance after public speaking over time (Guastella et al., 2009), an effect that may be due to reduced amygdala hyperactivity in response to threatening social stimuli (Labuschagne et al., 2010).

It has been hypothesized that oxytocin may reduce the potential threat associated with ambiguous or fearful social interactions (Kirsch et al., 2005) as it engages a wide range of neural systems that underpin social behavior, including dopamine-modulated reward networks (McGregor et al., 2009; Ross and Young, 2009). Potential anxiolytic effects, however, may be due to not only a general decrease in amygdala activation to fearful social stimuli (Domes et al., 2007a; Petrovic et al., 2008), but a decrease in functional connectivity between amygdala and brainstem regions that engage the fear response (Kirsch et al., 2005). It has therefore been suggested that oxytocin may reduce the uncertainty associated with ambiguous social stimuli by depressing natural threat-related responses (Domes et al., 2007a). For example, attenuated amygdala responses to faces conditioned with shock after oxytocin administration was found to be specific to faces with direct gaze, indicating a specific attenuation of neural fear responsivity to socially relevant stimuli (Petrovic et al., 2008). However, the majority of studies reported to date in this area have been conducted in males, and sexually dimorphic effects on emotion recognition and corresponding functional activation have been reported in females (e.g. Domes et al., 2010).

Oxytocin acts to influence the accurate detection and appraisal of emotional social information at both automatic and strategic levels of processing (Guastella and MacLeod, 2012). Studies using static photographs of human faces have demonstrated speeded detection of emotions under oxytocin relative to placebo (Lischke et al., 2012), an effect that may be more pronounced for positive emotions (Marsh et al., 2010; Schulze et al., 2011). Recently, oxytocin was argued to attenuate effortful processing of sad faces and moderate automatic attentional bias towards angry faces in individuals with a propensity towards depression (Ellenbogen et al., 2012). In terms of subjective and cognitive appraisals of socially relevant stimuli, oxytocin appears to increase ratings of attractiveness and trustworthiness of neutral faces (Theodoridou et al., 2009), increase positive evaluative ratings of social images (Norman et al., 2011), and facilitate subsequent recall of positive social memories (Guastella et al., 2008b). These studies suggest that oxytocin facilitates early and rapid detection of emotional stimuli, with enhanced cognitive appraisals of social stimuli at later, elaborative stages of processing.

Under conditions of stress or anxiety, however, biases in detecting and processing emotional or threatening stimuli are well established (Beck and Clark, 1997). Higher levels of both trait and state anxiety, in both student populations and clinically anxious individuals, are associated with not just the initial speed at which attention is drawn to threat, but impaired ability to switch attention away from threat, and preferential avoidance of attention away from threat at later stages of processing (Calvo and Avero, 2005; Pflugshaupt et al., 2005; Cisler and Koster, 2010; Veljaca and Rapee, 1998). A recent attentional bias review found that both trait anxiety and the induction of state anxiety using stressor tasks result in attentional biases at both automatic and strategic levels of processing (Cisler and Koster, 2010).

Given the role of oxytocin in modulating physiological, behavioral, and subjective responses to stress, we aimed to examine whether oxytocin may also influence attentional and cognitive biases associated with anxiety. Public speaking tasks, such as the Trier social stress test (TSST; Kirschbaum et al., 1993), reliably induce physiological and cognitive responses, which have previously been shown to be sensitive to oxytocin administration (Heinrichs et al., 2003). However, it is still yet to be determined whether oxytocin moderates earlier attentional stages of social information processing during stress, or later stages of evaluative processing. If oxytocin acts to reduce the impact of social stress, it may do so by modulating attention away from threat and towards the processing of positive social information. Further, these effects may also relate to changes in negative post-speech cognitive self-appraisals, in line with our previous findings (Guastella et al., 2009). Using an impromptu public speaking task, participants were shown a prerecorded audience of actors displaying dynamic emotional expressions whilst eye gaze was assessed. As sexually dimorphic effects of oxytocin have previously been described (Domes et al., 2010), and possible interactions between fluctuating levels of estrogen

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