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A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder

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Summary In humans, oxytocin nasal administration reduces social-threat perception and improves processes involved in communication and the encoding of positive social cues. The aim of this study was to determine whether oxytocin given as an adjunct to exposure therapy improves treatment for social anxiety disorder (SAD) as indicated by a comprehensive set of symptom outcome measures. In a randomized, double-blind, placebo-controlled trial, we administered 24 IU of oxytocin or a placebo in combination with exposure therapy to twenty-five participants who met primary diagnosis for SAD. Participants administered with oxytocin showed improved positive evaluations of appearance and speech performance as exposure treatment sessions progressed. These effects did not generalize to improve overall treatment outcome from exposure therapy. Participants who received oxytocin or placebo reported similar levels of symptom reduction following treatment across symptom severity, dysfunctional cognition, and life-impairment measures. This study shows that the administration of oxytocin improves mental representations of self, following exposure therapy. These effects may be either short term or situation specific. Future research is now needed to determine whether oxytocin can enhance treatment outcomes for SAD when used with greater frequency, with a wider variety of social learning experiences, and in conjunction with interventions that more specifically target change in broader dysfunctional cognitions.

In nonhuman mammals, the neuropeptide and hormone oxytocin (OT) plays an important role in the regulation of social behavior. OT enhances social recognition and facilitates the development of sexual behavior in both males and females across a broad range of mammalian species (see Young and

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Wang, 2004; Neumann, 2008 for recent reviews), although some species-specific differences have been noted (Donaldson and Young, 2008). In addition to its role in social and sexual behavior, OT inhibits stress-induced activity of the hypothalamic–pituitary–adrenal (HPA) axis (Neumann et al., 2000; Windle et al., 2004; Parker et al., 2005) and amygdala activation in the modulation of autonomic fear (Huber et al., 2005). OT has been shown to influence anxiety related behaviors in rats via a protein kinase A dependent mechanism acting on the central nucleus of the amygdala (Bale et al., 2001). It has further been shown that in rats the anxiolytic function of OT involves ERK 1/2 activation in the hypothalamic paraventricular nucleus (PVN; Blume et al., 2008). Interestingly, OT appears to play an integral role in the anxiolysis experienced during post-coitus in male rats (Waldherr and Neumann, 2007) suggesting that OT enhanced social behavior is mediated by its anxiety alleviating properties.

In humans, OT nasal administration markedly reduces amygdala responsiveness to social stimuli, irrespective of stimuli valence (Kirsch et al., 2005; Domes et al., 2007a). It also promotes trust (Kosfeld et al., 2005), gaze to the eye region of human faces (Guastella et al., 2008b), the identification of emotional states from the eyes of others (Domes et al., 2007b) and the benefits of social support during social-stress induction tasks (Heinrichs et al., 2003). More recently, studies have shown that OT enhances cognitive processing for positive social cues over neutral and threatening social cues: OT enhances the encoding of positive social cues so that this information is more likely to be retrieved (Guastella et al., 2008c) and it facilitates the recognition of positive sex and relationship words (Unkelbach et al., 2008). OT attenuates negative affective evaluations associated with aversively conditioned faces through modulation of the amygdala and fusiform gyrus in non-clinical adults (Petrovic et al., 2008), further outlining the action of OT on the amygdala during the perception of threatening social cues. Effect sizes from OT on these outcome measures have varied widely from large (Guastella et al., 2008b) to small (Kosfeld et al., 2005). This research has been conducted with male students and it is yet to be determined how these findings generalize to clinical populations or females.

This research has led to speculation that OT administration could provide a useful adjunctive treatment for social anxiety disorder (SAD; Heinrichs and Gaab, 2007). SAD is a common and debilitating psychiatric disorder that has an estimated lifetime prevalence of 12.1% (Kessler et al., 2005). Patients with SAD suffer significant impairment in functioning characterized by social fear, avoidance, dysfunctional cognitions, and life interference (Stein et al., 1996; Wittchen et al., 1999). While there are effective treatments for SAD, such as psychological therapy (i.e., cognitive–behavioral therapy), many patients remain symptomatic following treatment (Davidson et al., 2004). There is evidence, however, that one can augment psychological interventions for SAD with medication (e.g., D-cycloserine) to improve adaptive learning during therapy (Hofmann et al., 2006; Guastella et al., 2008d).

A key characteristic of SAD is an excessive fear of negative evaluation by others (APA, 2000). Patients with SAD show cognitive biases for social-threat information and overly negative self-representations (Hirsch and Clark, 2004; Mogg et al., 2004; Rapee and Abbott, 2006). Such cognitive biases are thought to play a causal role in the development and maintenance of SAD by reinforcing dysfunctional negative beliefs and by inhibiting the processing of positive corrective feedback (Hirsch and Clark, 2004; Hirsch et al., 2006). We have argued (Guastella et al., 2008c) that OT could facilitate adaptive social learning by improving the encoding of positive social experiences and reducing the impact of exaggerated social-threat biases.

The aim of this study was to conduct the first evaluation of OT-enhanced exposure therapy treatment for SAD in a sample of community patients. First, we hypothesized that OT would enhance adaptive learning during exposure tasks. To demonstrate changes in adaptive learning we evaluated the effect of OT on cognitive appraisals following exposure tasks. We predicted that patients receiving OT would display more positive and less dysfunctional evaluative cognitions following each exposure therapy task. Second, we hypothesized that OT would augment exposure therapy treatment outcomes. That is, participants who received OT would obtain greater long-term symptom improvements following therapy in comparison to placebo.

1. Methods and materials

1.1. Participants

Participants were recruited from the community if they met DSM-IV diagnosis for SAD using the Anxiety Disorder Interview Schedule for Adults (ADIS-IV; Brown et al., 1994) and reported fear of public speaking on self-report measures. All participants were recruited through the University of New South Wales Psychology Clinic. Assessment and treatment sessions were conducted by registered or provisionally registered clinical psychologists and were supervised by a senior clinical psychologist (AJG). Exclusion criteria included: a primary diagnosis of a psychotic disorder, severe kidney disease, epilepsy, current substance dependence, reported suicide ideation, traumatic brain injury, and current participation in any other psychological therapy. In order to minimize any possible interactions with OT or confounding influences of other substances on brain function, participants were asked to refrain from caffeine, nicotine, and alcohol on days that they received treatment, and all food and drink, except water, two hours before receiving the nasal spray. Ethical approval was provided by the UNSW Ethics Committee (06074).

Forty-two male participants self-referred from media advertisements. Thirty eligible male adults were offered participation; 25 accepted and were randomly assigned to OT ($N = 12$; four puffs per nostril each with 3 international units (IU; Novartis, Switzerland)) or placebo ($N = 13$) at the start of the second therapy session. The matched placebo contained all ingredients except the active OT. A random allocation sequence was developed by the compounding chemist and concealed from all individuals involved in patient care, evaluation, or supervision until assessments were complete.

As this was the first trial of OT for SAD we planned to examine data once 25 patients had completed treatment, a point when there would be sufficient power to detect any large effects sizes from OT on treatment outcome (Cohen, 1988; Hofmann et al., 2006). The progress of participants is