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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

shown in the supplementary information. Of the 25 male participants (mean age = 42.28, SD = 11.27, range = 25—65) recruited into this trial, 83% did not identify with a non-Caucasian ethnic group, 76% were employed and 52% had a tertiary degree. *t*-Tests and Chi-square analysis indicated that there were no differences across drug condition on any sample characteristics such as age, baseline clinical ratings, ethnicity, or education. All participants met criteria for SAD. Furthermore, 24% (*N* = 6) of these participants had an additional secondary anxiety disorder, 28% (*N* = 8) had a secondary mood disorder, and 8% (*N* = 2) had both an additional mood and anxiety disorder. A total of 16% (*N* = 4) participants were taking anti-depressant medications, evenly distributed across OT and placebo groups and stabilized for a period of at least six weeks. Some participants were also taking cardiovascular (12%, *N* = 3) and gastrointestinal (8%, *N* = 2) medications.

1.2. Treatment

All participants received a 5-session weekly group exposure therapy protocol that was based on previous research (Hofmann et al., 2006; Guastella et al., 2008d). Participants were provided with an exposure-based model of treatment for SAD at the first treatment session. At the start of session 2, participants randomly selected one coded bottle that contained the OT or placebo nasal spray. The nasal spray was administered before each weekly session from Sessions 2 to 5. Participants received a total of four administrations of the nasal spray. Forty-five to ninety minutes following each of these drug administrations, each member gave a speech in front of group members about increasingly difficult topics. These topics have been outlined in previous research (Hofmann et al., 2006; Guastella et al., 2008d). The first topic was a description of the social anxiety model and subsequent topics were gradually more difficult (i.e., personal, revealing, and potentially embarrassing).

1.3. Measures

1.3.1. Outcome measures

Self-report outcome measures were obtained within one month before the first treatment session, immediately following the completion of the last treatment session, and one month following the last treatment session. Following previous research (Guastella et al., 2008d), we used four self-report measures to assess SAD symptoms: the Social Phobia and Anxiety Inventory (SPAI; Turner et al., 1996) and the Liebowitz Social Anxiety Scale (LSAS; Leibowitz, 1987) provided a general measure of social phobia fear and avoidance symptoms, the Brief Fear of Negative Evaluation Scale (BFNE; Leary, 1983)) assessed dysfunctional cognitions associated with social anxiety, and the Life Interference Scale (LIS; Rapee et al., 2007) provided a general measure of how much social anxiety interferes with everyday functioning. Detailed descriptions of the psychometric properties of these scales have been provided previously (Guastella et al., 2008d).

1.3.2. Treatment credibility

We administered the Credibility/Expectancy Questionnaire (CEQ; Hofmann et al., 2006) to measure expectancy and credibility of treatment. Participants were asked to rate the perceived logic of treatment on a 9-point scale (1 = ''not at all logical'', 9 = ''very logical'') after the first treatment session. Participants were also asked whether they believed that they had received OT or placebo each week of the exposure treatment sessions.

1.3.3. Anxiety

Immediately following each speech task, participants rated their experienced fear/anxiety during the speech on a 100-point scale (0 = no fear/anxiety to 100 = extreme fear/anxiety).

1.3.4. Appraisals of speech appearance and performance

After the exposure task, participants completed two self-report measures of speech performance to tap into some of the common negative evaluative mental representations that characterize SAD. The first was the Appearance Scale (Rapee and Abbott, 2006), a 6-item measure of how the participant felt the audience perceived their appearance on a 4-point scale (0 = ''not at all attractive'', 4 = ''very attractive''). This questionnaire assesses the occurrence of common negative self-image beliefs of patients with SAD (Rapee and Abbott, 2006). The second was the Speech Performance Questionnaire (SPQ; Rapee and Lim, 1992). The SPQ evaluates negative self-appraisals and mental representations commonly displayed by SAD patients when performing in front of a group (e.g., 'seemed to tremble or shake'; 'appeared nervous'; 'made a good impression' (Abbott and Rapee, 2004)). This was measured on a 5-point scale (0 = ''not at all'', 4 = ''very much''). Higher total scores on each scale indicated a more positive mental representation of one's appearance and speech performance. Previous research has shown good internal consistency and inter-rater reliability for both scales (Rapee and Hayman, 1996; Rapee and Abbott, 2006) and discriminates between patients with SAD and non-clinical participants (Rapee and Hayman, 1996; Rapee and Abbott, 2006). SAD patients also show lower ratings on these scales in comparison to independent (Rapee and Abbott, 2006; Rapee and Hayman, 1996) and objective measures of their speech performance (Abbott and Rapee, 2004).

1.4. Analysis

Data were entered by a research assistant blind to drug assignment, and analyzed with the SPSS statistical software package (SPSS V14 Inc, Chicago, Ill). We employed intention to treat (ITT) analysis and Last observation carry forward was used to replace missing data for all participants assigned to receive OT or placebo. For the outcome analysis, a drug (OT, Placebo) by time (pre-treatment, post-session 5 treatment, one-month follow-up) repeated-measures MANOVA was conducted on total scores from the SPAI, LSAS, BFNE, and LIS. We conducted a drug (OT, Placebo) by exposure treatment session (Sessions 2—5) repeated-measures MANOVA to determine whether there were differences between drug groups on the mental representation measures following speech performance.

2. Results

2.1. Participant beliefs about treatment

Participant ratings on expectation and credibility scales were moderate to high and not different between the two groups (largest t (23) = 1.05, p = 0.30). There was no difference between drug conditions with regard to guessing to which drug condition subjects believed they had been assigned at any time point [largest $t(21)$ = 1.21, p = 0.26]. On average, 46.8% of OT-assigned participants and 51.8% of placebo-assigned participants believed they had received OT. On average, 4 OT and 3 placebo participants reported side effects at each treatment session. Reported side effects over the four weeks included feeling relaxed (N = 7), light headed (N = 2), anxious (N = 1), and fuzzy sensations (N = 1).

Table 1 shows the means and standard deviations of the four self-report outcome measures (SPAI, LSAS, BFNE, LIS). One-way t-tests indicated that there were no pre-existing differences across symptom outcome measures (largest t (23) = −0.69, p = 0.50. A drug (OT, Placebo) × time (Pre, Post, one-month post) repeated-measures MANOVA with all total scores from self-report outcome measures revealed a main effect of time [$F(8,16)$ = 4.19, p = 0.007], showing a reduction in self-reported SAD symptoms from pre-treatment to post-treatment that was maintained at follow-up. There was no main effect for drug [$F(4,20)$ = 0.46, p = 0.76], or a drug × time interaction [$F(8,16)$ = 0.65, p = 0.72]. We examined drug × time interactions for each individual outcome measure. Results indicated no significant interactions [largest F = 0.55, p = 0.58].

2.2. Process measures

A drug (OT, Placebo) × exposure treatment session (Sessions 2—5) repeated-measures ANOVA was conducted on self-reported anxiety during the speech task. Analysis indicated a main effect for exposure treatment session [$F(6,18)$ = 4.69, p = 0.005]. Participant anxiety decreased as sessions progressed. There was no main effect of drug [$F(2,22)$ = 2.28, p = 0.13], nor an interaction between exposure treatment session and drug [$F(6,18)$ = 0.99, p = 0.46]. A drug (OT, Placebo) × exposure treatment session (Sessions 2—5) repeated-measures MANOVA was conducted on the Appearance Scale and the SPQ. Analysis indicated a main effect for Session [$F(6,18)$ = 6.44, p = 0.001], no main effect of drug [$F(2,22)$ = 1.48, p = 0.25] and an interaction between exposure treatment session and drug [$F(6,18)$ = 2.70, p = 0.04]. Examination of interaction effects for each scale indicated that participants who received OT rated their appearance [$F(3,21)$ = 4.24, p = 0.008], and performance [$F(3,21)$ = 2.37, p = 0.07] as more significantly improved as sessions progressed, in comparison to placebo administered counterparts. To determine whether participants in both drug group improved on these process measures as treatment sessions progressed, paired t-tests comparing change from the first exposure session (session 2) to the last treatment session (session five) was run on performance and appearance scales. Analysis showed that both OT [$t(11)$ = −4.36, p = 0.001] and placebo [$t(12)$ = −3.759, p = 0.003] treated participants improved their ratings of speech performance as sessions progressed. Paired t-tests examining appearance ratings also showed improvement for OT [$t(11)$ = −2.903, p = 0.014] but not placebo [$t(12)$ = 0.15, p = 0.883] treated participants. This is illustrated in Fig. 1.

Table 1 Means and SDs for Self-Report and Clinician-Ratings across Assessments. SPAI: Social Phobia Anxiety Inventory; LSAS: Leibowitz Social Anxiety Scale; BFNE: Brief-Fear of Negative Evaluation; LIS: Life Interference Scale.

		Pre	Post	Follow-up
SPAI (range = 38—144)	OT	101.81 (26.85)	96.57 (20.19)	89.57 (20.12)
	Placebo	106.81 (28.68)	91.41 (30.59)	90.70 (30.75)
LSAS: (range = 12—140)	OT	76.92 (22.66)	62.16 (37.41)	62.75 (38.21)
	Placebo	74.23 (20.71)	52.30 (21.30)	52.38 (22.36)
BFNE (range = 29—60)	OT	46.17 (9.17)	41.83 (8.35)	40.41 (8.10)
	Placebo	48.72 (4.89)	43.46 (6.66)	41.15 (8.00)
LIS (range = 3—48)	OT	33.17 (11.41)	29.41 (12.26)	24.25 (15.79)
	Placebo	31.08 (6.07)	28.76 (8.38)	22.23 (10.73)

SPAI, Social Phobia Anxiety Inventory (Total Score); LSAS, Leibowitz Social Anxiety Scale (Total Score); BFNE, Brief Fear of Negative Evaluation Scale; LIS, Life Interference Scale.

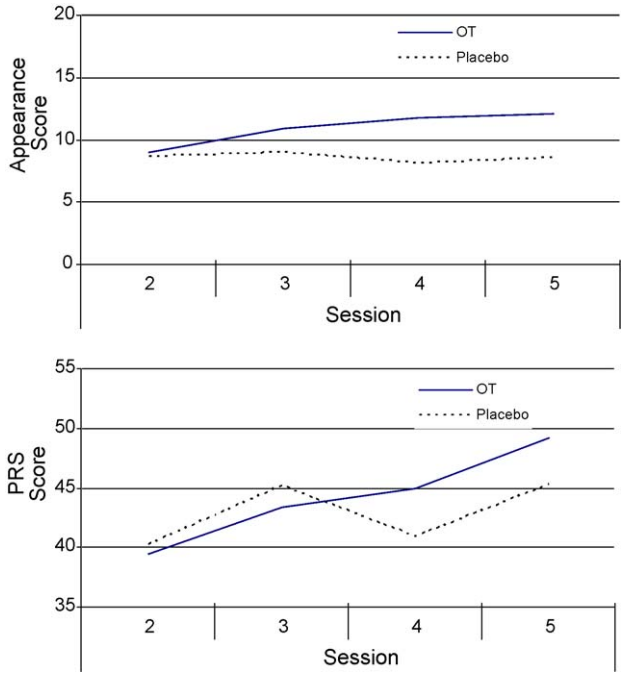

Figure 1 Total Appearance and Speech Performance Questionnaire (SPQ) scores as indicated by each participant following their each exposure session according to oxytocin (OT) and placebo drug groups.

3. Discussion

This is the first trial of OT as an adjunct to exposure therapy for SAD. Results partially confirmed hypotheses. OT reduced the exaggerated negative mental representations of self which are typically displayed by SAD patients following a speech exposure task. Participants who received OT showed greatest improvements in both their ratings of speech performance and their speech appearance in comparison to placebo treated patients. There was, however, no evidence that these benefits generalized to increase long-term improvements from exposure therapy. There was no difference between OT and placebo groups on SAD symptom outcome measures at post-treatment and at one-month follow-up.

Research has shown that OT plays a key role in promoting positive social cognition over social-threat (Guastella et al., 2008c; Unkelbach et al., 2008) and we recently argued for a bio-cognitive model of OT (Guastella et al., 2008a) emphasizing its biological-evolutionary role (Heinrichs et al., 2004) in promoting processing for positive social-cues and reducing threat when there is opportunity to conceptually process meaning at top-down levels of processing (Williams et al., 1997). In this study, OT did not reduce the immediate threat response as indicated by anxiety levels during the speech task. Rather, effects were found on appraisal measures following the speech task. SAD patients who received OT reported less negative and dysfunctional appraisals as treatment progressed. This included making more eye contact and being received positively by group members, which is consistent with previous oxytocin research (Guastella et al., 2008b,c). By the end of treatment, OT-administered SAD patients reported similar levels of positive and negative appraisals of appearance and performance that are typically displayed by non-anxious student controls (Rapee and Abbott, 2006). This suggests that OT facilitated a more adaptive and accurate appraisal of performance following the speech task. As we did not have any objective measures of speech performance, it remains unclear whether participants actual performance improved or whether it was only the subjective evaluation of their performance. Finally, placebo participants did show some improvements in their negative evaluations of performance as treatment progressed but there was no evidence of improvements for ratings of appearance. It is difficult to conclude, however, that there was no improvement from placebo treatment as assessed by the appearance scale. Each of the exposure treatment sessions was more difficult and more revealing than the previous session, with the most difficult being the fourth session ('talk about something potentially revealing or embarrassing to yourself'). Given the increasing difficulty of speech tasks, the expected outcome for someone not involved in any treatment would be a gradual decrease in performance and appearance ratings across time.

Research indicates that SAD patients show enhanced activation of the medial prefrontal cortex (MPFC) in conjunction with the amygdala during self-referential threat based processing (Blair et al., 2008). This type of processing involves top-down influences similar to the self-reported measures of speech performance used in this study. There has been some research showing OT reduces amygdala activation but its effects on the MPFC remain unclear. Given our hypothesis that OT has greater influences on the processing of social valence for top down socio-cognitive processes (Guastella et al., 2008a), it would be worthwhile for future research to explore the relationship between the changes observed in negative appraisals following speech performance following OT and MPFC activation within each session.

Despite these acute benefits, the addition of OT to exposure therapy did not enhance treatment outcomes for SAD in the long-term. There was no indication of a trend across any outcome measure. Even when one simply examines the descriptive mean change data from pre-treatment to post-treatment, there was not a single outcome showing greater symptom reduction (significant or non-significant) for those participants that had received OT over placebo. With 25 patients already recruited and no trend in a positive direction, it is extremely unlikely that increasing the sample size could make any difference to the conclusion of this study and we decided to cease recruitment. It would seem that OT may not offer the degree of benefit that has been shown previously with adjunctive pharmacotherapeutics such as D-cycloserine when used as an adjunct to exposure based therapies (Ressler et al., 2004; Hofmann et al., 2006; Guastella et al., 2008d). Unlike this other medication, which is believed to enhance learning through extinction-based mechanisms, the effects of OT on fear-extinction mechanisms in humans is not clear.

This study further supports our previous research (Guastella et al., 2008c; Unkelbach et al., 2008) by showing that OT subtly enhances the cognitive processing of positive social information over social-threat but these changes did not alter psychopathology in the long-term. It remains unclear in cognitive psychology how much change in biased threat processing within a single treatment sessions might be required for clients

to obtain long term benefit. Further, it remains unclear whether the effects from OT can be sustained long term or are only present under drug administration. Thus, the amount of change in threat biased cognition in this study may not have (1) generalized to produce change in settings outside of the speech task or (2) been powerful enough for sustained long-term benefits. It may be that four short exposure therapy sessions with OT do not sufficiently target the wide variety of negative self-representations that both drive and characterize SAD. OT may be best applied as a repeated component of longer treatment packages that target change in negative self-representations, such as image re-scripting and other cognitive approaches (Holmes et al., 2007).

Future research evaluating the effect of OT on treatment programs for anxiety should focus on its potential role in shifting long-term dysfunctional cognitions in task-specific situations (e.g., to reduce dysfunctional cognitions associated with speech performance specifically), or with interventions that aim to target change in dysfunctional cognitions more broadly. Further, objective physiological measures should be employed in order to provide insight into the function of OT so as to further dissociate between the effects of OT on stress and anxiety related social behavior. Finally, it should be noted that our selection of dose (24 IU) was based on the majority of previous human research that has found influences from OT on cognition. It remains unclear whether increasing the dose of intranasal OT would lead to greater benefits. Overall, this study demonstrates the beneficial effects of OT in enhancing the processing of positive social cues while reducing social-threat dysfunctional cognition. Future research is now needed to determine whether OT could be used to benefit the treatment of SAD patients long-term.

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Conflict of interest

Dr. Guastella, Dr Dadds, Dr. Mitchell Miss Howard and Mr Carson report no biomedical financial interests or potential conflicts of interest.

Disclosure

This treatment trial is registered on the Australian Clinical Trials Registry: A randomized controlled trial to evaluate the effect of oxytocin in combination with exposure therapy in the treatment of social anxiety disorder to improve the severity of social anxiety disorder symptoms; #12607000256471, URL: http://www.actr.org.au/).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psyneuen.2009.01.005.

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