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Working hard for oneself or others: Effects of oxytocin on reward motivation in social anxiety disorder

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ABSTRACT

There is some evidence to suggest that oxytocin promotes social behavior, especially for disorders characterized by social dysfunction, such as social anxiety disorder (SAD). The goal of this study was to examine the effect of oxytocin on reward motivation in SAD. We tested whether oxytocin promotes prosocial, or antisocial, self-directed decisions, and whether its effects depended on social anxiety severity and attachment. Fifty-two males with SAD received 24 international units of oxytocin or placebo, and completed a reward motivation task that measured willingness to work for self vs. other monetary rewards. Although there was no main drug effect, social anxiety severity moderated the effect of oxytocin. Less socially anxious individuals who received oxytocin worked harder for other vs. own rewards, compared to high socially anxious individuals. Attachment did not moderate this effect. Among people with SAD, oxytocin enhances prosocial behaviors in individuals with relatively lower levels of social anxiety.

National Institutes of Health ClinicalTrials.gov Registry #NCT01856530.
https://clinicaltrials.gov/ct2/show/NCT01856530?term=oxytocin+pro-social&rank=2.

1. Introduction

Oxytocin, a hypothalamic neuropeptide, is a promising pharmacologic target for modulating social cognition (Hurlemann & Scheele, 2016; Shahrestani, Kemp, & Guastella, 2013). Individuals with social anxiety disorder (SAD) display anxiety and self-consciousness in social situations (Hofmann, 2007), which may be modulated by oxytocin (Labuschagne et al., 2010; Shamay-Tsoory & Abu-Akel, 2016).

Several theories have been put forth to explain the effects of oxytocin: a prosocial, affiliative account (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), a social salience enhancing account (De Dreu et al., 2010; Shamay-Tsoory et al., 2009; Shamay-Tsoory, 2010), a social approach/withdrawal account (Kemp & Guastella, 2011), and an anxiety reduction account (Bartz, Zaki, Bolger, & Ochsner 2011).

The prosocial theory of oxytocin proposes that oxytocin increases a wide range of "prosocial" behaviors, which are defined broadly as voluntary acts that benefit other people, and are driven by non-specific motives (Eisenberg & Miller, 1987). Reciprocal altruism is more narrowly defined as a prosocial behavior that benefits another even at personal cost, but with the expectation of being helped at a later point (Eisenberg & Miller, 1987). Reciprocal altruism has been linked behaviorally to empathic concern for unfamiliar others (De Waal, 2008), which are both oxytocin-dependent processes (Bartz et al., 2010; Hurlemann et al., 2010). The social salience account hypothesizes that oxytocin alters the perceptual salience of social information depending on the context of the situation itself (Shamay-Tsoory et al., 2009; Shamay-Tsoory, 2010). Oxytocin may either increase prosociality in cooperative social contexts, or promote envy and gloating (Shamay-Tsoory et al., 2009), and defense-motivated aggression (De Dreu et al., 2010), in competitive out-group interactions. The social approach/withdrawal hypothesis proposes that oxytocin may enhance approach-related emotions (including negative emotions, such as anger or jealousy) or inhibit social withdrawal-related emotions (such as anxiety and fear) (Kemp & Guastella, 2011). In patients with SAD, oxytocin led to reduced negative self-appraisals after exposure therapy despite having no changes on social anxiety symptom severity, relative to placebo, which supports this hypothesis that oxytocin alters cognitive biases involved in processing threat (Guastella et al., 2009). The anxiety reduction hypothesis proposes that oxytocin leads to beneficial social effects by reducing anxiety, especially social anxiety (Bartz et al., 2011; Heinrichs et al., 2003).

Each of these theories has different implications for how oxytocin

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may be potentially advantageous for individuals with SAD. The prosocial and anxiety reduction models hypothesize that oxytocin would facilitate social approach behavior, by reducing anxiety and fear in social situations. The social salience and social approach/withdrawal models hypothesize that oxytocin could be potentially harmful to patients with SAD by magnifying negative emotional or attentional tendencies. They also propose that oxytocin could be potentially beneficial by modulating emotional experiences and attentional processing to facilitate a more favorable self-view, and promote social engagement. In particular, some evidence suggests that oxytocin may induce a favorable self-bias, as studies in healthy male subjects have shown that oxytocin enhanced positive attitudes towards oneself, compared to placebo, in an adjective sorting task (Colonnello & Heinrichs, 2014), and enhanced the ability to recognize differences between self and other using a face morphing task (Colonello, Chen, Panksepp, & Heinrichs, 2013). However, some findings suggest that oxytocin may actually blur the self-other distinction and reduces medial prefrontal cortex responses and connectivity with other cortical midline regions involved in self-referential processing (Zhao et al., 2016). Thus, it remains unclear if oxytocin could be advantageous to individuals with SAD, who are excessively and negatively self-focused in social settings (Hofmann, 2007; Ingram, 1990; Spurr and Stopa, 2002).

In the current study, our objective was to test divergent accounts of oxytocin's effects on self-other reward motivation among individuals with SAD. We operationalized reward motivation as one's willingness to expend effort in exchange for monetary rewards for oneself vs. monetary rewards that would be given to a stranger. Given competing accounts of oxytocin's effects, we hypothesized that in patients with SAD who display excessive social anxiety and negative self-focus, oxytocin would either (1) promote motivation to work harder for others' rewards (pro-social, affiliative account (Kosfeld et al., 2005), and anxiety reduction account (Bartz et al., 2011; Heinrichs et al., 2003)), or (2) oxytocin would promote more self-oriented behavior to reward oneself (social salience account (Olff et al., 2013; Shamay-Tsoory, 2010) and social approach/withdrawal account (Kemp & Guastella, 2011)). Our previous work showed that in a sample of male SAD patients, oxytocin improved cooperative behavior toward a rejecting, but initially cooperative, player during a social ostracism paradigm called Cyberball, but *only* for those who were less severe in their avoidant attachment style (Fang, Hoge, Heinrichs, & Hofmann 2014). This is consistent with prior research demonstrating that individual difference factors moderate oxytocin's effects (Olff et al., 2013), and that oxytocin may have the most potent effects for individuals only within a certain range of functioning (Scheele et al., 2014). Thus, we also hypothesized that the effects of oxytocin would be moderated by social anxiety symptom severity and attachment orientation.

2. Materials and methods

2.1. Participants

Participants were recruited through an outpatient specialty anxiety clinic and through advertisements in the community. All participants were adult men with a principal or co-principal diagnosis of SAD, who met a symptom severity cutoff score of ≥ 60 on the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). Exclusion criteria included the following: significant nasal pathology; smoking ≥ 15 cigarettes per day; serious medical illnesses; active suicidal or homicidal ideation; current diagnosis of schizophrenia, psychotic disorder, bipolar disorder, or substance abuse or dependence; and, use of psychotropic medications, except for antidepressants taken at a stable dose for at least 2 weeks prior to study entry. Women were excluded from the study due to fluctuations in oxytocin during their menstrual cycles, as well as sex differences in responses to oxytocin (Dumais & Veenema, 2015). Please refer to the CONSORT diagram for a full description of participant recruitment and trial design. Our final sample consisted of 52 participants (mean age = 24.42 years, SD = 6.63, range = 18–45). See Table 1 for demographic and clinical data for the final sample.Of these 52 participants, 3 participants displayed unusual behavior on the reward motivation task: one chose all hard trials, one timed out on a larger percentage (10%) of trials, and one stopped responding halfway through the task. Removing these subjects from the analyses did not affect the main findings (effects of drug), so they were included in the analyses. There were no differences between groups on demographic or baseline clinical characteristics (all p's > 0.05). The study was approved by the Boston University Medical Center Institutional Review Board.

Table 1
Demographic and Clinical Data.

Demographic variable	Oxytocin group (n = 26)	Placebo group (n = 26)	t/X^2	p
Age (in years), Mean (SD)	24.65 (7.28)	24.19 (6.05)	−0.25	0.81
Ethnicity, n (%)			0.75	0.39
Hispanic or Latino	4 (15.40)	2 (7.70)		
Not Hispanic or Latino	22 (84.60)	24 (92.30)		
Race, n (%)			1.27	0.74
Caucasian	18 (69.20)	16 (61.50)		
African American	2 (7.70)	2 (7.70)		
Asian	4 (15.40)	7 (26.90)		
Other	2 (7.70)	1 (3.80)		
Marital Status, n (%)			4.02	0.26
Single	22 (84.60)	23 (88.50)		
Living with partner	1 (3.80)	3 (11.50)		
Married	2 (7.70)	0		
Divorced	1 (3.80)	0		
Highest Educational Level, n (%)			6.29	0.10
Graduate School	2 (7.70)	8 (30.80)		
College Graduate	9 (34.60)	6 (23.10)		
Partial College	14 (53.80)	9 (34.60)		
High School Graduate	1 (3.80)	3 (11.50)		
Occupational Status, n (%)			0.60	0.90
Full-time employment	5 (19.2)	5 (19.20)		
Part-time employment	6 (23.1)	6 (23.1)		
Dependent on spouse or is a student	9 (34.6)	11 (42.30)		
Other	6 (23.1)	4 (15.4)		
Clinical Variable				
LSAS Total, Mean (SD)	82.00 (18.16)	83.00 (16.39)	0.21	0.84
SIAS Total[a], Mean (SD)	50.40 (10.35)	47.96 (11.93)	−0.77	0.44
ECR Avoidant Attachment Subscale[b], Mean (SD)	3.43 (.89)	3.61 (.98)	0.49	0.63
ECR Anxious Attachment Subscale[b], Mean (SD)	4.47 (1.02)	3.90 (1.13)	−1.33	0.20

LSAS = Liebowitz Social Anxiety Scale; SIAS = Social Interaction Anxiety Scale; ECR = Experiences in Close Relationships Inventory.
[a] n = 25 per group.
[b] n = 12 (placebo), n = 13 (oxytocin).

2.2. Materials

Social Interaction and Anxiety Scale (SIAS) (Mattick and Clarke, 1998). The SIAS is a 20-item self-report measure that assesses anxiety in social interaction situations. Responses to items are given on a 5-point Likert scale, with 0 = not at all characteristic of me, and 4 = extremely characteristic of me. Total scores range from 0 to 80. The SIAS has been shown to be a valid measure of social interactional anxiety, and has also been demonstrated to have good internal consistency and reliability, in samples of patients with SAD (Clark et al., 1997). The SIAS was administered at baseline. In the current sample, the internal consistency was $\alpha = 0.88$, and the SIAS scores were highly correlated with LSAS scores ($r = 0.58$, $p < 0.001$). The SIAS was selected as our measure of social anxiety to assess the moderating effect of oxytocin, rather than