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Effect of intranasal oxytocin on pro-social behavior in social anxiety disorder

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Dissertation

EFFECT OF INTRANASAL OXYTOCIN ON PRO-SOCIAL BEHAVIOR IN
SOCIAL ANXIETY DISORDER

by

ANGELA FANG
A.B., Dartmouth College, 2007
M.A., Boston University, 2010

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ANGELA FANG

Boston University Graduate School of Arts and Sciences, 2014

Major Professor: Stefan G. Hofmann, Professor of Psychology

ABSTRACT

Previous research suggests that intranasal oxytocin may promote trust, social cooperation, in-group favoritism, and empathic concern in humans. Oxytocin therefore has therapeutic implications for psychological disorders such as social anxiety disorder (SAD). In particular, oxytocin may have anxiety-buffering effects in the context of social rejection. Oxytocin may promote cooperative social behavior with other individuals despite being rejected by them, as research has shown that oxytocin facilitates decisions indicative of sustained trust even despite breaches of trust. Using a double-blind, placebo-controlled design, the current investigation examined whether oxytocin modulates responses to social rejection from an initially cooperative confederate, and whether it modulates attentional processes toward social stimuli (disgust, neutral, and happy face stimuli). Participants were 54 individuals with SAD, who were randomly assigned to receive 24 international units (IU) of oxytocin or placebo nasal spray. Following drug administration, participants completed a computerized ball-tossing game called Cyberball, in which they were led to believe that they were playing “on-line” with three other fictitious players. The amount of reciprocation displayed by other players was
manipulated, such that Player 1 was programmed to play cooperatively during the first half of the game (tossed 70% of his balls to the participant), and then switched to less cooperative play during the second half (tossed 10% of balls to the participant). After Cyberball, participants completed a modified version of the Posner Task. Results showed that oxytocin improved cooperation with Player 1 in the second half of the game, but only for individuals with low attachment avoidance. Oxytocin also amplified subjective ratings of perceived rejection by others during Cyberball for individuals with high rejection sensitivity. Furthermore, oxytocin led to facilitated disengagement from all social cues regardless of emotional valence and speeded up detection of disgust and neutral faces, compared to placebo, but only for individuals with high attachment avoidance. These findings suggest that oxytocin may promote social cooperation, as well as a flexible attentional pattern toward social cues, at least for some individuals with SAD. Future research should address individual differences in responses to oxytocin, and further investigate the comparative effects of oxytocin in healthy individuals.
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Introduction

First described by the British physiologist Sir Henry Hallett Dale in 1906, oxytocin is a nine amino acid neuropeptide, which is produced in the paraventricular and supraoptic nuclei of the hypothalamus. It is then secreted via the posterior pituitary gland into peripheral circulation or released into the central nervous system to act on receptors widely distributed throughout the brain in the limbic system, midbrain, and brainstem. Sir Henry Hallett Dale coined the name oxytocin from the Greek words meaning “swift birth,” due to his observations that extracts from the human posterior pituitary gland contracted the uterus of a pregnant cat. In 1953, oxytocin was sequenced and synthesized by Vincent du Vigneaud, making it the first peptide hormone to be synthesized. Today, synthetic oxytocin (marketed as Pitocin® and Syntocinon®) is commonly administered intravenously to induce or augment labor in pregnant women.

Traditionally, oxytocin has been examined for its role in childbirth, lactation, and maternal attachment. Following recent advances in translational neuroscience to deliver oxytocin directly to the central nervous system, studies have revealed that oxytocin has much broader functions in social cognition and behavior than previously thought. Animal studies have shown that central administration of oxytocin to pairs of rats increases the duration of physical contact with each other (Witt, Winslow, & Insel, 1992), whereas administration of an oxytocin receptor antagonist in male rats is associated with reduced social exploration of a con-specific male rat (Lukas et al., 2011). Similarly, male knockout mice who lack oxytocin receptors in the forebrain do not discriminate between familiar and novel females, and spend significantly less time investigating new females.
they have met for the first time, compared to normal mice (Macbeth, Lee, Edds, & Young, 2009).

In humans, intranasal delivery of oxytocin appears to promote pro-social behaviors such as in-group favoritism (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011), trust and cooperation (De Dreu, 2012b; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), empathy (Hurlemann et al., 2010), and emotion recognition (Schulze et al., 2011). Intranasal oxytocin also appears to have anxiolytic properties, as it buffers responses to social stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), dampens amygdala activity to emotional stimuli (Domes et al., 2007), and reduces cortisol levels during couple conflict (Ditzen et al., 2009). However, recent research has shed light on the context-dependent and divergent effects of oxytocin, and suggests that its effects may depend on certain individual difference factors such as sex, hormonal status, attachment orientation, and psychiatric status (for a review, see MacDonald, 2013). Such research indicates that under certain conditions, oxytocin may even exert anxiogenic effects. Evidence from studies examining the effect of intranasal oxytocin in various clinical populations also reflects this mixed picture (Bartz et al., 2011). Nevertheless, intranasal oxytocin is a promising agent and has major treatment implications for psychiatric disorders involving deficits in social functioning such as autism, schizophrenia, borderline personality disorder, and social anxiety disorder. In particular, oxytocin may represent a candidate endophenotype for social anxiety disorder, as it may serve as a biological indicator associated with stable behavioral phenotypes that confer risk for social anxiety disorder (e.g., behavioral inhibition, abnormalities in
information processing such as attentional biases to social threat information). Oxytocin may also serve as a cognitive enhancer for psychological treatments (e.g., cognitive-behavioral therapy) that rely on specific learning processes, such as fear extinction and memory consolidation. Further research is needed to better understand oxytocin’s mechanisms of action and the conditions under which it demonstrates beneficial effects.

Toward this end, the current project aimed to investigate the pro-social effects of oxytocin in individuals with social anxiety disorder, particularly in the context of social rejection and attentional processing of social stimuli. Intranasal oxytocin has the potential of serving as a novel treatment strategy for social anxiety disorder. The current research reflects an innovative translational approach to examining core patterns of psychopathology underlying social anxiety disorder, which may inform potential mediators of symptom severity, and thereby ultimately elucidate mechanisms to target in treatment intervention. Given recent research highlighting the benefits of psychopharmacological agents in facilitating change in psychopathology (Hofmann, Smits, Asnaani, Gutner, & Otto, 2011; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011), this project aimed to significantly advance knowledge regarding the proposed benefit of a promising agent.

*Oxytocin Studies in Healthy Samples*

**Effects on pro-social behavior.** A seminal study by Kosfeld and colleagues (2005) examined the effect of a single administration of 24 international units (IU) of an oxytocin nasal spray (or placebo) on monetary transfers in a social trust game and a non-
social risk game. The sample consisted of 194 healthy adult males (mean age = 22 years), who had no medical or psychiatric illnesses and were medication-free. Participants were randomly assigned the role of “Investors” or “Trustees.” During the trust game, Investors were given an initial endowment of 12 monetary units, and were then asked to provide a transfer to a Trustee in the amount of 0, 4, 8, or 12 monetary units, which the experimenter tripled. The Trustee was then asked to provide a back transfer amount ranging between 0 to 48 monetary units. Investors who were given oxytocin transferred significantly more money to Trustees, compared to Investors who were given placebo, despite the risk of Trustees not returning any proceeds of the transfer. During a risk game that served as a non-social control condition, which involved a random mechanism to generate back transfer amounts to the Investor, there was no effect of oxytocin. This suggests that oxytocin’s effects may be specific to social interactions.

While the results of this study provided compelling evidence for the “pro-trust” effects of oxytocin, they highlighted several methodological issues germane to the study as well as the oxytocin literature more broadly. Aside from the question of whether results would generalize to women, older adults, children, or those with psychiatric illnesses, one major issue is the ecological validity of the experimental paradigm, and whether it captures the motivational aspects underlying real social interactions. For example, these results may not be generalizable to social interactions involving familiar others, where giving low back transfer amounts may impact future interactions. Participants were relatively anonymous in the study, which is often atypical of human interactions. In addition, more social information is typically present in real face-to-face
interactions, which may impact norms to reciprocate. Therefore, further research is needed to elucidate for whom and under what social contexts oxytocin’s pro-social effects may apply.

Indeed, several studies have replicated oxytocin’s effects on trust and cooperation in healthy samples (De Dreu, Greer, Handgraaf, Shalvi, & Van Kleef, 2012; Klackl, Pfundmair, Agroskin, & Jonas, 2013; Mikolajczak et al., 2010). One meta-analysis (Van Ijzendoorn & Bakermans-Kranenburg, 2012) reported that oxytocin’s effects may depend on in-group and out-group categorization, as oxytocin may elevate levels of in-group trust, but may not impact out-group trust. The combined effect size for in-group trust was moderate and significant \((d = 0.48)\), whereas the combined effect size for out-group trust was not significant. These findings provided support for the moderating impact of in-group or out-group status on oxytocin’s effects; however, this meta-analysis was subject to the same methodological issues of the individual studies that comprised it, such as biased samples (largely inclusive of adult males), different dose amounts, and varied designs and task demands. These discrepancies significantly limited the interpretability of the results and prohibited moderator analyses, which sought to examine the impact of sex and type of placebo used.

**Effects on social cognition.** Studies examining the effects of intranasal oxytocin on social cognition largely comprise two broad categories: facial recognition of emotional expressions and attentional orienting toward social information. The same meta-analysis described above (Van Ijzendoorn & Bakermans-Kranenburg, 2012) reported combined effects of oxytocin on emotion recognition and found a significant,
but weak, effect ($d = 0.21$). This is consistent with a more recent meta-analysis, which showed that intranasal oxytocin improved emotion recognition, with a combined Hedges’ $g = 0.29$ (Shahrestani, Kemp, & Guastella, 2013). Using similar inclusion criteria, this meta-analysis included seven randomized controlled trials of intranasal oxytocin with placebo controls, healthy participants (no clinical samples), and only full-face images of basic emotions from validated stimulus sets. All studies used either the 24 IU or 40 IU dose of oxytocin. Oxytocin facilitated the accurate recognition of all basic emotions. It was more beneficial for recognizing anger, happiness, and combined emotions at the automatic, implicit level, and more beneficial for recognizing fear at the explicit, controlled processing level. These findings suggest that a single administration of oxytocin may facilitate the accurate identification of basic human emotions at both automatic and effortful stages of processing. However, the mechanisms underlying this effect remain unclear. Some proposed mechanisms may be an increased salience of social cues (Prehn et al., 2013), increased pupil dilation (Leknes et al., 2012), or faster orienting toward social cues (Ellenbogen, Linnen, Grumet, Cardoso, & Joobber, 2012).

A related aspect of social cognition that has been investigated is whether oxytocin facilitates attentional orienting of social and emotional information (for a review, see Guastella & MacLeod, 2012). Typically, these studies assess the effect of a single administration of oxytocin or placebo on attentional engagement and disengagement from emotional faces by measuring response times to categorize neutral target stimuli, which appear in congruent and incongruent locations as a visual probe. For example, one study examined the effect of intranasal oxytocin on attention shifting to emotional faces using
this type of spatial cueing paradigm (Ellenbogen et al., 2012). Fifty-seven participants (30 females, ages 18-35), who were without any medical or psychiatric illnesses, without sensory impairments, and were non-smokers and non-drug users, took part in the study. After receiving a nasal spray containing either 24 IU of oxytocin or placebo, participants were instructed to respond as quickly as possible when a target stimulus (black dot) appeared in the left or right side of the computer screen. Prior to each target presentation, a cue appeared on either side of the screen, consisting of a picture of a sad, angry, or neutral face (either male or female), which were taken from a validated facial stimulus set (Ekman & Friesen, 1976). A unique aspect of this study was the use of short (17 ms) and long (250 and 750 ms) stimulus exposure latencies to examine the differential impact of oxytocin on automatic and effortful processing.

Investigators found that oxytocin attenuated engagement toward sad faces and facilitated disengagement from sad and angry faces during effortful processing, but did not attenuate engagement toward emotional faces during automatic processing. Interestingly, depression levels significantly moderated oxytocin’s effects during automatic processing, as oxytocin appeared to normalize disengagement patterns for masked angry faces for those with high depression scores. Sex was found to have no significant main or interaction effects.

While these results may not be extrapolated to clinically depressed individuals, they are consistent with previous findings showing that oxytocin enhances the processing of social information, regardless of emotional valence (Gamer, Zurowski, & Büchel, 2010). Where these findings depart from previous studies of attention is that some studies
have found effects of oxytocin specifically on early stages of attention processing (Domes, Sibold, et al., 2013). One explanation for these disparate findings is that studies have employed various study designs, emotional stimuli, and tasks. Nevertheless, these studies reflect a common theme, that oxytocin impacts social information processing by moderating attentional mechanisms. Future research should examine whether oxytocin impacts other cognitive processes, such as memory consolidation or fear learning, as initial research in this area has already begun. For example, researchers discovered that oxytocin impairs extinction training in rats and mice when given prior to extinction training, which suggests that the effects of oxytocin on fear learning may depend on the timing of administration (Toth, Neumann, & Slattery, 2012).

**Anxiolytic and anxiogenic effects.** Oxytocin’s anxiolytic effects have been well-documented in several studies (Bakermans-Kranenburg & Van Ijzendoorn, 2013; Domes et al., 2007; Heinrichs et al., 2003). For example, oxytocin reduces cortisol levels in response to physical stress in a dose-dependent manner (Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013), and modulates social fear-related neural circuitry by dampening amygdala reactivity to emotional faces regardless of valence (Domes et al., 2007). Studies also show that oxytocin’s anxiolytic effects are more pronounced in the context of social stimuli (e.g., faces compared to non-social scenes) (Kirsch et al., 2005). Furthermore, one study examining the effect of oxytocin on responses to a social stress task found that oxytocin had an enhanced buffering effect in the presence of social support (Heinrichs et al., 2003). Subjects were 37 healthy men (mean age = 23.8 years) devoid of chronic diseases, mental disorders, medication, smoking, and drug or alcohol
abuse. They were instructed to attend the experiment either with their best friend (male or female) or alone, and that support providers were to be as helpful as possible during the 10-minute preparation period for the task called the Trier Social Stress Test. After being randomly assigned to receive a 24 IU dose of oxytocin or placebo, participants were introduced to the speech task, in which they were asked to give a 5-minute public speaking task for a job interview, and to perform a 5-minute mental arithmetic task out loud. Salivary cortisol levels were also measured at eight time periods before and after the stress period.

Researchers found that those receiving either social support or oxytocin, or both, showed increasing subjective feelings of calmness and decreasing anxiety during the stress task. In addition, the lowest cortisol concentrations during stress were found for subjects who received both oxytocin and social support. These findings suggest that oxytocin enhances the protective properties of social support during psychosocial stress. Given that those subjects who received both social support and oxytocin showed the strongest anxiolytic effects, these findings generate a new hypothesis that a dysregulated oxytocin system may impair or lessen the stress-buffering effect of social support, particularly in those with psychological disorders involving deficits in social functioning.

Results from this study contrast with contradictory findings showing anxiogenic effects of oxytocin in healthy adults. For example, one study found that oxytocin increased anxiety in response to unpredictable threat (Grillon et al., 2013). Subjects (43 healthy men and women) received oxytocin, placebo, and a related neuropeptide, vasopressin, on three separate sessions, and completed a startle paradigm involving
predictable and unpredictable shocks. Defensive responses, as measured by startle response magnitude, were significantly increased by oxytocin, compared to the other drug conditions, and only in response to unpredictable shocks. The authors concluded that these anxiogenic effects may explain why oxytocin impacts responses to in-group and out-group members differently, as out-group members may be perceived as more unpredictable. However, the generalization of these findings to the social domain may be questionable, given that the paradigm used in this study may not reflect the complex emotional, biological, and psychological processes inherent to social interactions. Rather, what it may show is that oxytocin can have anxiogenic effects, particularly under conditions of uncertainty. Further research is needed to elucidate these mixed findings showing both anxiolytic and anxiogenic effects of oxytocin, perhaps by exploring the moderating effects of individual difference factors and employing within-group designs.

Oxytocin Studies in Clinical Samples

Effect on pro-social behavior and social cognition. The available literature on oxytocin in clinical samples is relatively lacking, and reflects the mixed findings that have been found in healthy samples. On the one hand, evidence has shown that oxytocin may normalize dysfunctional social cognitive processes in individuals with high-functioning autism (Andari et al., 2010), schizophrenia (Averbeck, Bobin, Evans, & Shergill, 2011), and social anxiety disorder (Labuschagne et al., 2010). In contrast, studies have found no effects of oxytocin on emotion recognition (Davis et al., 2013), as well as hindering effects of oxytocin (Bartz et al., 2011; MacDonald et al., 2013), in
clinical populations. As in the healthy human literature, methodological differences in
study design, dose amount, dose frequency, and timing of oxytocin administration may
explain these contradictory findings. In addition, an emerging line of research suggests
that mixed findings can be partially attributed to individual difference factors, such as
sex, hormonal status, attachment orientation, and psychiatric status, which have not been
systematically measured or controlled in previous studies.

An influential study by Bartz and colleagues (2011) tested the hypothesis that
intranasal oxytocin may not universally improve trust and cooperative behavior. The
investigators examined the comparative effects of oxytocin in 14 individuals with
borderline personality disorder (BPD) and 13 healthy adults (mean age = 35 years).
Healthy controls had no Axis I or II psychiatric comorbidities, and individuals with BPD
were excluded if they had any current substance use disorders, major depression, eating
disorders, schizophrenia, bipolar, or mental retardation. Subjects were not taking
psychotropic or other medications for at least two weeks before the study began (five
weeks for fluoxetine). After being randomly assigned to receive an oxytocin (40 IU) or
placebo nasal spray, subjects were briefly introduced to a partner (confederate) for the
Assurance Game, which is a variation of the Prisoner’s Dilemma. In this variation, the
highest payoff ($6) for both players occurs when they mutually cooperate. If both players
defect, they each would win $2, and if only one player defects, that individual would win
$4 and the other would win $0. Researchers found that BPD participants expected their
partners to be significantly less cooperative after receiving oxytocin, compared to
placebo, and were more likely to defect during a hypothetical scenario in which their
partner cooperated. In contrast, healthy participants showed reverse effects in which oxytocin facilitated trust. Effects of age or sex were not reported in this study.

When collapsing across diagnostic categories, further analyses revealed that these outcomes were moderated by attachment orientation, as oxytocin resulted in less trusting expectations for anxiously attached participants, but had no effect for those who were low in anxious attachment. Interestingly, oxytocin enhanced actual cooperation for high anxious/low avoidant participants, but decreased cooperation for high anxious/high avoidant participants. Whereas attachment anxiety refers to anxiety about rejection and abandonment by others, attachment avoidance refers to discomfort with closeness and intimacy (Brennan, Clark, & Shaver, 1998). These findings are consistent with another study documenting oxytocin’s anxiogenic effects in patients with major depressive disorder, especially in contexts involving an unfamiliar other, which suggest that the presence of psychiatric illness may moderate the divergent effects of oxytocin (MacDonald et al., 2013).

**Effect on psychiatric symptoms.** A recent meta-analysis (Bakermans-Kranenburg & Van Ijzendoorn, 2013) examining the effect of intranasal oxytocin across various clinical populations, including autism, social anxiety, depression, obsessive-compulsive disorder, schizophrenia, borderline personality disorder, and posttraumatic stress disorder, found a small to moderate effect size ($d = .32$) on psychiatric symptomatology and social competence indicators. However, the results should be interpreted cautiously, given the heterogeneity of the samples, dose amounts, and dose frequencies included in the study. For example, it remains unclear how acute versus chronic administration of
intranasal oxytocin affects psychiatric outcomes. Available studies show mixed evidence for chronic administrations of oxytocin, even within the same disorder (Dadds, MacDonald, et al., 2013; Tachibana et al., 2013).

**Oxytocin and Social Anxiety Disorder**

Although the application of oxytocin is particularly amenable to the study of social anxiety disorder (SAD), this area of research is still in its nascent stages and is extremely limited. SAD is a highly distressing psychological disorder that is characterized by a persistent fear of negative evaluation by others in social or performance situations (American Psychiatric Association, 2013). With a lifetime prevalence of 12.1% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005), SAD is the most common anxiety disorder in the U.S., and is associated with significant impairment in occupational, academic, and interpersonal functioning (Hofmann & Otto, 2008; Ruscio et al., 2008). Existing psychological treatments for SAD are efficacious, particularly cognitive-behavioral therapy; however, evidence suggests that there is still room for improvement, as approximately 50% of patients still remain symptomatic following CBT with or without medication treatment (Davidson et al., 2004; Hofmann & Smits, 2008).

The available literature on the use of intranasal oxytocin in SAD patients has provided some insight into potential mechanisms underlying oxytocin’s behavioral effects in this patient population. To date, only three studies have been conducted applying intranasal oxytocin in SAD patients (Guastella, Howard, Dadds, Mitchell, & Carson, 2009; Labuschagne et al., 2010; Labuschagne et al., 2011), and two additional
studies have measured plasma oxytocin levels in patients with SAD (Hoge, Pollack, Kaufman, Zak, & Simon, 2008; Hoge et al., 2012). It appears that greater symptom severity of SAD may actually be associated with greater endogenous levels of plasma oxytocin, as oxytocin may be produced in greater quantities to compensate for dysfunctional oxytocin receptors in patients with social deficits (Hoge et al., 2008). This suggests that SAD patients may have abnormal plasma oxytocin levels compared to healthy individuals (Hoge et al., 2008). Furthermore, recent evidence suggests the presence of an altered pattern of oxytocin levels in patients with SAD, as they were found to have lower levels of plasma oxytocin after a Trust Game, compared to healthy controls, after controlling for sex and estradiol levels (Hoge et al., 2012). It remains unclear how intranasal versus systemic administration of neuropeptides differentially impacts uptake in the cerebrospinal fluid (CSF) and bloodstream, although some evidence suggests that intranasal delivery of neuropeptides may occur without uptake into the blood (Born et al., 2002). Nevertheless, studies examining plasma oxytocin may provide relatively weak evidence for the role of oxytocin in SAD, as peripheral levels of oxytocin may not be correlated with central release (Meyer-Lindenberg et al., 2011).

Among studies that have administered intranasal oxytocin to SAD patients, one study examined the effect of administering oxytocin as an adjunct to exposure therapy for SAD and found that patients treated with oxytocin showed greater improvements in their ratings of speech performance and speech appearance, compared to patients treated with placebo, although there were no differences between groups on SAD symptom outcomes following treatment (Guastella et al., 2009). Another study demonstrated that intranasal
oxytocin attenuated amygdala reactivity to fearful faces in patients with generalized SAD using an emotional face matching paradigm with fearful, angry, and happy faces (Labuschagne et al., 2010). A more recent finding from the same research group showed that intranasal oxytocin attenuated cortical hyperactivity in the medial prefrontal cortex to sad faces (a non-threatening negative social cue) in patients with generalized SAD to a level similar to that of controls (Labuschagne et al., 2011). Taken together, these studies are consistent with previous research in healthy individuals showing pro-social effects of oxytocin in humans, and suggest that oxytocin’s dampening effects on fear-related neural circuitry may potentially mediate treatment outcomes for SAD patients.

More specific to the current study, oxytocin’s perceptual and behavioral effects have direct implications for buffering responses to social rejection and reducing the fear of or sensitivity to social rejection in SAD patients. Indeed, the fear of social rejection represents a core construct involved in the psychopathology of SAD. Cognitive models of SAD propose that the fear of social rejection is associated with cognitive biases, such as hypervigilance to social threat and a tendency to interpret and anticipate rejection from others (Clark & Wells, 1995; Hofmann, 2007; Rapee & Heimberg, 1997). Individuals with SAD may process information in such a way as to confirm their fear of being negatively evaluated or being rejected, which may contribute to the reinforcement of beliefs (e.g., “I have to make a good impression”), as well as behaviors (e.g., avoidance of social situations) that maintain the disorder. Accordingly, understanding the factors that impact the processing of social rejection in SAD may represent a particularly important research area that can inform and improve existing treatments for SAD.
Rationale for Current Study

The current study aimed to investigate whether oxytocin modulates responses to social rejection in patients with SAD. A widely-used paradigm in the study of social ostracism and rejection is called the Cyberball Task (Williams, Cheung, & Choi, 2000; Williams & Jarvis, 2006), which is a virtual ball-tossing game that can be used both as a manipulation of rejection and as a measure of social behavior (e.g., ball-tossing behavior). In Cyberball, participants are led to believe that they are playing the game with other online players in real time. Ostracism is induced when the players deny ball tosses to the participant.

One study examined the effect of oxytocin on responses to rejection in healthy individuals using Cyberball (Alvares, Hickie, & Guastella, 2010). Participants were randomly assigned to receive either oxytocin or placebo, and were then randomized again to be either included or ostracized during Cyberball. Alvares and colleagues (2010) found that oxytocin promoted a greater willingness to re-engage socially with the other players when they were included in the game, but not when they were ostracized. As oxytocin may increase trust of in-group members (Van Ijzendoorn & Bakermans-Kranenburg, 2012), a potential explanation for this finding is that oxytocin’s effects were moderated by the categorization of others into social in-groups and out-groups.

The current study aimed to explore this in-group hypothesis by examining the effect of oxytocin when a cooperative player switches to less cooperative play. According to studies demonstrating oxytocin’s parochial effects on cooperation, that is, oxytocin enhances in-group, rather than out-group, cooperation (for a review, see De Dreu, 2012a),
it was expected that oxytocin-treated participants would continue to engage with the cooperative player even after the switch, compared to placebo-treated participants, who would adapt their behavior to toss fewer balls to this player after the switch (*Hypothesis 1*).

It was also expected that oxytocin-treated participants would provide greater ratings of trust toward the cooperative player, compared to placebo-treated participants (*Hypothesis 2*). A previous study investigating the effect of oxytocin on ball-tossing behavior during Cyberball in patients with high-functioning autism spectrum disorders found that patients who were given placebo did not discriminate between different play patterns of other players, who were programmed to display cooperative, uncooperative, and neutral playing profiles (Andari et al., 2010). In contrast, patients who were given oxytocin showed normalized and socially appropriate ball-tossing behavior that was more similar to that of healthy individuals. Given that the current study used a similar modification of Cyberball, it was hypothesized that the cooperative player would be particularly favored after receiving oxytocin compared to placebo.

Furthermore, the current study aimed to investigate the effect of oxytocin on attentional engagement toward and disengagement from social threat cues. Previous research using spatial cueing paradigms such as the Posner Task has shown that patients with SAD have maladaptive attentional biases toward social threat cues, and may have difficulty disengaging from them, which may constitute a cognitive factor that maintains the disorder (Amir, Elias, Klumpp, & Przeworski, 2003; Mogg & Bradley, 2002). It was expected that oxytocin would facilitate disengagement from social threat cues (emotional
faces) versus social non-threat cues (neutral faces), when compared to placebo
(Hypothesis 3). Investigating the effect of oxytocin on attentional processes would reveal
a potential mechanism by which oxytocin exerts pro-social effects in patients with SAD.

Methods and Materials

Participants
Sixty adult male participants consented for the study. All participants met inclusion and
exclusion criteria. Specifically, participants were males at least 18 years of age or older,
with a principal or co-principal diagnosis of SAD, and had a current LSAS score of ≥ 60.
Females were excluded from the study due to complications associated with the use of
oxytocin in pregnancy, as well as potential fluctuations of oxytocin during menstrual
phases. No participants had significant nasal pathology (e.g., atrophic rhinitis, recurrent
nose bleeds, history of hypophysectomy), were smokers who smoked more than 15
cigarettes per day, had a serious medical illness, had active suicidal or homicidal ideation,
had a current diagnosis of schizophrenia, psychotic disorder, bipolar disorder, or
substance abuse/dependence, and no participants were concurrently taking psychotropic
medications, except for antidepressants that had been taken at a stable dose for at least
two weeks prior to study entry. Participants received $40 in compensation for their
participation in the study, and additional earnings from the Cyberball Task. The study
was approved by the Boston University Medical Center Institutional Review Board and
was registered with the National Institutes of Health ClinicalTrials.gov Registry
(NCT01856530).
Measures

Mini Adult Diagnostic Interview Schedule for DSM-IV (Mini-ADIS-IV; DiNardo, Brown, & Barlow, 1994): The Mini-ADIS-IV is a brief clinician-administered, semi-structured interview that assesses current mood and anxiety disorders. It was administered at the beginning of the study visit to assess eligibility for the study.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item semi-structured interview that assesses fear and avoidance of social situations in the past week. It is widely used in treatment studies for SAD. The LSAS has been validated in clinical samples and has high internal consistency ($\alpha = .82-.92$) (Heimberg et al., 1999). The LSAS was used to confirm the SAD severity criterion for inclusion in the study.

Social Interaction and Anxiety Scale (SIAS; Mattick & Clarke, 1998): The SIAS is a 20-item measure that assesses anxiety in social interaction situations. The SIAS has been shown to be a valid measure of social interaction anxiety, and has been demonstrated to have good internal consistency and reliability in samples of patients with SAD (Clark et al., 1997). The SIAS was administered before and after drug administration to assess levels of social interaction anxiety.

Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996): The BDI-II is a widely used self-report measure of severity of depressive symptoms that are congruent with the diagnostic criteria of major depressive disorders in the DSM-IV. The BDI-II was given to assess baseline levels of depressive symptoms.

Interpersonal Sensitivity Measure (IPSM; Boyce & Parker, 1989): The original IPSM is a 36-item self-report measure to assess sensitivity to rejection. The current study
employed a 29-item, modified version for use among SAD patients (Harb, Heimberg, Fresco, Schneier, & Liebowitz, 2002). It has demonstrated good internal consistency, as well as convergent validity with other self-report measures of social anxiety. The IPSM was given to examine baseline levels of rejection sensitivity.

*Experience in Close Relationships Inventory* (ECR; Brennan et al., 1998): The ECR is a 36-item self-report questionnaire that measures attachment anxiety and avoidance in adults. It yields two subscales reflecting attachment anxiety (anxiety about being rejected or abandoned) and attachment avoidance (discomfort with closeness and intimacy). The ECR was administered at baseline to assess participants’ general attachment styles in close relationships. In the current study, the two subscales were not significantly correlated, $r = -.32, n = 25, p = .12$.

*Positive and Negative Affect Scales* (PANAS; Watson, Clark, & Tellegen, 1988): The PANAS is a 20-item self-report measure of positive and negative affect, which was administered before and after drug administration to examine state changes in mood.

*Trust, Preference, Empathy, Perceived Rejection, and Willingness to Re-Engage Ratings*: Participants were asked to provide ratings on a 7-point Likert scale on trust, preference, empathy, perceived rejection, and willingness to re-engage in another round of Cyberball for each of the other players in the game. This questionnaire was completed immediately following the Cyberball Task.

*Adverse Events Form*: Participants were asked to report whether they experienced a negative reaction to the oxytocin and placebo nasal sprays (yes or no), and if so, to describe the nature of the negative reactions. In the current study, no participants
endorsed serious adverse events. The adverse events form was completed immediately following the Cyberball Task.

Assessment of Blind Questionnaire: Participants were asked which condition they believe they were randomized to (oxytocin or placebo), to rate their degree of certainty, and to describe their reasons why.

Drug

Investigational new drug information. Oxytocin is currently approved by the Food and Drug Administration (FDA) in an intravenous form for the purpose of facilitating childbirth. The approved dosage is approximately .5-1 mU/min, which can be increased to 1-2 mU/min until the desired contraction pattern has been reached. Synthetic oxytocin (e.g., Syntocinon® or Pitocin®) is typically administered intravenously in neonatal settings to induce labor. It is widely distributed throughout the extracellular fluid and causes uterine response almost immediately. Its removal from the blood is facilitated by the kidney and liver, and has a plasma half-life of approximately 1 to 6 minutes (per Pitocin® package insert). Intranasal delivery of oxytocin enables actions within the brain and produces pro-social behavioral effects in humans. Although the duration of action of oxytocin in the central nervous system is unclear, data from a closely-related neuropeptide, vasopressin, indicate that elevated CSF levels occur within 10 minutes to an hour, and that its duration of action may last anywhere between two to eight hours (Born et al., 2002). Oxytocin, however, is not approved for use in patients with SAD, and a nasal form of the drug is not approved. In this study, the purpose, dose, and manner of
administration of oxytocin are considered experimental. The current study has been allowed to proceed under Investigational New Drug Application (IND) #113,827.

*Oxytocin dose and route of administration.* The oxytocin and placebo nasal sprays used in the current investigation consisted of 24 IU of oxytocin, and were dispensed in metered-dose spray bottles to deliver exactly 4 IU per spray. The placebo sprays were identical to the oxytocin nasal sprays, except for the addition of 0.65% sodium chloride to the placebo nasal spray, which helped to minimize nasal irritation to the participant. The 24 IU dose was selected for the study, as this reflects the most commonly used intranasal dose in previous human trials (25 out of 38 studies) (MacDonald et al., 2011).

**Tasks**

*Cyberball Task (Williams et al., 2000; Williams & Jarvis, 2006).* Cyberball is a four-person computerized ball-tossing game, which was designed to manipulate ostracism. Participants are led to believe that they are playing with three “others” in real time. The program was modified to create three different behavioral profiles for the fictitious others. For the first 80 trials (*Play Condition*), Player 1 was programmed to toss on average 70% of his balls to the participant, whereas Player 4 tossed 30%, and Player 3 tossed only 10% of them, to the participant. The participant was always Player 2. Each trial consisted of a single ball toss exchange, which was represented by a short animation of one player tossing the ball and another player catching the ball. The participant had the choice to toss the ball to a player when he received the ball from a previous trial. Participants were told that the purpose of the game was to obtain as many points as
possible, which would be converted to real monetary rewards at the end of the task. They were informed that they would receive 20 points ($0.20) each time a ball was tossed to them, and lose 10 points ($0.10) each time the ball was tossed to someone else. After 80 trials, the behavioral profiles switched (Switch Condition), such that Player 1 was programmed to toss only 10% of his played balls to the participant. After the switch, the participant played Cyberball for another 80 trials. The decision time for the fictitious players was varied from trial to trial to enhance the believability of realistic play behavior. The participant was represented by a fourth cartoon on the computer screen taken from a first person perspective. The display also provided ongoing feedback for the participant’s total points throughout the game. Ratings of trust, empathy, preference, perceived rejection, and willingness to re-engage in another game of Cyberball with each player, were measured on a 7-point Likert scale at the end of the task. The entire task consisted of 160 trials in total and took approximately eight minutes to complete.

*Modified Posner Task (Posner, 1980; Posner, Snyder, & Davidson, 1980).* The Posner Task measures attentional engagement toward and disengagement from social threat cues. The stimuli for this task were modified to include a set of disgust, happy, and neutral faces. The task consisted of 360 trials. During each trial, the participant saw a fixation cross. On each trial, a face (disgust, happy, or neutral) appeared within either the top or bottom half of the screen (the other half of the screen would remain blank) and then disappeared. Then, a probe (the letter “E” or “F”) appeared in the top or bottom half of the screen. The participant was instructed to identify the letter as quickly and accurately as possible by clicking the left or right mouse button (left for “E”, right for
“F”). Upon responding, the next trial commenced. For valid trials, the probe appeared in the position previously occupied by the face stimulus, whereas for invalid trials, the probe appeared in the empty half of the screen. Reaction times to valid and invalid trials reflected the participant’s attentional engagement towards threat and disengagement from threat, respectively. The entire task took 10 minutes to complete.

**Procedure**

Participants were recruited from the community using approved print and online advertisements, as well as from the clinic waitlist at the Center for Anxiety and Related Disorders. Potential participants were phone screened to ensure they met basic eligibility requirements for the study, and were asked not to have caffeine, alcohol, or nicotine for 24 hours prior to the study appointment. Participants were then scheduled for a single visit lasting approximately four hours.

During the study visit, participants first gave written informed consent and were assessed for eligibility through a diagnostic evaluation and medical screen. The diagnostic evaluation consisted of administration of the Mini-ADIS-IV, which was used to confirm diagnostic eligibility. Participants then met with the study physician to complete the medical screen, which consisted of assessing concurrent psychotropic medications, significant nasal pathology, as well as measuring vitals (e.g., blood pressure, pulse). Participants were then asked to complete a set of self-report questionnaires to collect demographic information, as well as to assess baseline levels of depression, social anxiety, attachment orientation, rejection sensitivity, and subjective mood.
Next, participants were randomly assigned to receive a nasal spray containing either oxytocin or placebo using a computer-generated pre-randomization sheet. The study was double-blind, such that neither the study physician nor the experimenter were aware of participants’ assigned drug condition. Using a standardized protocol, participants self-administered a metered-dose nasal spray with three puffs per nostril (4 IU of oxytocin or placebo per puff) in the presence of the study physician or nurse. After nasal spray administration, participants’ vitals were measured again.

Participants were then asked to sit in an isolated waiting room for 45 minutes before starting the computer tasks, as this reflects a standard wait period following intranasal oxytocin administration. After 45 minutes, participants were led to a common waiting area for the study, where they were told that they would have an opportunity to briefly meet three other study participants for the first task. The experimenter led the participant and three male confederates individually into the waiting area, and asked each participant to introduce their first name to the group. At this time, participants were individually led to their separate experimental rooms.

Participants played Cyberball first, and then completed the post-Cyberball questionnaires, as well as other self-report questionnaires, which assessed potential adverse events related to the drug and their beliefs about their assigned drug condition. Participants then completed the modified Posner Task. The experiment concluded with a debriefing session.
Statistical Analyses

*Primary analyses.* First, to address *Hypotheses 1-3*, a series of mixed between-within analyses of variance (ANOVAs) were conducted to examine group effects on social outcomes during Cyberball, and attentional outcomes during the Posner Task. Specifically, Cyberball outcomes included: 1) number of balls thrown to Player 1 during the *Play* and *Switch* conditions, 2 (Group: oxytocin, placebo) x 2 (Time: balls tossed to Player 1 during *Play* and *Switch* conditions), 2) the number of balls thrown to each of the other players during the *Play* condition, 2 (Group: oxytocin, placebo) x 3 (Player: balls tossed to Player 1, 3, and 4), and 3) overall trust and rejection ratings for each of the players, 2 (Group: oxytocin, placebo) x 3 Player (trust and rejection ratings for Player 1, 3, and 4). On the Posner Task, faster response latencies when detecting validly cued targets following disgust faces indicated an attentional “engagement” or bias toward threat-relevant information. Slower response latencies when detecting invalidly cued targets following disgust faces indicated difficulty disengaging attention away from threat-relevant information. To examine the effect of oxytocin on attentional engagement and disengagement by face type, a mixed 2 (Group: oxytocin, placebo) x 2 (Cue Type: valid, invalid) x 3 (Face Type: disgust, neutral, happy) ANOVA was conducted with repeated measurement on the last two factors. To examine group differences on demographic characteristics and baseline clinical measures, *t*-tests were conducted for continuous variables and chi-square tests were conducted for categorical variables. Given that there were no significant differences in age and social anxiety symptom severity between groups, and that inclusion of covariates would significantly reduce test power,
we did not control for covariates in the analyses. Thus, covariates were not included in the reported analyses moving forward.

*Secondary analyses.* A regression approach was adopted to explore the interactions between drug and continuous moderators (rejection sensitivity, attachment anxiety, and attachment avoidance) on Cyberball outcomes (ball-tossing behavior, ratings of trust and rejection), as well as outcomes during the Posner Task (attentional engagement and disengagement scores for each face type and cue type). Hierarchical regression analyses were conducted on all participants in the sample to examine the effects of drug group (dummy coded: 1 = oxytocin and 0 = placebo), and mean-centered rejection sensitivity (entered in step 1), and their two-way interaction (entered as a product term in step 2), on each outcome. The regressions were then repeated to examine the effects of drug group (dummy coded: 1 = oxytocin and 0 = placebo), and mean-centered attachment anxiety and attachment avoidance (entered in step 1), and their two- and three-way interactions (entered as product terms in steps 2 and 3, respectively) on the same outcomes. Regression analyses were followed up by generating predicted values based on each regression equation and plotting XY graphs to examine the nature of the interaction.

*Manipulation check.* A separate analysis was conducted to ensure that Cyberball successfully manipulated different player profiles by examining whether participants discriminated between the behavioral profiles. Participants’ perceptions of each player’s behavior during the *Play* and *Switch* conditions were measured on a 4-point Likert scale (e.g., “For Player 1, how much did he play with you at first?”). A repeated measures
ANOVA was conducted for each half of the game with ratings of each player’s behavior as the within-subjects factor.

Results

Demographic Characteristics

Six participants were excluded due to being ineligible for the study (three did not have SAD, two met criteria for substance dependence, and one had a principal diagnosis of posttraumatic stress disorder). The final sample included 54 participants (age range = 18-45 years). Two participants did not complete the Cyberball Task due to technical difficulties. This sample size was selected to allow adequate power (β = .80) to detect a medium effect size (f = .25) at an alpha level of .05. Chi-square and t-tests showed no differences between groups in demographic or baseline clinical characteristics (all p’s > .05) (See Table 1). The most common comorbid diagnosis was major depression (18.5%), followed by generalized anxiety disorder (16.7%), and panic disorder with agoraphobia (7.4%).

Primary Analyses

Effect on cooperation. Oxytocin, relative to placebo, did not lead to continued cooperation with Player 1 across the two conditions during the game, as there was no significant Group x Time interaction, Wilks’ Lambda = 1.00, F(1,50) = .02, p = .88, ηp² = .00 (Hypothesis 1). Both groups showed a reduction in ball tosses to Player 1 during the game, Wilks’ Lambda = .66, F(1,50) = 26.37, p < .001, ηp² = .34, but this did not differ
by group, $F(1,50) = .70$, $p = .41$, $\eta^2_p = .01$. In addition, oxytocin, relative to placebo, was not significantly associated with more throws to Player 1 during the Play condition, compared to other players, as there was no significant Group x Player interaction, Wilks’ Lambda = .99, $F(2,49) = .24$, $p = .78$, $\eta^2_p = .01$. Both groups threw significantly more balls to Player 1, compared to other players, Wilks’ Lambda = .47, $F(2,49) = 27.32$, $p < .001$, $\eta^2_p = .53$, but this did not differ by group, $F(1,50) = .32$, $p = .57$, $\eta^2_p = .01$.

**Effect on perceived trust and rejection.** Oxytocin, relative to placebo, did not significantly impact trust ratings for Player 1, compared to other players, Wilks’ Lambda = .98, $F(2,47) = .44$, $p = .64$, $\eta^2_p = .02$ (Hypothesis 2). In addition, oxytocin, relative to placebo, did not significantly impact perceived rejection ratings from Player 1, compared to other players, Wilks’ Lambda = .99, $F(2,47) = .27$, $p = .77$, $\eta^2_p = .01$. However, those who received oxytocin reported lower ratings of overall rejection from all players during Cyberball, relative to those who received placebo, $F(1,48) = 3.98$, $p = .05$, $\eta^2_p = .08$.

**Manipulation check.** It was determined whether Cyberball successfully manipulated different behavioral profiles for the other players during the Play and Switch conditions of the game. Nine (17.3%) out of 52 participants who completed Cyberball reported that they did not notice a change in any player’s behavior during the game. However, of those who did notice a change, participants reported that Player 1 played the most with them at first, Wilks’ Lambda = .66, $F(2,44) = 11.15$, $p < .001$, $\eta^2_p = .34$, and that there was no significant difference between the other players’ behavior later on during the Switch condition of the game, Wilks’ Lambda = .95, $F(2,44) = 1.28$, $p = .29$, $\eta^2_p = .06$. This suggests that the manipulation was successful, as participants
discriminated that Player 1 played with them the most initially, and that this was no longer true later on.

**Effect on attentional engagement and disengagement of social cues.** First, response times for inaccurate trials were eliminated. Inaccurate trials consisted of trials where the probe was the letter “E” and the participant pressed the right mouse button or vice versa. This resulted in elimination of 2% of the trials. Response latencies less than 360 ms and greater than 2200 ms were considered outliers and eliminated from the analysis. Idiographic standardization of response times was then conducted, and response latencies from trials reflecting two standard deviations above or below an individual’s personal mean were eliminated from the analysis, which resulted in elimination of 4% of the trials. Finally, for each participant, a mean response time was calculated for each face type and cue condition (See Table 4).

Oxytocin, relative to placebo, was not associated with facilitated attentional engagement or disengagement scores for any face type, as there was no significant interaction of Group x Cue Type x Face Type, Wilks’ Lambda = .93, $F(2,50) = .44, p = .65$ (Hypothesis 3). We then conducted separate Group x Cue Type analyses for each face type, and found no significant interactions: disgust faces, Wilks’ Lambda = 1.00, $F(1,51) = .15, p = .70$; happy faces, Wilks’ Lambda = 1.00, $F(1,51) = .09, p = .77$; and, neutral faces, Wilks’ Lambda = .99, $F(1,51) = .70, p = .41$. There were no other significant main effects.
Secondary Analyses

Effect on cooperation. Regression analyses revealed a significant Group x Attachment Avoidance interaction on difference scores in balls tossed to Player 1 during Cyberball, $B = 6.90$, $t(19) = 2.11$, $p = .05$. The attachment interaction terms contributed to the overall model by explaining an additional 19.9% of the variance in ball tosses, $F$ change $(2, 19) = 2.72$, $p = .09$. Among participants with low Attachment Avoidance, oxytocin resulted in smaller difference scores in the number of balls tossed to Player 1 between the Play and Switch conditions compared to placebo, which suggested greater cooperation with Player 1 (Figure 1). Among participants with high Attachment Avoidance, oxytocin resulted in greater difference scores across the Cyberball conditions compared to placebo, which suggested decreased cooperation with Player 1. There was no significant Group x Attachment Anxiety interaction on difference scores in balls tossed to Player 1, $B = -0.91$, $t(19) = -0.32$, $p = .75$, as well as no significant Group x Rejection Sensitivity interaction on difference scores in balls tossed to Player 1, $B = .30$, $t(42) = 1.23$, $p = .23$.

Effect on perceived trust and rejection. Regression analyses showed a significant Group x Rejection Sensitivity interaction on overall ratings of perceived rejection from other players during Cyberball, $B = .07$, $t(42) = 2.44$, $p = .02$. The interaction effect explained a significant portion of variance in rejection ratings, $R^2$ change = .12, $F$ change $(1, 42) = 5.97$, $p = .02$. Among participants with high Rejection Sensitivity, oxytocin resulted in greater overall perceived rejection from the other players, compared to placebo (Figure 2). In contrast, among those with low Rejection Sensitivity, oxytocin
resulted in lower levels of overall perceived rejection from other players, compared to placebo. There was no significant Group x Rejection Sensitivity interaction on trust, $B = -.01$, $t(42) = -.16$, $p = .87$. There was also no significant Group x Attachment Anxiety interaction on trust, $B = -.004$, $t(19) = -.02$, $p = .99$, or rejection, $B = .37$, $t(19) = .84$, $p = .41$, and no significant Group x Attachment Avoidance interaction on trust, $B = .08$, $t(19) = .26$, $p = .80$, or rejection, $B = .41$, $t(19) = .82$, $p = .42$.

*Effect on attentional engagement and disengagement of social cues.* Regression analyses showed a significant Group x Attachment Avoidance interaction on engagement scores for disgust faces, $B = -106.12$, $t(18) = -2.34$, $p = .03$, and neutral faces, $B = -102.47$, $t(18) = -2.07$, $p = .05$, but not for happy faces, $B = -81.30$, $t(18) = -1.52$, $p = .15$. When given oxytocin, individuals with high Attachment Avoidance responded faster to validly cued disgust faces and neutral faces, whereas individuals with low Attachment Avoidance took longer to respond (*Figure 4*). For disengagement scores, there was a trend toward a group difference for the Group x Attachment Avoidance interaction for all face types: disgust faces, $B = -106.87$, $t(19) = -1.98$, $p = .06$; neutral faces, $B = -99.14$, $t(19) = -1.82$, $p = .09$; and, happy faces, $B = -93.32$, $t(19) = -2.03$, $p = .06$. When given oxytocin, individuals with high Attachment Avoidance responded faster to invalidly cued disgust, neutral, and happy faces, whereas individuals with low Attachment Avoidance took longer to respond. Although the product terms explained an additional portion of variance in engagement and disengagement scores, none of the changes in $R^2$ were significant, all $p$’s $> .05$. There was no significant Group x Attachment Anxiety interaction on engagement scores for disgust faces, $B = -56.84$, $t(18) = -1.46$, $p = .16$,
neutral faces, $B = -35.58$, $t(18) = -.81$, $p = .43$, or happy faces, $B = -2.66$, $t(18) = -.06$, $p = .96$. There was also no significant Group x Attachment Anxiety interaction on disengagement scores for disgust faces, $B = -16.62$, $t(19) = -.36$, $p = .73$, neutral faces, $B = -25.18$, $t(19) = -.53$, $p = .60$, or happy faces, $B = -28.64$, $t(19) = -.72$, $p = .48$.

Furthermore, although regression analyses showed no significant interactions between Group x Rejection Sensitivity on engagement and disengagement scores for any face type (all $p$’s > .05), there was a significant effect of Rejection Sensitivity on disengagement from happy faces, $B = 4.69$, $t(47) = 2.00$, $p = .05$, suggesting that greater rejection sensitivity was associated with longer response latencies for invalid trials involving happy faces.

**Self-Reported Mood and Social Interaction Anxiety**

Oxytocin did not significantly reduce self-reported negative mood, positive mood, or social interaction anxiety, as all of these interaction effects were non-significant (negative mood: Wilks’ Lambda = 1.00, $F(1,50) = .23$, $p = .63$, $\eta_p^2 = .01$; positive mood: Wilks’ Lambda = .99, $F(1,51) = .57$, $p = .45$, $\eta_p^2 = .01$; social interaction anxiety: Wilks’ Lambda = 1.00, $F(1,23) = .01$, $p = .91$, $\eta_p^2 = .001$). Interestingly, both groups showed improved positive mood during Cyberball, Wilks’ Lambda = .84, $F(1,51) = 9.61$, $p = .003$, $\eta_p^2 = .16$, but this did not differ by group, $F(1,51) = .74$, $p = .39$, $\eta_p^2 = .01$. 
Discussion

The current study investigated the effect of a single administration of oxytocin on pro-social outcomes among individuals with SAD. Specifically, the current study assessed how oxytocin impacted cooperative behavior during an online ball-tossing game, and whether oxytocin modulated attentional processes involving social threat cues.

**Hypotheses 1 and 2.** During Cyberball, Hypotheses 1 and 2 were partially supported. It was hypothesized that compared to placebo, oxytocin would contribute to continued cooperation with Player 1, even after the switch in his behavior. There were two main findings with respect to these hypotheses. First, oxytocin- and placebo-treated participants did not differ significantly in terms of balls thrown to Player 1 during the **Play** condition, nor in terms of trust ratings for Player 1. However, oxytocin was associated with greater cooperation with Player 1 after the switch, for participants who were low in attachment avoidance. Conversely, oxytocin was associated with less cooperation with Player 1 after the switch for participants who were high in attachment avoidance. Second, participants who were given oxytocin reported less rejection from other players during the game, compared to those who were given placebo, and it appeared that this effect was qualified by a significant interaction effect. Oxytocin led to greater subjective feelings of rejection from players when individuals were highly rejection sensitive, whereas it appeared to protect from feeling rejected for individuals who were low in rejection sensitivity.

There are many possibilities to explain the finding that oxytocin impacted cooperative behavior with Player 1 only for those with low attachment avoidance. First,
mounting research suggests that oxytocin motivates in-group favoritism and parochial cooperation, but not for out-groups (De Dreu, 2012a; Van Ijzendoorn & Bakermans-Kranenburg, 2012). Studies additionally suggest that oxytocin appears to help discriminate between familiar and unfamiliar others (Macbeth et al., 2009; Rimmele, Hediger, Heinrichs, & Klaver, 2009), although it remains unclear whether oxytocin specifically mediates the categorization of others into in-groups and out-groups (De Dreu, 2012a). In the current study, given that social categorization of players during Cyberball was not measured, it is difficult to know whether this mediated greater cooperation with Player 1 for individuals who were low in attachment avoidance. However, results from the manipulation check suggest that the majority of participants (83%) noticed that Player 1 played with them initially the most out of all of the players. Player 1 may have been associated with an in-group status once a ball-tossing alliance was formed early on in the game, and oxytocin may have enhanced the salience of this behavior, particularly for individuals with low attachment avoidance, who may have otherwise ignored Player 1’s efforts to engage. It therefore remains a possibility that oxytocin motivated individuals with low attachment avoidance to be more cooperative with Player 1 after the switch via a social categorization or social salience enhancing mechanism. It is notable that the analyses were repeated while omitting participants for whom the manipulation did not work, and there was no change in the effects of oxytocin on the primary analyses or moderator analyses during Cyberball.

Second, this finding is consistent with previous research demonstrating that oxytocin’s effects are dependent on individual difference factors, including attachment
orientation. For example, Bartz and colleagues (2011) found that across their entire sample of individuals with BPD and healthy controls, attachment orientation moderated the effects of oxytocin on trust and cooperative behavior. In that study, oxytocin impaired trust for individuals with high attachment anxiety, whereas in the current study, oxytocin had no effect for those with high attachment anxiety but rather impaired cooperation for those with high attachment avoidance. The divergent effects of oxytocin, as a function of attachment style, clearly require further research. It is possible that other contextual factors may play a role, such as the availability of social information (Declerck, Boone, & Kiyonari, 2010).

Third, it may be possible in the current study that oxytocin’s effects were mediated by reduced betrayal aversion, as this has been shown in previous research for individuals with high attachment avoidance (De Dreu, 2012b). In one study (De Dreu, 2012b), 77 healthy males (mean age = 20.81 years) with high attachment avoidance cooperated significantly more during an anonymous social dilemma task, gave higher ratings of trust toward their partner during the task, and displayed lower ratings on a measure of betrayal aversion, when they were given oxytocin compared to placebo, whereas participants with low attachment avoidance showed reverse findings on each outcome. In addition, attachment anxiety did not moderate the effects of oxytocin on any outcome. It is noteworthy that in the current sample, low scores on the attachment avoidance subscale reflected scores within the average range reported in other samples (Brennan et al., 1998), which highlights the relatively greater attachment insecurity characteristic of the current sample. Findings from De Dreu (2012b), which are consistent
with the results from the current study, suggest that oxytocin differentially benefits those who are fearful of intimacy and dependency (attachment avoidance) than those who are fearful of rejection and abandonment from others (attachment anxiety). Although the current data suggest that oxytocin did not increase trust toward any of the other players during the game, trust was measured by a single self-report item in the current study. Therefore, the construct of trust was not well-defined and thus not well-measured in the current study. This leaves open the possibility that oxytocin may impact different types of trust more than others (e.g., relationship trust versus financial trust).

Finally, there is a body of research comparing the effects of oxytocin administration between healthy individuals and psychiatric populations, which has shown that oxytocin may only be favorable for individuals who stand to gain in terms of socioemotional functioning, but not favorable for individuals who already function adequately (for a review, see Olff et al., 2013). For example, in studies examining the effect of intranasal oxytocin in patients with SAD, results have demonstrated that oxytocin modulates amygdala activity in response to emotional faces in the SAD group, but not in the healthy control group (Labuschagne et al., 2010; Labuschagne et al., 2011). In addition, evidence suggests that patients with SAD may have a dysregulated oxytocin system, as they displayed lower levels of plasma oxytocin after playing the Trust Game, when compared with controls (Hoge et al., 2012). Therefore, it may be possible that oxytocin is dysregulated in psychiatric populations such as SAD, and that patients may respond differently to exogenously administered oxytocin than healthy individuals. Without a healthy control group in the current study, it is impossible to compare the
effects of oxytocin in both groups. Further research is needed to explore these possibilities.

Interestingly, oxytocin did not universally benefit a group of severely symptomatic, highly rejection sensitive SAD patients, given that only those with low baseline levels of rejection sensitivity and attachment avoidance showed improved social outcomes during Cyberball after receiving oxytocin, relative to placebo. This finding is consistent with the amplification hypothesis, that for some individuals, oxytocin may amplify pre-existing interpersonal schemas, whether positive or negative (Bartz et al., 2011). The sample mean on the IPSM was 82.91, which is comparable to reported norms in SAD samples on this measure (Harb et al., 2001). This finding may be consistent with the notion that oxytocin may have strongest effects for those within a moderate range of abnormal functioning, but may have no benefits beyond that range. Furthermore, a recent study (Declerck, Boone, & Kiyonari, 2013) demonstrating oxytocin’s amplification effect showed that individuals with a pro-self (compared to pro-social) value orientation displayed exaggerated self-interested behaviors during a social dilemma game when given oxytocin, but only in the anonymous condition. When given the opportunity to meet their partner beforehand, these individuals showed enhanced cooperative behavior when given oxytocin. Thus, it appears that oxytocin interacts with multiple contextual and individual factors. In the current study, oxytocin’s effect on existing interpersonal schemas related to rejection sensitivity may be confounded by other contextual factors that were not measured or controlled (e.g., availability of social information).
Hypothesis 3. During the Posner Task, Hypothesis 3 was partially supported. It was expected that oxytocin would facilitate disengagement from emotional threat cues versus emotional non-threat cues, relative to placebo. Oxytocin did not impact attentional engagement or disengagement of social cues when comparing between threat (disgust) versus non-threat (neutral) cues. However, for individuals with high attachment avoidance, oxytocin did speed up response times for responding to face types when examined separately. For these individuals, oxytocin not only facilitated disengagement from all emotional cues (although this was not statistically significant), whether they depicted disgust, neutral, or happy faces, but also appeared to speed up detection of disgust and neutral faces. No such pattern was found for individuals with high attachment anxiety. Interestingly, after removing participants from the analyses for whom the manipulation failed during Cyberball, there was a robust moderation effect of oxytocin for all face types and cue types for individuals with high attachment avoidance.

There are many possible explanations for this finding. First, as already described above, this finding is consistent with research showing that oxytocin may benefit individuals within a certain range of abnormal social or emotional functioning. More broadly, this finding contributes to the existing literature on how oxytocin alters social attention (Guastella & MacLeod, 2012), as previous research has shown that oxytocin has dual effects on social cognition: oxytocin may enhance the salience of social cues in the immediate social environment (Prehn et al., 2013), and it may also reduce attention to social threat (such as unfamiliar, emotional faces), which thereby reduces vigilance toward such threat (Ebitz, Watson, & Platt, 2013; Ellenbogen et al., 2012). The current
findings support the latter hypothesis and provide further evidence that oxytocin may normalize the dysfunctional attentional processes associated with high attachment avoidance by facilitating disengagement from social cues.

Second, oxytocin may lead to biased recall of information that is congruent with one’s interpersonal schemas. A previous study examining the effect of oxytocin on retrospective recollections of maternal care and closeness found that individual differences in attachment anxiety moderated oxytocin’s effects, such that those with high attachment anxiety remembered their mother as being less caring and less close after receiving oxytocin relative to placebo (Bartz et al., 2010). Consistent with this finding, the current results suggest that individuals with insecure attachment are biased to detect social stimuli faster after receiving oxytocin. One may speculate that this sets in motion a “priming” effect, such that oxytocin activates information congruent with one’s attachment representations and that individuals with insecure attachment styles may have negative attachment schemas (Bartz et al., 2010). The current findings also suggest that for individuals with high attachment avoidance, oxytocin facilitated disengagement from all social cues, regardless of emotional valence, which contrasts with previous studies showing that oxytocin may specifically bias information processing in a positive direction. For example, oxytocin may improve the encoding of positive social memories (Guastella, Mitchell, & Mathews, 2008). Further research is needed to test whether oxytocin primes attachment-relevant memories using implicit paradigms, and to determine whether these discrepant findings may be due to differential effects of oxytocin at various levels of information processing (e.g., attention versus memory). Research is
also needed to test whether cognitive mechanisms such as selective attention or biased recall of social information mediates oxytocin’s effects on pro-social behavior, as it remains unclear how these mechanisms translate to behavioral outcomes.

Lastly, these findings join a body of research showing that oxytocin promotes a flexible gaze pattern (Ellenbogen et al., 2012; Guastella et al., 2008). This explanation may be the most parsimonious, and may help to reconcile the discrepancies between findings on divergent effects of oxytocin on attentional processes. Results from the current study suggest that oxytocin facilitates both the detection and disengagement of social cues, which is consistent with prior work demonstrating that oxytocin enhances attentional shifting to and from emotional faces (Ellenbogen et al., 2012), and that oxytocin increases eye gaze as well as the number of fixations toward the eye region of faces (Domes, Steiner, et al., 2013; Guastella et al., 2008). In addition, other studies have documented that oxytocin facilitates eye gaze even toward neutral faces, as this may reflect one’s efforts to explore changes in others’ facial expressions, as they become less ambiguous (Domes, Steiner, et al., 2013). Thus, oxytocin’s effects on attention may not be strictly valence-based, but depend on the social context, and the motivations derived from it. Perhaps oxytocin’s regulation of attentional shifting, as reflected in the current study findings, has evolved to be particularly adaptive in situations where social threat is ambiguous (e.g., meeting strangers, entering novel contexts). Flexible attentional shifting thus may have two important functions: one, to monitor changes in social threat across the social milieu, and two, to reduce a persistent state of vigilance or gaze toward potential threats, which would promote cooperation with others. Especially in light of
evidence that individuals with SAD may have difficulty disengaging their attention from social threat cues (Amir et al., 2003), the current findings suggest that intranasal oxytocin may benefit individuals with SAD by promoting more flexible attentional patterns.

**General Discussion**

The current study highlights several major themes within the oxytocin literature and brings to bear important areas for further research. First, results from both study tasks revealed that oxytocin’s effects were dependent on individual difference factors, such as rejection sensitivity and attachment orientation. These findings contribute additional evidence demonstrating that oxytocin has divergent effects and may not have universal benefits across individuals (Bartz et al., 2011). More broadly, they suggest that one’s pre-existing beliefs and expectations about others play a role in determining how oxytocin facilitates or hinders social cognition and behavior.

Future research may benefit from clarifying similarities and differences between certain individual factors, such as attachment style, rejection sensitivity, and social anxiety, in order to better examine the specificity of oxytocin’s effects. Although the moderators in the current study all describe various interpersonal styles in the social domain, they have important differences. For example, attachment anxiety and rejection sensitivity may overlap with regard to fear of interpersonal rejection and hypervigilance of social threat cues. However, they may differ in terms of underlying motivational need states and the reference group. Attachment anxiety may reflect a specific need to be loved by a close other, whereas rejection sensitivity may reflect a broader construct reflecting a
need to belong and be included by a more general group. Thus, to refine our understanding of oxytocin’s effects, it may be important to clarify these constructs and distinguish them in future investigations. Given the strong evidence for individual variation in response to oxytocin, future research may also benefit from employing within-subject crossover designs rather than between-subject designs.

Second, a major theme in the oxytocin literature is the external validity of available studies. Investigations span the full spectrum, from studies examining how oxytocin modulates basic social cognitive processes using single-dose administrations to studies examining how chronic, multiple administrations of oxytocin impact social and psychiatric outcomes. Aside from disparities in terms of dose amount and dose frequency, studies have varied widely in terms of sample characteristics. Typically, studies include healthy young males between the ages of 18-45 without any medical or psychiatric conditions. In terms of clinical research studies, they differ significantly with regard to comorbidities included in the sample, as well as use of concurrent medications. Additionally, studies are disparate in terms of methodology (e.g., study design, experimental procedures). The experimental tasks vary in terms of task demands, which may impact participants’ motivation and impose varying amounts of cognitive load during the task.

Of all of the threats to external validity in published studies, perhaps the two greatest threats involve the sample selection biases, and the generalizability of results from experimentally-controlled laboratory paradigms. The age and sex bias in studies is especially problematic in light of data showing sex differences in plasma oxytocin levels.
(Ozsoy, Esel, & Kula, 2009; Weisman, Zagoory-Sharon, Schneiderman, Gordon, & Feldman, 2012), sex differences in amygdala reactivity after oxytocin administration (Domes et al., 2007; Domes et al., 2010), and age-related differences in the association between oxytocin receptor polymorphisms and brain activations during an emotional face processing task (Ebner, Maura, MacDonald, Westberg, & Fischer, 2013). Our sample included only six participants older than 30, and within this older age group, a scatterplot of cooperation scores during Cyberball showed no evidence of age-related effects. Furthermore, studies frequently employ laboratory-based paradigms to test cognitive and behavioral outcomes, such as the well-known Trust Game. It is unclear how well these paradigms capture social dilemmas as they occur in the real world and whether results would translate to meaningful behavior change. Additionally, Cyberball was used to measure social cooperation in a relatively anonymous manner, and reflects only one facet of pro-social behavior, a construct with multiple forms and levels (Penner, Dovidio, Piliavin, & Schroeder, 2005). Whether the current findings translate to social cooperation in one’s personal relationships or in the workplace, where behavior is determined by multiple complex factors impacting social motivation and judgments, such as the presence of more social information, social desirability characteristics, and the influence of potential future interactions, is still subject to empirical investigation.

Third, the current study begs the question of potential mechanisms of action of oxytocin. While it is clear that oxytocin is not a universal anxiolytic, more research is needed to understand whom it works for and under what conditions. Research has begun to identify some potential moderators of oxytocin’s effects, which attempt to address the
question of when oxytocin has effects, such as social versus non-social contexts (Heinrichs et al., 2003), familiarity (Macbeth et al., 2009; Rimmele et al., 2009), in-group versus out-group status (De Dreu, 2012a), individual difference factors (e.g., sex, age, attachment history, psychiatric status, genetics, social value orientation, etc.; Chen et al., 2011; De Clerck et al., 2013; MacDonald et al., 2013; McQuaid, McInnis, Stead, Matheson, & Anisman, 2013), and the presence of social information and social incentives (De Clerck et al., 2010). These studies have shown that under certain circumstances, oxytocin may either promote or hinder social cognition and behavior, or even may reach a ceiling effect and show no effects (Guastella et al., 2010).

With regard to mediators, fewer studies have examined mediation, which attempts to answer the question of how oxytocin has effects. Neuroimaging studies have shown that oxytocin reduces amygdala activation to unpleasant stimuli (Kirsch et al., 2005) and to human faces regardless of valence (Domes et al., 2007), which suggests that oxytocin’s anxiolytic effects are potentially mediated by the amygdala. A more recent study found that oxytocin’s divergent effects on attention and eye gaze may be explained by oxytocin’s differential regulation of amygdala subregions (Gamer et al., 2010). Specifically, investigators found that consistent with earlier findings, oxytocin attenuated activation in the lateral and dorsal regions of the anterior amygdala when attending to fearful faces, but also enhanced activation in this area for happy faces. Furthermore, oxytocin increased reflexive gaze shifts toward the eye region of faces regardless of emotional expression, which was correlated with increased (rather than decreased) activation in the posterior amygdala, as well as enhanced functional coupling of that
region to the superior colliculi. These findings suggest that oxytocin regulates attentional mechanisms in a valence-dependent manner, such that up-regulation of the posterior amygdala may actually enhance gaze patterns and improve processing of socially relevant information. Indeed, one may speculate from the current findings whether the attentional changes caused by oxytocin correlated with reliable, functional changes at the neural level, specifically in these subregions of the amygdala. Future research should expand upon this line of investigation by honing in on attentional constructs that have relatively clear neurobiological underpinnings, such as attentional biases and reflexive eye gaze shifts, in order to better understand oxytocin’s mechanisms. It will also be especially important to replicate these data in clinical populations such as SAD to better inform treatment.

Lastly, a major theme stemming from the oxytocin literature is the application of findings to mental health. Perhaps the primary question of clinical relevance is the clinical utility and predictive value of oxytocin in a treatment context. The current study has important clinical implications, as the results suggest that oxytocin may improve social cooperation, and that oxytocin may promote flexible attentional awareness, for at least some individuals with SAD. However, for other individuals, the results also suggest that oxytocin may hinder social cooperation, as well as increase subjective feelings of rejection during social interactions. Taken together, the study findings tell a cautionary tale about oxytocin’s direct applications to SAD. Especially in the absence of a healthy control group in the current study, it cannot be concluded that the results would be the same in healthy individuals.
The clinical implications for the use of intranasal oxytocin in individuals with SAD fall into two major questions of clinical relevance—one, whether oxytocin can be used to augment treatment, and two, whether oxytocin can be used to predict treatment response. The first question raises the issue of whether oxytocin can augment psychological treatments in the same way as cognitive enhancers, which are a class of pharmacologic agents thought to facilitate learning processes such as fear acquisition, fear extinction, and memory consolidation (Hofmann, Fang, & Gutner, 2013). Given that fear extinction is a core learning process of exposure-based therapies for SAD, oxytocin may serve as a potential cognitive enhancer for SAD if it can be shown that it modulates fear-related learning. Indeed, studies have demonstrated that oxytocin differentially impacts fear extinction, depending on timing of administration, as some animal studies have shown that microinfusion of oxytocin prior to fear conditioning facilitated extinction, but not when administered before extinction training (Toth et al., 2012). Other studies have revealed that injecting oxytocin in the basolateral amygdala before fear conditioning may increase fear responding in rats (Lahoud & Maroun, 2013). In healthy humans, one study examining the effect of intranasal oxytocin when administered prior to extinction training found that oxytocin did not facilitate fear extinction compared to placebo, with both groups showing reduced responding (Acheson et al., 2013). However, oxytocin did facilitate extinction recall, which was measured 24 hours later. Taken together, these studies suggest that oxytocin may impact fear extinction in a time-dependent manner. Oxytocin therefore has potential to augment extinction-based treatments for SAD. Specifically, it remains unknown whether oxytocin speeds up
extinction learning, which may reduce the number of treatment sessions needed, or whether oxytocin facilitates the consolidation of extinction memories for effective exposures, which may enable patients to engage more fully in exposures.

Future research should explore these possibilities, and further examine the impact of timing of administration on extinction learning in patients with SAD. More research into the neural correlates of oxytocin’s effects may also advance our understanding of the specificity of oxytocin’s role in regulating fear. In addition, it will be important for future research to clarify any differences between acute and chronic administrations of oxytocin, and oxytocin’s optimal dose and dosing frequency, before application to treatment for SAD.

The second question refers to oxytocin’s potential to predict treatment response, and its utility as a candidate endophenotype for SAD. There is emerging evidence that oxytocin modulates dysfunctional fear circuitry associated with SAD, as intranasal oxytocin appears to attenuate hyperactivity in the amygdala to fearful faces (Labuschagne et al., 2010), and in the medial prefrontal cortex and dorsal anterior cingulate regions to sad faces in individuals with SAD, to levels similar to that of healthy controls (Labuschagne et al., 2011). These findings suggest that oxytocin may normalize abnormal neural activation patterns during emotional processing in SAD, and give rise to a new hypothesis that oxytocin may improve emotion regulation by enhancing functional connectivity between the medial prefrontal cortex and amygdala. Furthermore, research on common polymorphisms of the oxytocin receptor gene has demonstrated associations between oxytocin genotypes and certain behavioral outcomes, such as depressive
symptomatology (McQuaid et al., 2013), psychopathy (Dadds, Moul, et al., 2013), and pervasive aggressive behavior (Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012). Thus, it may be possible that certain oxytocin and oxytocin receptor gene variants confer risk, or interact with environmental stressors to confer risk for social deficits. With regard to prediction of treatment response, research in this area is extremely limited; however, available evidence suggests that variations of the oxytocin and oxytocin receptor genes are associated with clozapine treatment response and symptom severity in schizophrenia (Souza, de Luca, Meltzer, Lieberman, & Kennedy, 2010). It remains to be tested whether oxytocin’s effect on baseline neural activation patterns or whether genotyping of oxytocin and oxytocin receptor polymorphisms prior to treatment may reliably predict treatment response in SAD. Given the promising research showing the beneficial role of oxytocin in modulating abnormalities in social information processing across emotional disorders thus far, its utility as a baseline assessment tool for prediction of treatment response may be a valuable avenue of exploration.

The current study findings should be interpreted in the context of certain limitations. First, the lack of a healthy control group prohibits conclusions about comparisons between individuals with SAD and healthy individuals in the current study, particularly with regard to the effects of oxytocin. An important follow-up question will be to examine oxytocin’s effects in a healthy control group. Second, the current study findings may not generalize to females, children, or older adults, given that the sample consisted of relatively young adult males between the ages of 18 and 45 years old. Lastly, although the primary manipulation in Cyberball appeared to be noticed by the majority of
the sample, 17% did not notice a change in Player 1’s behavior. Conclusions are therefore more limited with regard to the impact of Player 1’s behavior during the game.

**Conclusions**

Broadly, the current study represented an innovative approach to apply the translation of neuroscience to clinical phenomena, in an effort to better understand the neurobiological underpinnings of social deficits associated with SAD. Specifically, the current study investigated the role of a well-known neuropeptide, oxytocin, on social behavior and social attentional processing in individuals with SAD. Consistent with study hypotheses, results suggested that intranasal oxytocin may improve social cooperation and promote a flexible attentional pattern toward social cues, for at least some individuals with SAD. An important theme from the current work, which aligned with emerging research on oxytocin’s effects in the central nervous system, was that oxytocin was highly dependent on individual difference factors. More work is needed to extend these findings to SAD and to better inform the pathophysiology and treatment of SAD.
Appendix A

Individual Differences Moderate Oxytocin’s Effects on Pro-Social Behavior and Attentional Processing in Individuals with Social Anxiety Disorder

Angela Fang, M.A.\textsuperscript{1,2}, Stefan G. Hofmann, Ph.D.\textsuperscript{1}

\textsuperscript{1}Boston University, Boston, MA
\textsuperscript{2}Massachusetts General Hospital/Harvard Medical School, Boston, MA

Address for correspondence:
Angela Fang, M.A.
Massachusetts General Hospital/
Harvard Medical School
185 Cambridge Street, 2\textsuperscript{nd} Floor
Boston, MA 02114
Tel: (617) 724-6300 ext. 111-134-2044
E-mail: afang@mgh.harvard.edu

Date of submission: XX/XX/XXXX

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Abstract

**Background:** Previous research suggests that intranasal oxytocin may promote trust, social cooperation, and emotion recognition in humans. In addition, oxytocin’s effects may be moderated by individual difference factors. The current investigation examined whether oxytocin impacts cooperative behavior toward a rejecting but initially cooperative confederate, and whether it modulates attentional processes toward social stimuli, as a function of individual differences.

**Methods:** Using a double-blind, placebo-controlled design, 54 individuals with SAD were randomly assigned to receive 24 international units (IU) of oxytocin or placebo nasal spray. Following drug administration, participants completed a computerized ball-tossing game called Cyberball, which measured social cooperation toward three other fictitious players, who were programmed to follow different behavioral profiles reflecting various degrees of cooperative play. After Cyberball, participants completed a modified version of the Posner Task.

**Results:** Oxytocin, relative to placebo, improved cooperation during Cyberball, but only for individuals with low attachment avoidance. Relative to placebo, oxytocin also amplified subjective ratings of perceived rejection for individuals with high rejection sensitivity. Furthermore, oxytocin, relative to placebo, led to facilitated disengagement from all social cues regardless of emotional valence, although this was not statistically significant, and speeded up detection of disgust and neutral faces, but only for individuals with high attachment avoidance.
**Conclusions:** These findings suggest that oxytocin may promote social cooperation, as well as a flexible attentional pattern toward social cues, at least for some individuals with SAD. Future research should address individual differences in response to oxytocin, and further investigate the comparative effects of oxytocin in healthy individuals.

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Individual Differences Moderate Oxytocin’s Effects on Pro-Social Behavior and Attentional Processing in Individuals with Social Anxiety Disorder

Oxytocin is a nine amino acid neuropeptide, which is produced in the paraventricular and supraoptic nuclei of the hypothalamus. It is then secreted via the posterior pituitary gland into peripheral circulation or released into the central nervous system to act on receptors widely distributed throughout the brain, including the limbic system, midbrain, and brainstem.

Traditionally, oxytocin has been examined for its role in childbirth, lactation, and maternal attachment. Following recent advances in translational neuroscience to deliver oxytocin directly to the central nervous system, studies have revealed that oxytocin has much broader functions in social cognition and behavior than previously thought. For example, intranasal delivery of oxytocin appears to promote pro-social behaviors such as in-group favoritism (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011), trust and cooperation (De Dreu, 2012b; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and emotion recognition (Schulze et al., 2011). Intranasal oxytocin also appears to have anxiolytic properties, as it buffers responses to social stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), and dampens amygdala activity to emotional stimuli (Domes et al., 2007). However, recent research has shed light on the context-dependent and divergent effects of oxytocin, and suggests that under certain conditions, oxytocin may even exert anxiogenic effects. Evidence from clinical samples also reflects this mixed picture and highlights the moderating role of individual difference factors such as...
attachment orientation (Bartz et al., 2011). Nevertheless, intranasal oxytocin is a promising agent and has major treatment implications for psychiatric disorders involving deficits in social functioning such as social anxiety disorder (SAD).

Among individuals with SAD, intranasal oxytocin does not appear to reduce symptom severity when given as an adjunct to exposure therapy (Guastella et al., 2009). However, oxytocin attenuates amygdala reactivity in response to fearful faces (Labuschagne et al., 2010), as well as cortical hyperactivity in the medial prefrontal cortex to sad faces (Labuschagne et al., 2011). Evidence also points to an altered oxytocin system in SAD patients, as they exhibit lower levels of plasma oxytocin after a trust game, compared to healthy controls (Hoge et al., 2012). More research is needed to better understand the contexts under which oxytocin is likely to benefit patients with SAD. For example, oxytocin may activate motivational approach schemas in social situations, and may affect social information processing biases associated with SAD.

Toward this end, the current study aimed to investigate the effect of oxytocin on social behavior and social attentional processing in individuals with SAD. Specifically, the current study assessed how oxytocin impacted cooperative behavior toward a rejecting but initially cooperative confederate, and whether oxytocin modulated attentional processing of social threat cues, both while taking into account the moderating impact of individual differences.
Methods and Materials

Participants

Participants were 60 males at least 18 years of age or older, with a principal or co-principal diagnosis of SAD, and had a current Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) score of ≥ 60. Females were excluded from the study due to complications associated with the use of oxytocin in pregnancy, as well as potential fluctuations of oxytocin during menstrual phases. No participants had significant nasal pathology (e.g., atrophic rhinitis, recurrent nose bleeds, history of hypophysectomy), were smokers who smoked more than 15 cigarettes per day, had a serious medical illness, had active suicidal or homicidal ideation, had a current diagnosis of schizophrenia, psychotic disorder, bipolar disorder, or substance abuse/dependence, and no participants were concurrently taking psychotropic medications, except for antidepressants that had been taken at a stable dose for at least two weeks prior to study entry. Participants received $40 in compensation for their participation in the study, and additional earnings from the social task. The study was approved by the Boston University Medical Center Institutional Review Board.

Six participants were excluded due to being ineligible for the study (three did not have SAD, two met criteria for substance dependence, and one had a principal diagnosis of posttraumatic stress disorder). The final sample included 54 participants (age range = 18-45 years). Two participants did not complete the Cyberball Task due to technical difficulties. This sample size was selected to allow adequate power (β = .80) to detect a medium effect size (f = .25) at an alpha level of .05. Chi-square and t-tests showed no
differences between groups in demographic or baseline clinical characteristics (all \( p \)'s > .05). The most common comorbid diagnosis was major depression (18.5%), followed by generalized anxiety disorder (16.7%), and panic disorder with agoraphobia (7.4%).

Tasks

*Cyberball Task (Williams et al., 2000; Williams & Jarvis, 2006).* Cyberball is a four-person computerized ball-tossing game, which was designed to manipulate ostracism. Participants are led to believe that they are playing with three “others” in real time. The program was modified to create three different behavioral profiles for the fictitious others. For the first 80 trials (Play Condition), Player 1 was programmed to toss on average 70% of his balls to the participant, whereas Player 4 tossed 30%, and Player 3 tossed only 10% of them, to the participant. The participant was always Player 2. Each trial consisted of a single ball toss exchange, which was represented by a short animation of one player tossing the ball and another player catching the ball. The participant had the choice to toss the ball to a player when he received the ball from a previous trial.

Participants were told that the purpose of the game was to obtain as many points as possible, by receiving 20 points each time a ball was tossed to them, and losing 10 points each time the ball was tossed to someone else. After 80 trials, the behavioral profiles switched (Switch Condition), such that Player 1 was programmed to toss only 10% of his played balls to the participant. After the switch, the participant played Cyberball for another 80 trials. The decision time for the fictitious players was varied from trial to trial to enhance the believability of realistic play behavior. The participant was represented by
a fourth cartoon on the computer screen taken from a first person perspective. The display also provided ongoing feedback for the participant’s total points throughout the game. Ratings of trust, empathy, preference, perceived rejection, and willingness to re-engage in another game of Cyberball with each player, were measured on a 7-point Likert scale at the end of the task. The entire task consisted of 160 trials in total and took approximately eight minutes to complete.

*Modified Posner Task (Posner, 1980; Posner, Snyder, & Davidson, 1980)*. The Posner Task measures attentional engagement toward and disengagement from social threat cues. The stimuli for this task were modified to include a set of disgust, happy, and neutral faces. The task consisted of 360 trials. During each trial, the participant saw a fixation cross. On each trial, a face (disgust, happy, or neutral) appeared within either the top or bottom half of the screen (the other half of the screen would remain blank) and then disappeared. Then, a probe (the letter “E” or “F”) appeared in the top or bottom half of the screen. The participant was instructed to identify the letter as quickly and accurately as possible by clicking the left or right mouse button (left for “E”, right for “F”). Upon responding, the next trial commenced. For valid trials, the probe appeared in the position previously occupied by the face stimulus, whereas for invalid trials, the probe appeared in the empty half of the screen. Reaction times to valid and invalid trials reflected the participant’s attentional engagement towards threat and disengagement from threat, respectively. The entire task took 10 minutes to complete.
Drug Information

The oxytocin and placebo nasal sprays were compounded by a local pharmacy under Investigational New Drug #113,827. They consisted of 24 international units (IU) of oxytocin, and were dispensed in metered-dose spray bottles to deliver exactly 4 IU per spray. The placebo sprays were identical to the oxytocin nasal sprays, except for the addition of 0.65% sodium chloride to the placebo nasal spray, which helped to minimize nasal irritation to the participant.

Procedure

Participants were recruited from the community using approved print and online advertisements, as well as from the waitlist of an outpatient anxiety disorders specialty clinic. Potential participants were phone screened to ensure that they met basic eligibility requirements, and were asked not to have caffeine, alcohol, or nicotine for 24 hours prior to the study appointment. Participants were then scheduled for a single visit lasting approximately four hours.

During the study visit, participants gave written informed consent and were assessed for eligibility through a diagnostic evaluation using the Mini Adult Diagnostic Interview Schedule for DSM-IV (DiNardo, Brown, & Barlow, 1994). Participants then met with the study physician to complete a medical screen, which consisted of assessing concurrent psychotropic medications, significant nasal pathology, as well as measuring vitals (e.g., blood pressure, pulse). Participants were then asked to complete a set of self-report questionnaires to collect demographic information, as well as to assess baseline
levels of depression using the Beck Depression Inventory- II (Beck, Steer, & Brown, 1996), social anxiety using the Social Interaction and Anxiety Scale (Mattick & Clarke, 1998), rejection sensitivity using the Interpersonal Sensitivity Measure (Boyce & Parker, 1989; Harb, Heimberg, Fresco, Schneier, & Liebowitz, 2002), subjective mood using the Positive and Negative Affect Scales (Watson, Clark, & Tellegen, 1988), and attachment orientation using the Experience in Close Relationships Inventory (ECR) (Brennan, Clark, & Shaver, 1998). The ECR is a 36-item self-report questionnaire that yields two subscales reflecting attachment anxiety (anxiety about being rejected or abandoned) and attachment avoidance (discomfort with closeness and intimacy). In the current study, the two subscales were not significantly correlated, \( r = -.32, n = 25, p = .12. \)

Next, participants were randomly assigned to receive a nasal spray containing either oxytocin or placebo using a computer-generated pre-randomization sheet. The study was double-blind, such that neither the study physician nor the experimenter were aware of participants’ assigned drug condition. Using a standardized protocol, participants self-administered a metered-dose nasal spray with three puffs per nostril (4 IU of oxytocin or placebo per puff) in the presence of the study physician or nurse. After nasal spray administration, participants’ vitals were measured again.

Participants were then asked to sit in an isolated waiting room for 45 minutes before starting the computer tasks, as this reflects a standard wait period following intranasal oxytocin administration. After 45 minutes, participants were led to a common waiting area for the study, where they were told that they would have an opportunity to briefly meet three other study participants for the first task. The experimenter led the
participant and three male confederates individually into the waiting area, and asked each participant to introduce their first name to the group. At this time, participants were individually led to their separate experimental rooms.

Participants played Cyberball first, and then completed the post-Cyberball questionnaires. Afterwards, participants completed the modified Posner Task. The experiment concluded with a debriefing session.

**Statistical Analyses**

**Primary Analyses.** First, a series of mixed between-within analyses of variance (ANOVAs) were conducted to examine group effects on social outcomes during Cyberball, and attentional outcomes during the Posner Task. Specifically, Cyberball outcomes included: 1) number of balls thrown to Player 1 during the *Play* and *Switch* conditions, 2 (Group: oxytocin, placebo) x 2 (Time: balls tossed to Player 1 during *Play* and *Switch* conditions), 2) the number of balls thrown to each of the other players during the *Play* condition, 2 (Group: oxytocin, placebo) x 3 (Player: balls tossed to Player 1, 3, and 4), and 3) overall trust and rejection ratings for each of the players, 2 (Group: oxytocin, placebo) x 3 Player (trust and rejection ratings for Player 1, 3, and 4). On the Posner Task, faster response latencies when detecting validly cued targets following disgust faces indicated an attentional “engagement” or bias toward threat-relevant information. Slower response latencies when detecting invalidly cued targets following disgust faces indicated difficulty disengaging attention away from threat-relevant information. To examine the effect of oxytocin on attentional engagement and
disengagement by face type, a mixed 2 (Group: oxytocin, placebo) x 2 (Cue Type: valid, invalid) x 3 (Face Type: disgust, neutral, happy) ANOVA was conducted with repeated measurement on the last two factors. To examine group differences on demographic characteristics and baseline clinical measures, t-tests were conducted for continuous variables and chi-square tests were conducted for categorical variables. Given that there were no significant differences in age and social anxiety symptom severity between groups, and that inclusion of covariates would significantly reduce test power, we did not control for covariates in the analyses. Thus, covariates were not included in the reported analyses moving forward.

*Secondary Analyses.* A regression approach was adopted to investigate the interactions between drug and continuous moderators (rejection sensitivity, attachment anxiety, and attachment avoidance) on Cyberball outcomes (ball-tossing behavior, ratings of trust and rejection), as well as outcomes during the Posner Task (attentional engagement and disengagement scores for each face type). We conducted hierarchical regression analyses on all participants in the sample to examine the effects of drug group (dummy coded: 1 = oxytocin and 0 = placebo), and mean-centered rejection sensitivity (entered in step 1), and their two-way interaction (entered as a product term in step 2), on each outcome. The regressions were then repeated to examine the effects of drug group (dummy coded: 1 = oxytocin and 0 = placebo), and mean-centered attachment anxiety and attachment avoidance (entered in step 1), and their two- and three-way interactions (entered as product terms in steps 2 and 3, respectively) on the same outcomes.
Regression analyses were followed up by generating predicted values based on each regression equation and plotting XY graphs to examine the nature of the interaction.

Results

Primary Analyses

Effect on cooperation. Oxytocin, relative to placebo, did not lead to continued cooperation with Player 1 across the two conditions during the game, as there was no significant Group x Time interaction, Wilks’ Lambda = 1.00, $F(1,50) = .02, p = .88, \eta^2_p = .00$. Both groups showed a reduction in ball tosses to Player 1 during the game, Wilks’ Lambda = .66, $F(1,50) = 26.37, p < .001, \eta^2_p = .34$, but this did not differ by group, $F(1,50) = .70, p = .41, \eta^2_p = .01$. In addition, oxytocin, relative to placebo, was not significantly associated with more throws to Player 1, compared to other players, as there was no significant Group x Player interaction, Wilks’ Lambda = .99, $F(2, 49) = .24, p = .78, \eta^2_p = .01$. Both groups threw significantly more balls to Player 1 compared to other players, Wilks’ Lambda = .47, $F(2,49) = 27.32, p < .001, \eta^2_p = .53$, but this did not differ by group, $F(1,50) = .32, p = .57, \eta^2_p = .01$.

Effect on perceived trust and rejection. Oxytocin, relative to placebo, did not significantly impact trust ratings for Player 1 compared to other players, Wilks’ Lambda = .98, $F(2,47) = .44, p = .64, \eta^2_p = .02$, nor did oxytocin significantly impact perceived rejection ratings from Player 1, Wilks’ Lambda = .99, $F(2,47) = .27, p = .77, \eta^2_p = .01$. However, those who received oxytocin reported lower ratings of overall rejection from
all players during Cyberball, relative to those who received placebo, $F(1,48) = 3.98, p = .05, \eta_p^2 = .08$.

**Effect on attentional engagement and disengagement of social cues.** First, response times for inaccurate trials were eliminated. Inaccurate trials consisted of trials where the probe was the letter “E” and the participant pressed the right mouse button or vice versa. This resulted in elimination of 2% of the trials. Response latencies less than 360 ms and greater than 2200 ms were considered outliers and eliminated from the analysis. Idiographic standardization of response times was then conducted, and response latencies from trials reflecting two standard deviations above or below an individual’s personal mean were eliminated from the analysis, which resulted in elimination of 4% of the trials. Finally, for each participant, a mean response time was calculated for each face type and cue condition.

Oxytocin was not associated with facilitated attentional engagement or disengagement scores for any emotional face type, as there was no significant interaction of Group x Cue Type x Face Type, Wilks’ Lambda = .93, $F(2,50) = .44, p = .65$. We then conducted separate Group x Cue Type analyses for each face type, and found no significant interactions: disgust faces, Wilks’ Lambda = 1.00, $F(1,51) = .15, p = .70$; happy faces, Wilks’ Lambda = 1.00, $F(1,51) = .09, p = .77$; and, neutral faces, Wilks’ Lambda = .99, $F(1,51) = .70, p = .41$. There were no other significant main effects.

**Cyberball manipulation check.** Nine (17.3%) out of 52 participants who completed Cyberball reported that they did not notice a change in any player’s behavior during the game. However, of those who did notice a change, participants reported that
Player 1 played the most with them at first, Wilks’ Lambda = .66, \( F(2,44) = 11.15, p < .001, \eta_p^2 = .34 \), and that there was no significant difference between the other players’ behavior later on during the Switch condition of the game, Wilks’ Lambda = .95, \( F(2,44) = 1.28, p = .29, \eta_p^2 = .06 \).

**Secondary Analyses**

*Effect on cooperation.* Regression analyses revealed a significant Group x Attachment Avoidance interaction on difference scores in balls tossed to Player 1 during Cyberball, \( B = 6.90, t(19) = 2.11, p = .05 \). The attachment interaction terms contributed to the overall model by explaining an additional 19.9% of the variance in ball tosses, \( F \) change \( (2,19) = 2.72, p = .09 \). Among participants with low Attachment Avoidance, oxytocin resulted in smaller difference scores in the number of balls tossed to Player 1 between the Play and Switch conditions compared to placebo, which suggested greater cooperation with Player 1. Among participants with high Attachment Avoidance, oxytocin resulted in greater difference scores across the Cyberball conditions compared to placebo, which suggested decreased cooperation with Player 1. There was no significant Group x Attachment Anxiety interaction on difference scores in balls tossed to Player 1, \( B = -.91, t(19) = -.32, p = .75 \), as well as no significant Group x Rejection Sensitivity interaction on difference scores in balls tossed to Player 1, \( B = .30, t(42) = 1.23, p = .23 \).

*Effect on perceived trust and rejection.* Regression analyses showed a significant Group x Rejection Sensitivity interaction on overall ratings of perceived rejection from
other players during Cyberball, \( B = .07, t(42) = 2.44, p = .02 \). The interaction effect explained a significant portion of variance in rejection ratings, \( R^2 \) change = .12, \( F \) change (1,42) = 5.97, \( p = .02 \). Among participants with high Rejection Sensitivity, oxytocin resulted in greater overall perceived rejection from the other players compared to placebo. In contrast, among those with low Rejection Sensitivity, oxytocin resulted in lower levels of overall perceived rejection compared to placebo. There was no significant Group x Rejection Sensitivity interaction on trust, \( B = -.01, t(42) = -.16, p = .87 \). There was also no significant Group x Attachment Anxiety interaction on trust, \( B = -.004, t(19) = -.02, p = .99 \), or rejection, \( B = .37, t(19) = .84, p = .41 \), and no significant Group x Attachment Avoidance interaction on trust, \( B = .08, t(19) = .26, p = .80 \), or rejection, \( B = .41, t(19) = .82, p = .42 \).

**Effect on attentional engagement and disengagement of social cues.** Regression analyses showed a significant Group x Attachment Avoidance interaction on engagement scores for disgust faces, \( B = -106.12, t(18) = -2.34, p = .03 \), and neutral faces, \( B = -102.47, t(18) = -2.07, p = .05 \), but not for happy faces, \( B = -81.30, t(18) = -1.52, p = .15 \). When given oxytocin, individuals with high Attachment Avoidance responded faster to validly cued disgust faces and neutral faces, whereas individuals with low Attachment Avoidance took longer to respond. For disengagement scores, there was a trend toward a group difference for the Group x Attachment Avoidance interaction for all face types: disgust faces, \( B = -106.87, t(19) = -1.98, p = .06 \); neutral faces, \( B = -99.14, t(19) = -1.82, p = .09 \); and, happy faces, \( B = -93.32, t(19) = -2.03, p = .06 \). When given oxytocin, individuals with high Attachment Avoidance responded faster to invalidly cued disgust,
neutral, and happy faces, whereas individuals with low Attachment Avoidance took longer to respond. Although the product terms explained an additional portion of variance in engagement and disengagement scores, none of the changes in $R^2$ were significant, all $p$’s > .05. There was no significant Group x Attachment Anxiety interaction on engagement scores for any face type (all $p$’s > .05). There was also no significant Group x Attachment Anxiety interaction on disengagement scores for any face type (all $p$’s > .05).

Furthermore, although regression analyses showed no significant interactions between Group x Rejection Sensitivity on engagement and disengagement scores for each face type, there was a significant effect of Rejection Sensitivity on disengagement from happy faces, $B = 4.69$, $t(47) = 2.00$, $p = .05$, suggesting that greater rejection sensitivity was associated with longer response latencies for invalid trials involving happy faces.

**Self-Reported Mood and Social Interaction Anxiety**

Oxytocin did not significantly reduce self-reported negative mood, positive mood, or social interaction anxiety, as all of these interaction effects were non-significant (negative mood: Wilks’ Lambda = 1.00, $F(1,50) = .23$, $p = .63$, $\eta^2_p = .01$; positive mood: Wilks’ Lambda = .99, $F(1,51) = .57$, $p = .45$, $\eta^2_p = .01$; social interaction anxiety: Wilks’ Lambda = 1.00, $F(1,23) = .01$, $p = .91$, $\eta^2_p = .001$). Interestingly, both groups showed improved positive mood during Cyberball, Wilks’ Lambda = .84, $F(1,51) = 9.61$, $p = .003$, $\eta^2_p = .16$, but this did not differ by group, $F(1,51) = .74$, $p = .39$, $\eta^2_p = .01$. 
Discussion

Previous literature on the effect of oxytocin in clinical samples shows mixed findings, as some studies demonstrate contrasting effects of oxytocin, even within the same disorder (Dadds et al., 2013; Tachibana et al., 2013). The current study sought to investigate the context-dependent effects of oxytocin under conditions of cooperation and rejection by relatively anonymous others, and the possible attentional mechanisms that may underlie oxytocin’s pro-social effects, among individuals with SAD.

The current findings show that oxytocin contributed to ongoing cooperative play with a rejecting but initially cooperative other (Player 1) for individuals with low attachment avoidance. In addition, we showed that oxytocin amplified subjective ratings of perceived rejection by others during Cyberball for those with high rejection sensitivity, and appeared to only buffer responses to rejection for those with already low rejection sensitivity. Finally, results suggest that for those with high attachment avoidance, oxytocin not only facilitated disengagement from all social cues depicting disgust, neutral, and happy faces, but also speeded up the detection of disgust and neutral faces in particular.

These findings join a body of literature showing that oxytocin’s effects are highly dependent on individual differences, such as attachment orientation (Bartz et al., 2011), and that oxytocin may only benefit individuals who stand to gain in terms of socioemotional functioning (Olff et al., 2013). It may be possible that oxytocin increased the salience of Player 1’s alliance-forming behavior early on in the game, particularly for individuals with low attachment avoidance, which facilitated the social categorization of
Player 1 as an in-group member (De Dreu, 2012a; Van Ijzendoorn & Bakermans-Kranenburg, 2012). It is also possible that oxytocin led to ongoing cooperation with Player 1 through reduced betrayal aversion, as this has been shown in previous research to be true only for individuals with high attachment avoidance (De Dreu, 2012b).

Interestingly, oxytocin did not universally benefit a group of severely symptomatic, highly rejection sensitive SAD patients, given that only those with low baseline levels of rejection sensitivity and attachment avoidance showed improved social outcomes after receiving oxytocin, relative to placebo. The sample mean on the IPSM was 82.91, which is comparable to reported norms in SAD samples on this measure (Harb et al., 2001). This may be consistent with the notion that oxytocin may have strongest effects for those within a moderate range of abnormal functioning, but may have no benefits beyond that range (Guastella et al., 2010).

Consistent with previous studies, our findings also suggest that oxytocin facilitates a flexible attentional pattern in individuals with SAD, such that it may promote an existing attentional bias toward social threat cues, but also enable faster disengagement from them (Domes et al., 2013; Ellenbogen et al., 2012; Guastella et al., 2008). In this way, oxytocin may enhance the very mechanisms targeted in attention retraining interventions for SAD (Amir et al., 2009).

The primary limitation of this study is the lack of a healthy control group, which restricts conclusions about the comparative effects of oxytocin. In addition, these findings may not generalize to females, children, or older adults, especially in light of sex and age effects on oxytocin. Future studies should replicate the study across these groups.
Notwithstanding, our study represents one of the earliest studies examining oxytocin in SAD, and extends previous work highlighting oxytocin’s potential to inform the pathophysiology and treatment of SAD.
References


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doi:10.1089/cap.2012.0048


Table 1. Demographic Characteristics by Group

<table>
<thead>
<tr>
<th></th>
<th>OT</th>
<th>PBO</th>
<th>Value(^a,b)</th>
<th>p-value</th>
</tr>
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<td></td>
<td>(n = 27)</td>
<td>(n = 27)</td>
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<td></td>
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<td>Age(^b) (years)</td>
<td>24.70 (7.14)</td>
<td>24.07 (5.96)</td>
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<td>.73</td>
</tr>
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<td></td>
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<td>Hispanic or Latino</td>
<td>14.81 (4)</td>
<td>11.11 (3)</td>
<td>0.16</td>
<td>.69</td>
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<tr>
<td>Non-Hispanic or Latino</td>
<td>85.19 (23)</td>
<td>88.89 (24)</td>
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<td></td>
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<tr>
<td>Race(^a) (%, (n))</td>
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<td>1.61</td>
<td>.66</td>
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<td>White</td>
<td>70.37 (19)</td>
<td>59.26 (16)</td>
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<td>7.41 (2)</td>
<td>11.11 (3)</td>
<td></td>
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<tr>
<td>Asian</td>
<td>14.81 (4)</td>
<td>35.93 (7)</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>7.41 (2)</td>
<td>3.70 (1)</td>
<td></td>
<td></td>
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<td>Marital status(^a) (%, (n))</td>
<td>4.02</td>
<td>.26</td>
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<tr>
<td>Single</td>
<td>85.19 (23)</td>
<td>88.89 (24)</td>
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<td></td>
</tr>
<tr>
<td>Living with partner</td>
<td>3.70 (1)</td>
<td>11.11 (3)</td>
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<td>Married</td>
<td>7.41 (2)</td>
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<tr>
<td>Divorced</td>
<td>3.70 (1)</td>
<td>0.00 (0)</td>
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<td></td>
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<tr>
<td>Education(^a) (%, (n))</td>
<td>6.27</td>
<td>.10</td>
<td></td>
<td></td>
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<tr>
<td>Graduate School</td>
<td>7.41 (2)</td>
<td>29.63 (8)</td>
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<tr>
<td>College Graduate</td>
<td>37.04 (10)</td>
<td>22.22 (6)</td>
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<tr>
<td>Partial College</td>
<td>51.85 (14)</td>
<td>37.04 (10)</td>
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<tr>
<td>High School Graduate</td>
<td>3.70 (1)</td>
<td>11.11 (3)</td>
<td></td>
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<tr>
<td>Occupational status(^a) (%, (n))</td>
<td>1.10</td>
<td>.78</td>
<td></td>
<td></td>
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<tr>
<td>Not applicable</td>
<td>35.93 (7)</td>
<td>14.81 (4)</td>
<td></td>
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<tr>
<td>Full-time employment</td>
<td>18.52 (5)</td>
<td>18.52 (5)</td>
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<tr>
<td>Part-time employment</td>
<td>22.22 (6)</td>
<td>35.93 (7)</td>
<td></td>
<td></td>
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<tr>
<td>Dependent on spouse or is a student</td>
<td>33.33 (9)</td>
<td>40.74 (11)</td>
<td></td>
<td></td>
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<td>Age of onset of SAD(^b)</td>
<td>14.70 (6.00)</td>
<td>14.19 (5.02)</td>
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<td>.73</td>
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<tr>
<td>LSAS(^b)</td>
<td>82.30 (17.87)</td>
<td>82.48 (16.30)</td>
<td>-0.04</td>
<td>.97</td>
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<td>SIAS(^b)</td>
<td>50.40 (10.35)</td>
<td>47.54 (11.89)</td>
<td>0.84</td>
<td>.37</td>
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<tr>
<td>BDI-II(^b)</td>
<td>15.08 (7.59)</td>
<td>15.30 (8.80)</td>
<td>-0.10</td>
<td>.92</td>
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<td>IPSM(^b)</td>
<td>83.74 (6.56)</td>
<td>81.88 (9.27)</td>
<td>0.63</td>
<td>.43</td>
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<td>ECR: Avoidance(^b)</td>
<td>3.43 (0.89)</td>
<td>3.61 (0.98)</td>
<td>0.24</td>
<td>.63</td>
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<tr>
<td>ECR: Anxiety(^b)</td>
<td>4.47 (1.02)</td>
<td>3.90 (1.13)</td>
<td>1.78</td>
<td>.20</td>
</tr>
</tbody>
</table>

Note. OT = Oxytocin; PBO = Placebo; SAD = Social Anxiety Disorder; LSAS = Liebowitz Social Anxiety Scale; SIAS = Social Interaction Anxiety Scale; BDI-II = Beck Depression Inventory; IPSM = Interpersonal Sensitivity Measure; ECR = Experience in Close Relationships Inventory

\(^a\)Chi-square statistics reported for selected variables

\(^b\)t-values reported for all clinical measures and age
Table 2. Summary of Hierarchical Regression Analysis for Effect of Group and Attachment Orientation on Ball-Tossing Behavior (n = 25)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
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<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
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<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td></td>
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<tr>
<td>Group</td>
<td>1.69</td>
<td>3.12</td>
<td>.12</td>
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<td>1.71</td>
<td>2.89</td>
<td>.12</td>
<td>2.29</td>
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<td>Attachment Avoidance</td>
<td>1.53</td>
<td>1.76</td>
<td>.19</td>
<td>-1.72</td>
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<td>Attachment Anxiety</td>
<td>-1.51</td>
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<td>-1.04</td>
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<td>-1.04</td>
<td>1.98</td>
<td>-.15</td>
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<td>Group x Attachment Avoidance</td>
<td>6.90</td>
<td>3.28</td>
<td>.58*</td>
<td>7.13</td>
<td>3.34</td>
<td>.60*</td>
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<td>Group x Attachment Anxiety</td>
<td>-0.91</td>
<td>2.84</td>
<td>-.09</td>
<td>-1.03</td>
<td>2.89</td>
<td>-.10</td>
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<tr>
<td>Group x Attachment Avoidance x Attachment Anxiety</td>
<td>1.81</td>
<td>2.67</td>
<td>.14</td>
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</table>

R²                  | .11         |       |       | .31         |       |       | .32         |       |       |

F for change in R²   | .83         |       |       | 2.72        |       |       | .46         |       |       |

Note. Group dummy coded (OT = 1, PBO = 0). Attachment Avoidance and Attachment Anxiety centered at their means.

* p < .05.
Table 3. Summary of Hierarchical Regression Analysis for Effect of Group and Rejection Sensitivity on Overall Ratings of Perceived Rejection (n = 46)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
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<th></th>
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<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
<td>β</td>
</tr>
<tr>
<td>Group</td>
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<td>.22</td>
<td>-.22</td>
<td>-.34</td>
<td>.21</td>
<td>-.24</td>
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<tr>
<td>Rejection Sensitivity</td>
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<td>-.05</td>
<td>-.03</td>
<td>.02</td>
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<tr>
<td>Group x Rejection Sensitivity</td>
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<td></td>
<td></td>
<td>.07</td>
<td>.03</td>
<td>.42*</td>
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<tr>
<td>$R^2$</td>
<td>.05</td>
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<td></td>
<td>.17</td>
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<tr>
<td>$F$ for change in $R^2$</td>
<td>1.16</td>
<td></td>
<td></td>
<td>5.97*</td>
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*Note. Group dummy coded (OT = 1, PBO = 0). Rejection Sensitivity centered at its mean.

*p < .05.
Table 4. Mean Response Latency (ms) by Cue Type and Face Type for Each Group

<table>
<thead>
<tr>
<th>Face type</th>
<th>Oxytocin</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td>Disgust</td>
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<td></td>
</tr>
<tr>
<td>Valid</td>
<td>603.13 (94.51)</td>
<td>646.08 (89.74)</td>
</tr>
<tr>
<td>Invalid</td>
<td>601.44 (101.20)</td>
<td>638.26 (108.98)</td>
</tr>
<tr>
<td>Neutral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valid</td>
<td>607.77 (95.68)</td>
<td>655.12 (104.71)</td>
</tr>
<tr>
<td>Invalid</td>
<td>600.10 (95.92)</td>
<td>635.54 (93.13)</td>
</tr>
<tr>
<td>Happy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valid</td>
<td>610.22 (107.27)</td>
<td>642.71 (92.22)</td>
</tr>
<tr>
<td>Invalid</td>
<td>598.84 (88.99)</td>
<td>635.53 (110.80)</td>
</tr>
</tbody>
</table>
Figure 1. Number of Ball Tosses Across Cyberball Conditions by Group\(^a,b\)

- Error bars indicate standard error of the mean.
- \(^*\) \(p < .001\).

\(^a\) Error bars indicate standard error of the mean.
\(^*\) \(p < .001\).
Figure 2. Significant Interaction Effect of Group x Attachment Avoidance on Difference Scores in Ball Tosses to Player 1 between Play and Switch Conditions (n = 25)
Figure 3. Significant Interaction Effect of Group x Rejection Sensitivity on Overall Ratings of Perceived Rejection (n = 46)
Figure 4. Significant Interaction Effect of Group x Attachment Anxiety on Attentional Engagement Toward Disgust Faces ($n = 24$)
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Curriculum Vitae

Angela Fang, M.A.

OFFICE
Massachusetts General Hospital
Richard B. Simches Research Center
185 Cambridge Street, 2nd Floor
Boston, MA 02114
Tel: (617) 724-6300, ext. 111-134-2044
Fax: (617) 643-3080
E-mail: afang@mgh.harvard.edu

HOME
530 Massachusetts Avenue #1B
Boston, MA 02118
Mobile: (516) 313-9016

EDUCATION

07/2013 – present
Clinical Fellow, Psychology/Psychiatry
Pre-doctoral Clinical Psychology Internship
Massachusetts General Hospital/Harvard Medical School
Boston, Massachusetts

09/2009 – present
Ph.D. Candidate, Clinical Psychology
Boston University
Boston, Massachusetts

09/2010
Master of Arts, Clinical Psychology
Boston University
Boston, Massachusetts

Bachelor of Arts, Psychology and Chinese
Dartmouth College
Hanover, New Hampshire

FELLOWSHIPS AND AWARDS

2012
John and Geraldine Weil Dissertation Award, John Leopold Weil and
Geraldine Rickard Weil Memorial Charitable Foundation (Award amount: $500)
2012 Clara Mayo Memorial Fellowship, Department of Psychology, Boston University (Award amount: $5,660)
2007 Phi Beta Kappa, Dartmouth College
2007 Presidential Scholar, Dartmouth College
2007 A.B. Magna cum Laude with High Honors in Psychology, Dartmouth College
2006 Kaminsky Family Fund Award, Department of Psychological and Brain Sciences, Dartmouth College (Award amount: $1,800)
2006 Lincoln Filene Undergraduate Summer Research Fellowship, Department of Psychological and Brain Sciences, Dartmouth College (Award amount: $3,000)
2005 – 2007 Rufus Choate Scholar, Dartmouth College
2003 – 2007 John Field Memorial Scholarship, Dartmouth College

**RESEARCH EXPERIENCE**

**Massachusetts General Hospital/Harvard Medical School**
Boston, Massachusetts
*Intern, 07/2013 – present*
Primary Advisor: Sabine Wilhelm, Ph.D.

- Serve as study therapist on study entitled, “An Open Trial of Cognitive-Behavioral Therapy (CBT) for Pediatric Body Dysmorphic Disorder (BDD)”
- Serve as study therapist on study entitled, “An Open Trial of CBT for BDD by Proxy”

**Psychotherapy and Emotion Research Laboratory, Center for Anxiety and Related Disorders**
**Boston University**
Boston, Massachusetts
*Doctoral Research Assistant, 09/2009 – 07/2013*
Primary Advisor: Stefan G. Hofmann, Ph.D.

- Conducted dissertation study entitled, “Effect of Intranasal Oxytocin on Pro-Social Behavior in Social Anxiety Disorder”
- Obtained FDA approval for Investigational New Drug (IND) application for oxytocin nasal spray to be used in dissertation study under IND#113,827
- Received training on FDA sponsor-investigator responsibilities through the Boston University Clinical Research and Resources Office
- Participate in various lab writing projects
- Conduct laboratory research on social anxiety disorder and related disorders
- Actively seek grant funding for independent research studies
- Served as data manager, independent evaluator, and study therapist for NIMH-funded multi-site grant entitled, “D-cycloserine Enhancement of Exposure in Social Phobia”
• Completed second year project examining rejection sensitivity as a link between social anxiety and body dysmorphic concerns
• Submitted two separate grant proposals to NIMH through Ruth L. Kirschstein National Research Service Award (NRSA) in the areas of oxytocin in social anxiety disorder, and the relationship between body dysmorphic disorder and social anxiety disorder

Cognitive and Affective Neuroscience Laboratory, McGovern Institute for Brain Research Massachusetts Institute of Technology
Cambridge, Massachusetts
Volunteer, 05/2010 – 05/2011
Supervisor: John Gabrieli, Ph.D.

• Received safety training on fMRI scanning procedures
• Obtained yellow badge to assist in the control room during scanning
• Assisted in clinical populations undergoing fMRI

OCD and Related Disorders Program, Massachusetts General Hospital/Harvard Medical School
Boston, Massachusetts
Supervisors: Sabine Wilhelm, Ph.D., Luana Marques, Ph.D.

• Managed NIMH-funded studies: “Pharmacotherapy Relapse Prevention in BDD” and “Fluoxetine in Pediatric BDD”
• Prepared and submitted IRB continuing reviews and NIMH progress reports
• Prepared and submitted materials to the Data Safety and Monitoring Board
• Coordinated study visits and managed data collection for over 50 subjects
• Prepared medications for subjects by working closely with the MGH research pharmacy, and performed laboratory examinations (phlebotomy and vitals)
• Organized digital recording files for all sessions with clinicians and psychiatrists
• Conducted telephone screening interviews
• Prepared weekly study updates for cross-site conference calls
• Served as a liaison for local newspapers, magazines, and other media companies to assist in designing new advertisements for study recruitment
• Gained familiarity with the assessment and treatment of OCD, BDD, and Tourette Syndrome
• Initiated the creation of a Research Assistant Manual for training new research assistants
• Assisted in the preparation of grant proposals for the NIMH

Department of Psychological and Brain Sciences, Dartmouth College
Hanover, New Hampshire
Supervisors: Todd F. Heatherton, Ph.D. (advisor), Paul J. Whalen, Ph.D. (second reader)
• Designed a research study for senior honors thesis entitled, “The Effect of Mood on Interpersonal Evaluations under Automatic and Controlled Processing,” examining automatic and controlled processes in social judgments associated with unattractiveness stigma
• Collected, coded and analyzed data for over 120 subjects
• Defended thesis to department committee
• Prepared and presented poster at department poster session
• Poster was nominated for the 2007 Department of Psychology Rentels Prize
• Research was funded by the Dean of Faculty Kaminsky Family Fund Award

Anxiety Disorders Service, Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Research Assistant, 01/2006 – 06/2007
Supervisors: Claudia Zayfert, Ph.D., Jason Goodson, Ph.D.

• Entered, checked, and scored data for a database of over 1,000 patients
• Gained familiarity with the measures used for the assessment of anxiety disorders such as the ADIS and CAPS
• Assisted with weekly Social Anxiety and Assertiveness treatment groups
• Conducted literature searches for papers and presentations

TEACHING EXPERIENCE

Department of Psychology, Boston University
Boston, Massachusetts
Teaching Fellow, 09/2009 – 06/2013
Supervisor: Joanne H. Palfai, Ph.D.

• Led four 50-minute, weekly discussion sections for Psychology 101 (Introduction to Psychology) and Psychology 371 (Abnormal Psychology) for seven semesters
• Prepared lectures, study guides, and exam review sessions for discussion sections
• Attended general lecture classes, prepared lecture notes, and assisted in preparing exams
• Taught over 10+ additional lectures as guest lecturer when professors needed coverage

Summer Challenge Program, Boston University
Boston, Massachusetts
Course Instructor, 07/2012
Supervisor: Alexandra Adams, Ph.D.

• Developed course curriculum, teaching materials, assignments, and syllabus for two-week course on Abnormal Psychology for high school students
• Led two-hour daily class for a two-week session with 24 students enrolled
• Integrated lecture, discussion, and interactive activities aimed at covering a broad range of topics within Abnormal Psychology

CLINICAL EXPERIENCE

Massachusetts General Hospital/Harvard Medical School
Boston, Massachusetts
Intern, 07/2013 – present
Primary Supervisor: Susan Sprich, Ph.D.
Secondary Supervisors: Lee Baer, Ph.D., Jennifer Greenberg, Psy.D., Jeanne Fama, Ph.D.

• Serve as individual therapist in CBT-based treatments in the Outpatient Psychiatry Department and carried a clinical caseload of 8 individual patients
• Serve as group co-leader in weekly Dialectical Behavioral Therapy (DBT) treatment for borderline personality disorder
• Attend weekly DBT team meetings
• Attend three hours of weekly didactic seminars covering evidence-based treatments for various psychopathologies, ethics, diversity, and clinical supervision
• Participate in four hours of weekly clinical supervision (group and individual)

Center for Anxiety and Related Disorders, Boston University
Boston, Massachusetts
Clinical Supervisor, 08/2012 – 06/2013
Clinical Director: Lisa Smith, Ph.D.

• Served as direct clinical supervisor for second year graduate student completing required practicum for BU Clinical Psychology Program
• Provided one hour of weekly individual supervision for supervisee’s caseload of two patients
• Provided live supervision and/or listen to audio recordings of sessions
• Attended a two-hour weekly didactic seminar covering supervisory issues such as models of supervision, case conceptualization, alliance building techniques, ethical issues, and diversity

Bipolar Clinic and Research Program, Massachusetts General Hospital/Harvard Medical School
Boston, Massachusetts
Practicum Student, 09/2011 – 07/2012
Supervisor: Thilo Deckersbach, Ph.D.

• Administered the Mini International Neuropsychiatric Interview (M.I.N.I. Plus), and provided CBT and supportive psychotherapy for patients with bipolar disorder
• Carried a clinical caseload of four to six individual patients
• Served as an independent evaluator on the CHOICE study by administering the Bipolar Inventory of Symptoms Scale (BISS), LIFE Range of Impaired Functioning Tool (LIFE-RIFT), and the Clinical Global Impression Scale (CGI) for Bipolar Disorder
• Attended didactic seminars for the first two months of practicum on the psychopathology and assessment of bipolar disorder, emotion regulation skills, problem-solving and behavioral strategies, and cognitive remediation

Center for Anxiety and Related Disorders, Boston University
Boston, Massachusetts
Staff Therapist, 09/2010 – 06/2013
Supervisors: Lisa Smith, Ph.D., Todd Farchione, Ph.D., Michael Otto, Ph.D.

• Provided weekly, individual CBT for patients with various mood and anxiety disorders
• Carried a clinical caseload of three to five individual patients
• Participated in one hour of weekly group supervision
• Served as co-therapist for social anxiety treatment groups (12 weeks), with 4-6 patients per group. Five groups completed to date.

Eating Disorders Program, Boston University
Boston, Massachusetts
Practicum Student, 09/2011 – 06/2013
Supervisor: Elizabeth Pratt, Ph.D.

• Provided individual cognitive-behavioral therapy for patients with eating disorders using the CBT for Eating Disorders (CBT-E) manual (Fairburn, 2008)
• Carried a clinical caseload of two individual patients
• Attended one hour of weekly group supervision for issues related to the assessment of eating disorders, case formulation, regular eating, and modifications to cognitive-behavioral therapy for obese patients

Psychological Services Center, Boston University
Boston, Massachusetts
Practicum Student, 08/2010 – 08/2011
Supervisors: Lisa Smith, Ph.D., Rosemary Toomey, Ph.D.
Student supervisors: Carl Kantner, M.A., Justin Centi, M.A.

• Conducted diagnostic interviews using the Mini-Anxiety Disorders Interview Schedule
• Received individual live supervision and weekly didactic seminars covering topics such as cognitive therapy, behavioral exposures, mindfulness, and motivational interviewing
• Provided weekly, individual cognitive-behavioral therapy for three patients with mood and anxiety disorders
• Completed the neuropsychology track of the practicum
Received individual supervision and weekly didactic seminars covering topics in the administration, scoring, interpretation, and report writing of neuropsychological assessments

Administered neuropsychological tests in the areas of intelligence, achievement, working memory, attention, executive functioning, and motor skills

Carried a caseload of three additional individual patients for neuropsychology track

Inpatient Psychiatry Unit, Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

*Activities Therapy Intern, 01/2006 – 03/2006*
*Volunteer, 06/2005 – 06/2007*

Supervisors: Linda Steele, Richard A. Ackerson

- Coordinated leisure program for both Inpatient Psychiatry units by recruiting, orienting, and training student volunteers from Dartmouth College
- Observed weekly groups led by activities therapists for Medicine Education, Patient and Family Education, Coping Skills, Problem Solving Skills, Communications, Relaxation Techniques, Therapeutic Adventure Challenge, Stress Management, Wellness Recovery, and Relapse Prevention
- Worked closely with multidisciplinary team of physicians, psychiatrists, residents, interns, and medical school students
- Attended grand rounds and team rounds
- Observed electroconvulsive therapy for three patients on the unit
- Internship was funded by the Tucker Foundation Dartmouth Partners in Community Service

**Professional Affiliations and Memberships**

2011 – present  
Student Member, Neurocognitive Therapies/Translational Research Special Interest Group, Association for Behavioral and Cognitive Therapies

2011 – present  
Student Member, Association for Psychological Science

2008 – present  
Student Member, Asian American Psychological Association

2007 – present  
Student Member, Association for Behavioral and Cognitive Therapies

2007 – present  
Student Member, American Psychological Association

2007 – present  
Phi Beta Kappa National Honor Society

**Editorial Services**

2013  
Ad Hoc Reviewer; *Clinical Psychological Science*

2013  
Ad Hoc Reviewer; *Anxiety, Stress, and Coping*

2011  
Ad Hoc Reviewer; *Psychiatry Research*
2008 Ad Hoc Reviewer; *Cognitive and Behavioral Practice*
2008 Ad Hoc Reviewer; *CNS Neuroscience & Therapeutics*

**PUBLICATIONS**


Hofmann, S. G., **Fang, A.,** & Brager, D. N. (under review). Effect of oxytocin on psychiatric symptoms associated with social processes: A meta-analysis.


model of anxiety disorders. Depression and Anxiety, 29, 409-416.

Academic Press.

S. (2011). Culturally adapted cognitive behavioral therapy for Body Dysmorphic 

sensitivity mediates the relationship between social anxiety and body dysmorphic 

Fang, A., & Hofmann, S. G. (2010). Relationship between social anxiety disorder and body 

Comparative prevalence, correlates of impairment, and service utilization for eating 
disorders across U.S. ethnic groups: Implications for reducing ethnic disparities in health 

Hofmann, S. G., Sawyer, A. T., & Fang, A. (2010). The empirical status of the “new wave” of 

Presentations

behavior in social anxiety disorder. Symposium presented at the 47th annual meeting of 
the Association for Behavioral and Cognitive Therapies. Nashville, TN.

retraining for social anxiety disorder on body dysmorphic symptoms. Symposium 
presented at the 46th annual meeting of the Association for Behavioral and Cognitive 
Therapies. National Harbor, MD.

Fang, A., Marques, L., Tart, C., Jacoby, R., Robinaugh, D., Rosenfield, D., Shiekh, M., 
Otto, M. W., & Pollack, M. H. (2012, April). Short term and long-term efficacy of d-


REFERENCES (in alphabetical order)

David H. Barlow, Ph.D., Founder and Director Emeritus of the Center for Anxiety and Related Disorders at Boston University, 648 Beacon St, 6th floor, Boston, MA 02215. dhbarlow@bu.edu.

Thilo Deckersbach, Ph.D., Director of Cognitive Neuroscience Research at the Bipolar Clinic and Research Program at Massachusetts General Hospital. 50 Staniford St, 5th floor, Boston, MA 02114. tdeckersbach@mgh.harvard.edu.
Stefan G. Hofmann, Ph.D., Professor of Psychology, and Director of the Psychotherapy and Emotion Research Laboratory at Boston University. 648 Beacon St, 4th floor, Boston, MA 02215. shofmann@bu.edu.

Sabine Wilhelm, Ph.D., Director of OCD and Related Disorders Program, Professor at Harvard Medical School. 185 Cambridge St, 2nd floor, Boston, MA 02114. swilhelm@mgh.harvard.edu.