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Attachment Style Moderates the Effects of Oxytocin on Social Behaviors and Cognitions During Social Rejection: Applying an RDoC Framework to Social Anxiety

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Abstract

Whereas the DSM categorizes individuals with similar self-reported symptoms, the Research Domain Criteria (RDoC) offers a new approach for classifying mental disorders based on dimensions of observable behaviors and neurobiological measures. The objective of this proof-of-concept study is to adopt this approach by distinguishing individuals based on disorder-related personality traits during an experimental manipulation that targeted a disorder-related biological mechanism. Specifically, we examined whether attachment style moderated the effect of oxytocin administration on social behaviors and cognitions during a social exclusion test in individuals with social anxiety disorder. When receiving oxytocin compared to placebo, only individuals with low attachment avoidance displayed more social affiliation and cooperation, and only those with high attachment avoidance showed faster detection of disgust and neutral faces. Thus, attachment style moderated oxytocin's effects among individuals who shared the same DSM diagnosis. We conclude that neurobiological tests can inform new classification strategies by adopting an RDoC framework.

Introduction

In 2008, the National Institute of Mental Health launched the Research Domain Criteria (RDoC) initiative with the goal to develop new ways of classifying mental disorders based on dimensions of observable behaviors and neurobiological measures (Insel et al., 2010). An example of such a dimensional construct is social affiliation and social avoidance within the social domain of RDoC (Morris & Cuthbert, 2012). A biological correlate of social affiliation and attachment is oxytocin, a nine amino acid neuropeptide, which is produced in the hypothalamus and acts as neuromodulators or neurotransmitters throughout the brain, including the limbic areas, midbrain, and brainstem (Heinrichs, von Dawans, & Domes, 2009; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011).

Studies have shown that intranasal delivery of oxytocin enhances social cognition by improving trust and cooperation (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and flexible attentional shifting (Ellenbogen et al., 2012). Although the effects of oxytocin on social behaviors and cognitions are relatively strong and robust, these effects appear to be specific to certain individuals and under certain conditions (Guastella et al., 2010; Olff et al., 2013). Specifically, individual differences in sex, hormone levels, attachment orientation, and psychiatric status appear to moderate oxytocin's effects (MacDonald, 2013). Furthermore, only a certain oxytocin receptor polymorphism has been linked to particular phenotypes, such as face recognition memory (Skuse et al., 2013). These studies suggest that there are meaningful individual differences in response to oxytocin administration, and that these differences might identify subgroups within the same DSM category, which is in line with the RDoC initiative.

The objective of this article is to conduct a proof-of-concept study adopting the RDoC framework in a clinical sample. Specifically, we examined whether attachment style moderates the effect of oxytocin on social behaviors and cognitions in a sample of individuals with a DSM-IV diagnosis of social anxiety disorder. We chose to focus on oxytocin and attachment style in severe social anxiety for a number of reasons. First, social anxiety disorder is a heterogeneous diagnostic category, with individuals differing on a number of dimensions (Hofmann, Heinrichs, & Moscovitch, 2004). One of these dimensions appears to be attachment style (MacDonald, 2013; Olff et al., 2013), which can be measured using dimensional self-report scales. Second, a neurobiological correlate of attachment is oxytocin, which is also implicated in social behaviors and cognitions (Meyer-Lindenberg et al., 2011). For example, it has been shown that individuals with high levels of social anxiety exhibit prominent deficits in social cognitions and behaviors (i.e., maladaptive attentional biases and social avoidance behaviors), which are in part regulated by oxytocin (Ellenbogen et al., 2012; Evans, Monte, Noble, & Averbeck, 2013; Heimrichs et al., 2003). Third, social behaviors and cognitions associated with social anxiety can be reliably measured and quantified in the laboratory. For example, previous investigators have measured behavioral response to social rejection using the Cyberball game (Williams & Jarvis, 2006) and early cognitive biases to social threat using the modified Posner task (Posner, 1980; Posner, Snyder, & Davidson, 1980).

This proof-of-concept study translates research from clinical science, neuroscience, and social science to shed light on the neurobiological dimension of a common mental health problem by adopting an RDoC framework. Our hypothesis was that attachment style moderates the effect of oxytocin on social behaviors and cognitions in response to social rejection in individuals with a DSM-IV diagnosis of social anxiety disorder.

Method

Participants

Participants were 60 males at least 18 years of age, with a principal or co-principal diagnosis of SAD, and had a current Liebowitz Social Anxiety Scale (Liebowitz, 1987) score of ≥ 60. Females were excluded from the study due to potential fluctuations of oxytocin during menstrual phases. No participants had significant nasal pathology, smoked > 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 taken at a stable dose for at least two weeks prior to study entry, as in other published work (Guastella et al., 2009). 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 registered by the National Institutes of Health ClinicalTrials.gov Registry #NCT01856530.

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 (mean age = 24.39 years, age range = 18-45 years). Two participants did not complete the Cyberball Task due to technical difficulties. Chi-square and *t*-tests showed no differences between groups in demographic or baseline clinical characteristics (all *p*'s > .05). The most common comorbid diagnoses were major depression (18.5%), generalized anxiety disorder (16.7%) and panic disorder with agoraphobia (7.4%).

Materials

Cyberball Task (Williams et al., 2000; Williams & Jarvis, 2006). Cyberball appears to the participant as a four-person computerized ball-tossing game, but is actually played by a single individual and is designed to simulate and manipulate rejection. Participants were led to believe that they were playing with three "others" in real time. The program was modified to create three different behavioral profiles for the confederates. For the first 80 trials (*Play Condition*), Player 1 was programmed to toss on average 70% of his balls, Player 4 tossed 30%, and Player 3 tossed only 10% of them, to the participant, who was always Player 2. Each trial consisted of a single ball toss exchange represented by a short animation of one player tossing the ball and another player catching the ball (*Figure 1*). The participant was instructed to send the ball to a player when he received it from a previous trial, and to obtain as many points as possible to be exchanged for real monetary rewards. After 80 trials, the profiles switched (*Switch Condition*), and Player 1 was programmed to toss only 10% of his balls to the participant for the next 80 trials. The decision time for other players was varied from trial to trial to enhance the believability of realistic play behavior. The primary outcome measure was the number of total balls tossed to each player during *Play* and *Switch* conditions. Ratings of trust, empathy, preference, perceived rejection, and willingness to re-engage in another game of Cyberball with each player, were also measured on a 7-point Likert scale at the end of the task. The entire task consisted of 160 trials and took approximately 8 minutes to complete.

Modified Posner Task (Posner, 1980; Posner et al., 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. During each trial, the participant saw a fixation cross displayed for 500 ms. Then, a face (disgust, happy, or neutral) appeared for 500 ms within the top or bottom half of the screen (the other half of the screen

remained 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 indicate the letter as quickly and accurately as possible by clicking the left or right mouse button (left for E, right for F). For valid trials, the probe appeared in the position previously occupied by the face stimulus. For invalid trials, the probe appeared in the empty half of the screen. The entire task consisted of 360 trials and took 10 minutes to complete.

Drug Information

The oxytocin and placebo nasal sprays were provided by a local compounding pharmacy under Investigational New Drug application #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; 6 sprays total were administered to each subject using alternating nostrils. The placebo sprays were identical to the oxytocin nasal sprays, except for the active oxytocin ingredient, and the addition of 0.65% sodium chloride to minimize nasal irritation to the patient, which was included at the recommendation of the compounding specialist. Assessment of blind revealed that participants could not distinguish between drug conditions. 63% of participants reported no adverse events, and there was no difference between groups in the frequency and nature of reported adverse events. The most common adverse events reported were jitteriness/restlessness (17%), anxiety/nervousness (11%), dry mouth (7%), and sedation/drowsiness (7%).

Procedure

Participants were recruited from community advertisements and an outpatient anxiety disorders clinic waitlist. Potential participants were phone screened for basic eligibility requirements, and asked to avoid caffeine, alcohol, and nicotine for 24 hours prior to their appointment.

During the study visit, participants gave written informed consent and were assessed for diagnostic eligibility (A.F.) using the Mini Adult Diagnostic Interview Schedule for DSM-IV (Mini-ADIS-IV; DiNardo, Brown, & Barlow, 1994). The study physician then conducted a medical screen to assess vitals, medical history, and concurrent medications. Next, participants completed a set of self-report questionnaires to assess social interaction anxiety using the Social Interaction and Anxiety Scale (SIAS; Mattick & Clarke, 1998), rejection sensitivity using the Interpersonal Sensitivity Measure (IPSM; Boyce & Parker, 1989; Harb, Heimberg, Fresco, Schneier, & Liebowitz, 2002), attachment style using the Experience in Close Relationships Inventory (ECR; Brennan, Clark, & Shaver, 1998), and subjective mood using the Positive and Negative Affect Scales (PANAS; Watson, Clark, & Tellegen, 1988). The ECR yielded two subscales reflecting attachment anxiety (anxiety about being rejected or abandoned) and attachment avoidance (discomfort with closeness and intimacy). In the current sample, the two subscales were not significantly correlated, $r = -.32$, $n = 25$, $p = .12$. Due to administrative issues, the ECR was added halfway through data collection, which contributed to sample size fluctuations between analyses. In the current sample, the test-retest reliability was fair for the SIAS ($r = .66$), PANAS positive ($r = .73$), and PANAS negative ($r = .64$). Internal consistency estimates ranged from good to excellent for the IPSM ($\alpha = .73$), SIAS ($\alpha = .88$), ECR Avoidance ($\alpha = .88$), and ECR Anxiety ($\alpha = .90$). No reliability or validity data were available for the Likert scale ratings of trust, empathy, preference, perceived rejection, and willingness to re-engage in another game of Cyberball with each player.

Participants were randomly assigned to receive a nasal spray containing either oxytocin or placebo. The study was double-blind such that neither the study physician nor the

experimenter was aware of assigned drug conditions. Using a standardized protocol, participants self-administered a nasal spray in the presence of the study physician or nurse.

Next, participants were asked to sit alone in a waiting room for 45 minutes before starting the computer tasks, which reflects a standard wait period following intranasal oxytocin administration, to allow the drug to be absorbed (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). After 45 minutes, the experimenter led the participant and three male confederates individually into a common waiting area, asked each participant to introduce his first name to the group, and then led them to separate experimental rooms, to enhance the credibility of the Cyberball Task. The order of the tasks was always Cyberball first, followed by the Posner Task. The experiment concluded with a debriefing session.

Data Analytic Plan

A regression approach was adopted to investigate the main effects of oxytocin and interactions between oxytocin and continuous moderators (attachment anxiety, and attachment avoidance) on outcomes during the Cyberball and Posner Tasks. Specifically, the primary outcome on the Cyberball Task was difference scores in the number of balls tossed to Player 1 during *Play* and *Switch* conditions. On the Posner Task, the primary outcomes were mean response latencies during valid and invalid trials following happy, neutral, or disgust facial stimuli. 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 interaction effects, we conducted hierarchical regression analyses on all participants to examine the effects of dummy coded drug group, 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 each outcome. These analyses reflected much smaller *n*'s because the ECR was included in the study midway through data collection. 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. 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.

Results

Cyberball Manipulation Check. The majority (82.7%) of participants who completed Cyberball reported noticing that Player 1 played the most with them at first, Wilks' Lambda = .66, $F(2,44) = 11.15$, $p < .001$, $\eta_p^2 = .34$, but there was no difference in other players' behavior later on during the *Switch* condition of the game, Wilks' Lambda = .95, $F(2,44) = 1.28$, $p = .29$, $\eta_p^2 = .06$.

Effects on Ball Tossing Behavior during Cyberball. 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 explained 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 across Cyberball conditions compared to placebo, suggesting greater cooperation with Player 1 (*Figure 2*). Among participants with high Attachment Avoidance, oxytocin resulted in greater difference scores compared to placebo, suggesting decreased cooperation with Player 1.

Without considering attachment style, oxytocin did not differ from placebo in ball tossing behavior as a result of the experimental manipulation. There was no significant Group x Time interaction, Wilks' Lambda = 1.00, $F(1,50) = .02$, $p = .88$, $\eta_p^2 = .00$. Both groups threw significantly more balls to Player 1 compared to other players, Wilks' Lambda = .47, $F(2,49) = 27.32$, $p < .001$, $\eta_p^2 = .53$, but this did not differ by group, $F(1,50) = .32$, $p = .57$, $\eta_p^2 = .01$.

Effects on Attention. 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.

Without considering attachment style, oxytocin 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, $F(2,50) = .44$, $p = .65$. Separate Group x Cue Type analyses were conducted 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, $F(1,51) = .70$, $p = .41$.

Effects on Self-Report Measures. Individuals who received oxytocin reported lower ratings of overall rejection from all players during Cyberball, relative to those who received placebo, $F(1,48) = 3.98$, $p = .05$, $\eta_p^2 = .08$. However, oxytocin, relative to placebo, did not significantly impact trust ratings for Player 1 compared to other players, Wilks' Lambda = .98, $F(2,47) = .44$, $p = .64$, $\eta_p^2 = .02$, nor did oxytocin significantly impact perceived rejection ratings from Player 1, Wilks' Lambda = .99, $F(2,47) = .27$, $p = .77$, $\eta_p^2 = .01$. Oxytocin also did not significantly reduce negative mood, positive mood, or social interaction anxiety, as all of these interaction effects were not 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, $F(1,23) = .01$, $p = .91$, $\eta_p^2 = .001$).

Discussion

Our approach demonstrated that individuals with severe social anxiety can be distinguished by attachment styles during an experimental manipulation of social exclusion which implicated oxytocinergic mechanisms. We predicted that attachment style moderated the effect of oxytocin on social behaviors and cognitions during a Cyberball social exclusion test in individuals with social anxiety disorder. Consistent with our hypothesis, oxytocin contributed to ongoing cooperation with a rejecting but initially cooperative partner only for those with low attachment avoidance. Moreover, in line with previous work showing that oxytocin promotes flexible attentional shifting (Ellenbogen, Linnen, Grumet, Cardoso, & Joober, 2012), our results demonstrated that oxytocin not only facilitated disengagement from all social cues depicting disgust, neutral, and happy faces for these individuals, but also speeded up the detection of disgust and neutral faces among individuals with high attachment avoidance.

This is consistent with previous work suggesting that oxytocin's effects are dependent on individual difference factors (Bartz et al., 2011). More specifically, our results showed that attachment style, which maps onto specific biological systems (Sanislow et al., 2010), moderates the effects of the oxytocin system on social behaviors and cognitions following social rejection. This distinguishes our approach from others that directly compare patients from various diagnostic categories against a comparison group to draw conclusions about diagnostic specificity. Indeed, intranasal delivery of oxytocin has been shown to improve social cognition across the diagnostic and developmental continuum, from youth with autism (Guastella et al., 2010) to adults with schizophrenia (Davis et al., 2013). In addition, our findings suggest that oxytocin administration in conjunction with an experimental rejection paradigm can identify meaningful subgroups of individuals that differ in attachment style. This does not only have important implications for the nosology of severe social anxiety, but may also contribute to the development of personalized and improved treatment strategies for this common mental disorder. It might further clarify interindividual variation in responding to oxytocin, which can ultimately inform biomarker validation in later phases of research on biomarker development (Niciu et al., 2013).

To further advance our understanding of the oxytocinergic mechanisms underlying psychopathology, an important question for future research is whether genetic polymorphisms of the oxytocin receptor gene are linked to attachment style to confer risk for psychopathology. Indeed, genetic findings point to associations between depression and certain genotype groups of two oxytocin receptor single nucleotide polymorphisms (Costa et al., 2009). Of note, the GG genotype of these polymorphisms was found to be associated with higher scores on certain attachment styles, which have been previously associated with depression (Costa et al., 2009).

Therefore, it is possible that attachment style is an endophenotype for the response to oxytocin during social rejection. It is quite possible that attachment style is not the only or even best measure of such an endophenotype. Other possible candidates that have been discussed include behavioral inhibition and impulsivity, both of which have been associated with functional polymorphisms of dopamine-related genes (Congdon, Lesch, & Canli, 2008). Thus, future research could examine these polymorphisms in individuals with mood and anxiety symptoms and examine whether these symptoms are associated with such personality styles that predict response to oxytocin during social rejection.

Another important future research question is to examine the association between the neuroendocrine responses to social rejection and the onset, course of the illness, and response to treatment in specific subgroups. To date, this research has been primarily focused on cortisol. For example, it has been shown that high levels of behavioral inhibition and elevated cortisol levels in early childhood are risk factors for the development of social anxiety disorder by adolescence (Essex, Klein, Slattery, Goldsmith, & Kalin, 2010). Moreover, elevated cortisol and temperament appears to be associated in children of mothers with social anxiety disorder, such that behaviorally inhibited children display elevated afternoon cortisol levels in general, and when confronted with a naturalistic stressor, they display elevated night-time cortisol levels (Russ et al., 2012), and lower cortisol awakening response (Hek et al., 2013). Therefore, we suggest that future research examines the association between oxytocin and other neuroendocrine measures, especially cortisol, during social rejection in vulnerable individuals, and encourage future studies to explore the role of oxytocin in the onset and development of anxiety problems.

Finally, we suggest that research examines oxytocin-relevant brain circuits linked to specific attachment styles in order to identify individuals who are at risk for developing anxiety

problems or social deficits (e.g., deficits in emotion recognition, trust or affiliative behavior, etc.). Recent studies suggest that fearful faces were associated with exaggerated amygdala activity in individuals with social anxiety disorder (relative to controls), which decreased after oxytocin treatment compared to placebo (Labuschagne et al., 2010). In a follow-up study, it was found that when viewing sad faces, individuals with social anxiety disorder responded with heightened reactivity (compared to controls) in the medial prefrontal cortex and the anterior cingulate cortex, and this reactivity decreased after oxytocin treatment (Labuschagne et al., 2011). Future studies should examine whether these brain activation patterns are linked to specific subgroups identified by attachment style and the aforementioned genetic polymorphisms. These research programs are in line with the RDoC initiative and would further contribute to the development of a new classification system for mood and anxiety problems that are based on neurobiological measures.

Our proof-of-concept study shows several limitations. First, we did not examine the oxytocin receptor polymorphism, which has been implicated in social behaviors and cognitions in several "distinct" psychopathologies, including depression (McQuaid, McInnis, Stead, Matheson, & Anisman, 2013), autism (Skuse et al., 2013), and schizophrenia (Montag et al., 2012). It remains uncertain whether attachment style is associated with this polymorphism in our sample. Furthermore, the origin of the attachment style remains unknown (such as childhood abuse or attachment history) and the same events can also impact the oxytocin system (Sanislow et al., 2010). Second, given that the ECR was added to the study halfway through data collection, several comparisons have much smaller sample sizes and weak statistical power. Relatedly, no reliability or validity data were available for the Likert scale ratings of trust, empathy, preference, perceived rejection, and willingness to re-engage in another game of Cyberball with

each player. It should be noted, however, that these ratings possess high face validity and they were not the primary outcome measures. Instead, we included these ratings as secondary measures and subjective correlates of participants' behaviors, as indexed by the number of times participants tossed the ball. Another issue involves the considerable controversy with regard to actual mechanisms of intranasal oxytocin delivery (for a review, see Evans et al., 2013). Notwithstanding these limitations, this study illustrates how neurobiological tests can inform empirically-based classification strategies by adopting an RDoC framework.

Author Note

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A. Fang and S. G. Hofmann developed the study concept and study design. A. Fang conducted all data collection and data analyses. E. A. Hoge and M. Heinrichs aided in developing the study concept, and provided essential direction with study drug procedures and consultation for study procedures. A. Fang and S. G. Hofmann wrote the manuscript with input from E. A. Hoge and M. Heinrichs. All authors contributed to writing the manuscript and approved the final version of the manuscript for submission.

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