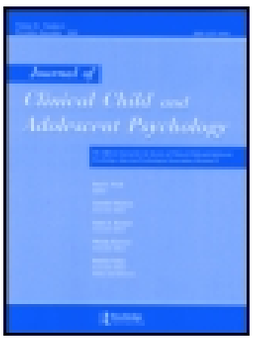

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Paradoxical Effects of Intranasal Oxytocin on Trust in Inpatient and Community Adolescents

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Research suggests that oxytocin, a neuropeptide implicated in attachment, is a promising clinical tool because it increases affiliation and attachment behaviors, which are reduced in a range of psychiatric disorders. Oxytocin has been recommended as a psychiatric treatment for adolescents, but this remains largely unstudied. Skepticism is warranted, based on mixed findings in adults and absence of data across development. The objective of this study was to examine the effect of intranasal oxytocin on attachment-related and non-attachment-related trust in an interactive game, determining how this effect differs among inpatient adolescents and healthy controls and whether this effect is moderated by attachment security. There were 122 adolescents (ages 12–17; $n = 75$ inpatient, 70% female, 37% Black, 24% Hispanic, 20% White, and 20% multiracial; $n = 46$ control, 55% female, 75% Caucasian) randomized to receive self-administered intranasal oxytocin or a placebo and play a trust game with their mother and a stranger over the Internet. Oxytocin only affected the trust game behavior of adolescents when attachment security was moderate or low. At these levels, oxytocin increased the trust of patients, such that their behavior was equivalent to that of healthy controls. Paradoxically, oxytocin reduced the investments of healthy control subjects. This study takes a first step toward determining whether, and for whom, oxytocin may have a trust-enhancing effect and challenges simplistic notions of oxytocin as the attachment-chemical of the brain—pointing instead to differential oxytocin effects based upon clinical status (patient vs. control) and attachment security.

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INTRODUCTION

Adolescence is a developmental stage heavily affected by psychopathology: 46.3% have a psychiatric diagnosis (Merikangas et al., 2010), adolescents are 90% more likely

than children to use mental health services, and total mental health costs are estimated at $8.9 billion (Agency for Healthcare Research and Quality, 2014). Attachment has been identified by the National Institute of Mental Health as a construct within the broader domain of social processes that underlies psychopathology and cuts across diagnostic categories in the matrix of the Research Domain Criteria described by Insel et al. (2010). Indeed, insecurity in an adolescent's attachment to their caregiver, assessed through interview and self-report, is associated with increased psychiatric hospitalization (Allen, Hauser, & Borman-Spurrell, 1996), varied psychopathology (Allen, 2008), and reduced ability to make use of social and therapeutic support (Venta, Sharp, & Newlin, 2015). From a biological perspective, research has linked adolescent psychopathology to disruptions in oxytocin—a neuropeptide implicated in lactation, nurturance, and bonding. Anomalous salivary/plasma oxytocin levels have been observed in youth with conduct problems (Levy et al., 2015), callous unemotional traits (Dadds et al., 2014), obsessive compulsive disorder (Swedo et al., 1992), and autism spectrum disorders (Preti et al., 2014). Genetic oxytocin receptor variants have also been associated with internalizing and externalizing disorders (Hostinar, Cicchetti, & Rogosch, 2014; Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012).

Despite enthusiasm about the potential of synthetic, intranasally administered oxytocin as a clinical intervention for teens to address attachment-related psychopathology (Netherton & Schatte, 2011), there are numerous limitations to note. First, although oxytocin has been shown to increase nurturance in animals (Keverne & Kendrick, 1992), and in human adults appears to increase maternal sensitivity (Feldman, Weller, Zagoory-Sharon, & Levine, 2007) and quality of interactions (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010), trust and generosity (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Mikolajczak et al., 2010; Zak, Stanton, & Ahmadi, 2007), mental state reasoning and facial recognition/memory (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), empathy (Hurlemann et al., 2010), and more stimulating and less hostile paternal behavior (Naber, Van IJzendoorn, Deschamps, Van Engeland, & Bakermans-Kranenburg, 2010), to date, intranasal oxytocin has been examined as a possible treatment only in the context of autism spectrum disorders in children and adolescents (Preti et al., 2014), with no study administering intranasal oxytocin to any other adolescent patient groups. Therefore, the effects of oxytocin in other developmental phases are largely unknown.

Second, prior research indicates that the effects of intranasal oxytocin are not uniform across participants—rather, specific to the interpersonal context in which administration takes place. Thus, there is little clinical utility in data gathered from tasks that fail to consider moderating variables. For instance, among adults playing a trust game, the trust-inducing effect of oxytocin is overridden when the game partner is untrustworthy (Mikolajczak, Gross, et al., 2010). Moreover, adult research reveals that oxytocin administration yields different effects depending upon the participant's attachment security (Bartz, Zaki, Bolger, & Ochsner, 2011)—increasing positive attachment memories among securely attached individuals but increasing negative attachment memories among anxiously attached individuals (Bartz et al., 2011). Moreover, oxytocin increases neuroeconomic cooperation game behavior of adults high in attachment avoidance but not those rated high in attachment anxiety (De Dreu, 2012). This literature echoes broader neurobiological research demonstrating that oxytocin circuitry is differentially activated in mothers with varying levels of attachment security (Strathearn, Fonagy, Amico, & Montague, 2009). To date, developmentally relevant moderating effects have not been studied for adolescent receptiveness to the effects of intranasal oxytocin, calling for research to address this gap.

In summary, the scientific premise of the current study is motivated by these gaps in the literature. We are guided by the evolution-based theoretical framework articulated by Pedersen, Chang, and Williams (2014) regarding the relevance of oxytocin for affiliation in social systems as well as modulation of brain systems implicated in psychopathology (e.g., anxiety, aggression). The present study sought to explore the effect of intranasal oxytocin by examining its effect on both attachment- and non-attachment-related trust in two subsamples: healthy control adolescents and adolescents recruited from an inpatient psychiatric unit. Although not a clinical trial of oxytocin, the present study utilized a randomized, double-masked, placebo-controlled design in which adolescents self-administered intranasal oxytocin or a placebo and played computerized trust games with their mother and a stranger over the Internet. This design allowed for the first evaluation of the effect of oxytocin in the context of both attachment-related (i.e., mother game) and non-attachment-related (i.e., stranger game) trust. Moreover, this design explored differential oxytocin effects related to attachment security (i.e., dimensionally rated attachment coherence) in order to examine whether the effect of oxytocin was dependent upon attachment security.

In this study, trust was measured through computerized game based on the versions initially proposed by Camerer and Weigelt (1988) and further developed by Berg, Dickhaut, and McCabe (1995). Broadly, trust games allow for the parameterization of interpersonal dynamics relevant to psychiatric disorders in adults (King-Casas & Chiu, 2012) as well as adolescents (Mellick, Sharp, & Ernst, 2015). Iterations of this game are plentiful (Johnson & Mislin, 2011; Sharp, Monterosso, & Montague, 2012). This study used a modified version of the multiround trust game used by Kosfeld et al. (2005) because it was previously shown to be sensitive to oxytocin effects. However, that task was adapted in the current study in two ways. First, to parse apart attachment-related and non-attachment-related trust two versions of the game were presented: (a) between the adolescent and his or her mother and (b) between the adolescent and a stranger. Second, following the example of Unoka, Seres, Áspán, Bódi, and

Kéri (2009), the participant did not receive feedback about their partner's return investments and was later debriefed that both versions of the game had actually been noninteractive. This modification was used in order to avoid the distressing possibility of low return investments from mothers, had a real version of the task been played. Although the effect of oxytocin on adolescent trust has not been previously examined, adult research (albeit with limitations) would suggest that oxytocin may increase investments made in other people during trust games. Therefore, we tested the hypothesis that oxytocin would raise the level of trust in both healthy and clinical adolescents.

Two moderation hypotheses were examined. First, we expected that oxytocin effects would be more profound in the inpatient sample due to clinical need. As aforementioned, various forms of psychopathology are associated with deficient oxytocin levels. If reduced oxytocin is a cross-cutting risk factor that acts on varied brain systems conferring risk for psychopathology (as suggested by Pedersen et al., 2014), then intranasal oxytocin affects symptoms (e.g., MacDonald & Feifel, 2014) because it mitigates this deficiency. Against this background, we expected that oxytocin would increase the trust of adolescents in the study overall but would be moderated by participant subgroup such that the effects would be greater for the inpatient sample, who presumably experiences psychopathology due (in part) to oxytocin deficiency.

Second, attachment security was hypothesized as a moderator of oxytocin effects across both samples and in both games. Prior research conducted in adults has revealed that oxytocin administration increases positive attachment memories among securely attached individuals but increases negative attachment memories among insecurely attached individuals (Bartz et al., 2011). Thus, it was expected that adolescents (across patient and healthy control subgroups) with high attachment coherence (i.e., a proxy for security) would experience greater trust enhancing effects from oxytocin than those with low attachment coherence. Although moderation was hypothesized across games (i.e., mother and stranger), we are aware of additional evidence indicating that the trust-inducing effect of oxytocin can be overridden based on pregame knowledge of the partner (Mikolajczak, Gross, et al., 2010). Because adolescents would have prior knowledge about their mother's trustworthiness, we expected the moderating role of attachment to be present, but attenuated, for the attachment-related trust game.

METHODS

Participants

Adolescents were recruited from an urban psychiatric unit that treats severe emotional and behavioral disorders; all admissions that met inclusion criteria were approached for consent. Healthy controls were recruited from urban schools and public advertising via self-selection. All recruitment took place in the Southwestern United States. Inclusion criteria across both groups were ages 12 to 17, English literacy, and a living mother. Exclusion criteria for inpatients included a diagnosis of psychosis, intellectual disability, or neurological disorder (assessed at admission by clinical staff), leaving only inpatients with emotional and/or behavioral disorders in the sample. Exclusion criteria in the healthy control sample included any significant psychopathology ($T > 65$ on dimensional symptoms ratings; Achenbach & Rescorla, 2001). In both groups, participants were excluded for consumption of alcohol or tobacco during the 24 hr prior to oxytocin administration, consumption of food or drink within 2 hr of administration, and pregnancy.

Eighty-four inpatient adolescents and their parents enrolled in this study. Missing or corrupted video data led to the exclusion of six adolescents; three adolescents had problematic trust game data (i.e., investments made were outside of the 1-to-12-point range, reflecting poor understanding of the task) and were excluded, resulting in a final sample of 75 inpatients. Adolescents with treatment refractory symptoms typically populate the recruitment unit; approximately 55% of the sample had been previously admitted for acute psychiatric hospitalization (i.e., 1–5 days) and 55% for extended psychiatric hospitalization (i.e., 5+ days); 89% were prescribed psychiatric medications at admission. Overall, the rate of psychopathology in this sample was high as measured by parent report on the Child Behavior Checklist (see Table 1) and according to structured clinical interviews, which indicated that approximately 77% met criteria for a depressive disorder, 33% for an externalizing disorder (attention deficit/hyperactivity disorder, oppositional defiant disorder, or conduct disorder) and 64% for an anxiety disorder. Sixty-two healthy control adolescents and their parents enrolled in this study. Missing or corrupted video data led to the exclusion of 10 participants, three participants were excluded due to significant psychopathology, and three participants had problematic trust game data (i.e., out of range) and were excluded, resulting in a final sample of 46 healthy controls. Descriptive data for both samples are presented in Table 1.

Measures

Demographics

A questionnaire was used to assess demographics including age, birth date, birth sex, ethnic/racial background, use of oral contraception, and menstrual cycle. These variables were assessed in order to identify possible confounds and adequately describe the samples. The measure was created for this study.

Psychiatric severity

Psychopathology was assessed using the Child Behavior Checklist (Achenbach & Rescorla, 2001), a widely used parent-report questionnaire for youth ages 11–18. It includes 112 problem items, each scored on a 3-point scale, and yields a dimensional Total Problems score that reflects

TABLE 1
Descriptive Data for Both Samples

Dimensional Variables	*Control M (SD)*	*Patient M (SD)*	*t*	*p*
Age	14.43 (1.86)	15.35 (1.47)	−2.83	.006
Attachment Security	5.71 (1.74)	4.61 (1.77)	3.33	.001
WRAT Word Reading Grade Level	9.20 (3.25)	—	—	—
CBCL Total Problems	45.30 (9.89)	68.70 (5.58)	−14.59	< .001
Categorical Variables	*Control % (n)*	*Patient % (n)*	χ^2	*p*
Female	69.6% (32)	54.7% (41)	2.64	.104
Ethnicity	—	—	48.22	< .001
Caucasian	19.6% (9)	75.0% (54)		
Hispanic	23.9% (11)	4.2% (3)		
Asian	0.0% (0)	4.2% (3)		
Black or African American	37.0% (17)	2.8% (2)		
Multiracial, Other, or No Answer	19.6% (9)	13.9% (10)		
Currently Menstruating	8.7% (4)	24.0% (18)	11.44	.003
Using Oral Contraceptives	0.0% (0)	10.7% (8)	9.97	.007

Note: WRAT = Wide Range Achievement Test 4; CBCL = Child Behavior Checklist; *n* = number endorsed.

overall symptom severity. Sample items include "Would rather be alone than with others," "Self-conscious or easily embarrassed," and "Inattentive or easily distracted." Previous psychometric evaluations have been conducted by the authors of these measures and have demonstrated adequate validity and reliability in clinical and community samples of adolescents (Achenbach & Rescorla, 2001).

Trust

Trust was assessed using a trust game modified from the games used by Unoka et al. (2009) and Kosfeld et al. (2005), which do not require immediate feedback from the partner, thus making the task practically feasible in inpatient settings. The task was modified to increase its attachment relevance through inclusion of a condition played with the participant's mother. Task instructions were as follows:

> In this game, you will be the Investor. In each of 5 rounds, you will receive 12 dollars. You will then decide how many you want to send to your partner over the Internet. Whatever you decide to send will be tripled on the way to your partner. Your partner then decides how many dollars she wants to keep and how many she wants to send back to you. The object of the game is to have as much money as possible. You will play two games that will come up in random order. Either you will play with your mother first, or with another woman who is a stranger to you. They will connect over the Internet in order to play the game with you. When you are playing with your mother, it is completely up to her how many dollars you get back in each round. When you are playing with the stranger, the amount you get back is completely up to her.

The adolescent was told that his or her partner would receive the same instructions, provided a chance to ask questions, and asked to repeat the instructions before progressing. The adolescent was told that the study payment was dependent upon the amount received from each game partner but that he or she would not know the amount received until the end of the assessment session. Despite not receiving feedback between trials (i.e., partner responses are not shown to the adolescent), this game has previously discriminated between diagnostic groups expected to show differences in trust behavior (Unoka et al., 2009). Both game conditions were programmed electronically to randomize order and simulate an Internet game. In this study, total dollars invested in the stranger game was utilized as a parameter of non-attachment-related trust, and total dollars invested in the mother game was utilized as a parameter of attachment-related trust. Adolescents were subsequently debriefed about the study's use of deception (i.e., both tasks were played only with the computer and payment was standardized across participants and irrelevant to task performance) and asked to rate how much they believed they were playing with their mothers on a scale from 1 to 7; mean believability was 5.12 (SD = 1.78).

Attachment Security

The Child Attachment Interview (CAI; Target, Fonagy, Shmueli-Goetz, Datta, & Schneider, 2007) is an interview-based measure assessing attachment organization by accessing children and adolescents' mental representations of their attachment figures. For instance, interviewees are asked to give three words to describe their relationship with each caregiver and asked specifically about times of loss, illness, and death. The interview is conducted in private and videotaped. Interviews are coded from videotapes on the basis of 11 scales. The Coherence Scale, used in the present study, integrates other scales to determine overall interview quality, which most

closely mirrors overall attachment security. Indicators of coherence include fresh speech, comprehensibility, and reflectiveness and low inhibited narrative production, contradiction, inconsistency, perseveration, and dysfluency. This measure has demonstrated excellent psychometrics in clinical and community samples of youth and adolescents (Shmueli-Goetz, Target, Fonagy, & Datta, 2008; Venta, Shmueli-Goetz, & Sharp, 2014). All CAI coders for this study completed a 3½-day training through the Anna Freud National Centre for Children and Families and achieved reliability benchmarks for accreditation. Interrater agreement based on 50 randomly selected interviews and two independent coders revealed a large, significant intraclass correlation for the coherence scale (intraclass correlation coefficient = .70), $F(48) = 3.34$, $p < .001$.

Reading Level

The Wide Range Achievement Test 4 (Wilkinson & Robertson, 2006) was utilized in the healthy control sample to assess grade-equivalent reading level in order to characterize the sample and ensure successful understanding of study procedures. Although specific item content is protected, the task utilized in the current study included asking the participant to read words of increasing difficulty aloud. Previously published psychometric data includes grade- and age-based norms derived from a nationally representative sample that includes adolescents (Wilkinson & Robertson, 2006). This task was not utilized with the patient subgroup, as many admissions to this unit undergo psychoeducational testing upon admission with approximately average abilities characterizing the sample (Full Scale Intellectual Quotient M = 106.4, SD = 13.5; Kavish, Bailey, Sharp, & Venta, 2017).

Procedures

This study was approved by the responsible institutional review committees. Data were collected at one time point, upon admission to the inpatient unit and in one assessment session at a university laboratory (healthy control sample). In both groups, written informed consent from parents was collected first, and if granted, written informed assent from adolescents was obtained. Following assent, adolescents completed the CAI, then completed questionnaire-based measures, self-administered oxytocin or a placebo, waited 50 min, then completed the trust game. Thus, the entire assessment session generally lasted approximately 3 hr, with the interview and trust game at opposite ends of the protocol. Following all study procedures, participants were debriefed about deception involved in the trust game and compensated with a $30 gift card for their participation.

The current study used a randomized, double-masked, placebo-controlled design to examine the experimental effect of intranasal oxytocin on trust (the study did not endeavor to be a clinical trial of oxytocin). Adolescents from each sample were randomized to self-administer a placebo or oxytocin nasal spray. Specifically, a random number generator was used to assign a number to each nasal spray, which was then administered in ascending order. Both the researcher and the adolescent were masked to their assignment. Oxytocin administration followed standard procedures (Kosfeld et al., 2005); subjects self-administered a standard dose (MacDonald et al., 2011): three puffs of a nasal spray in each nostril for a total of 24 IU oxytocin (Syntocinon-Spray, Novartis) or placebo spray containing all inactive ingredients, 50 min before the start of the trust game. A random number (used to randomize participants) was assigned to each bottle and linked to experimental condition in a document that was sealed until study completion. A symptom checklist before, immediately after, and 45 min after administration revealed no adverse effects in this study. The effects of intranasal oxytocin are thought to peak 50 min postadministration. Adolescents watched the same predetermined movie without relevance to attachment during the intervening time. Subsequently, the researcher explained the trust game.

Data Analytic Strategy

The aim of this study was to determine the differential effect of oxytocin on trust game behavior in inpatient and healthy control adolescents while examining the potential moderating role of attachment security. Thus, a moderated-moderation

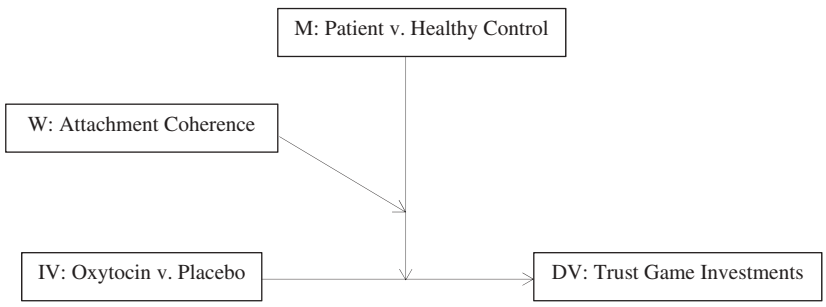

FIGURE 1 Hypothesized moderated-moderation model. *Note*: M = moderator; W = moderator of moderation; IV = independent variable, DV = dependent variable.

model, displayed in Figure 1, was evaluated twice: first with attachment-related (i.e., total investment in mother game) trust as the outcome variable and second with non-attachment-related (i.e., total investment in stranger game) trust as the outcome.

RESULTS

Preliminary Analyses

In the healthy control group, 25 adolescents received oxytocin and 21 received placebo. In the patient group, 42 adolescents received oxytocin and 33 received placebo. There were no significant differences between the placebo and oxytocin groups with regard to age ($t = -.22$, $p = .83$) or psychopathology ($t = .68$, $p = .50$). Likewise, there was no evidence of a significant relation between experimental condition and sex ($\chi^2 = .35$, $p = .56$) or experimental condition and race/ethnicity ($\chi^2 = 5.75$, $p = .22$).

Differences between patient groups are presented in Table 1; age, ethnicity, menstrual status, and oral contraceptive use differed between groups and were therefore controlled for in subsequent analyses. No participant was pregnant at the time of the study. Grade-equivalent reading level was assessed in the healthy control group; average grade equivalence corresponded to age, suggesting age-appropriate reading abilities.

Effect of Oxytocin on Trust

Mean total attachment-related trust across experimental conditions and patient groups was as follows: healthy control group that received oxytocin, $M = 30.88$, $SD = 14.01$; healthy control group that received placebo, $M = 34.76$, $SD = 10.89$; patient group that received oxytocin, $M = 33.52$, $SD = 12.97$; patient group that received placebo, $M = 32.64$, $SD = 15.45$. No evidence of significant group differences was noted in analyses of variance, $F(120) = .35$, $p = .79$. Mean total non-attachment-related trust across experimental conditions and patient groups was as follows: healthy control oxytocin, $M = 22.80$, $SD = 11.01$; healthy control placebo, $M = 28.57$, $SD = 8.39$; patient oxytocin, $M = 30.31$, $SD = 13.09$; patient placebo, $M = 23.58$, $SD = 11.97$. Evidence of significant group differences was noted across experimental conditions and patient groups, $F(120) = 3.24$, $p = .03$. Post hoc pairwise comparisons indicated a significant difference between oxytocin and placebo experimental conditions within the patient group ($M_{diff} = 6.73$, $p = .015$) such that individuals in the oxytocin experimental condition made significantly higher investments during the stranger game. In addition, a significant difference was noted between the oxytocin patient and healthy control groups ($M_{diff} = 7.51$, $p = .012$), such that patients who received oxytocin invested significantly more during the stranger game than healthy control subjects who received oxytocin. No significant difference was noted between the patient oxytocin and healthy control placebo groups, suggesting that oxytocin normalized the stranger trust game investments of patients to a health control level (post hoc equivalence test; Weber & Popova, 2012; $t = -1.71$, $\Delta = .30$, $p = .25$). Figure 2 graphically illustrates these results.

To examine the differential relations between oxytocin and trust game behavior based upon patient group (i.e., healthy control vs. patient) and attachment security (i.e., attachment coherence), two moderated-moderation models were tested. Both models controlled for age, ethnicity, menstrual status, and oral contraceptive use based upon bivariate analyses. Both models tested hypotheses illustrated in Figure 1, differing only with regard to the outcome variable. The PROCESS SPSS Macro (Hayes, 2013) computation tool was used to evaluate moderated-moderation in both models.

In the first model, non-attachment-related trust served as the dependent variable. In this model, significant main effects of experimental condition ($t = 2.11$, $p = .04$) and patient group ($t = 2.74$, $p = .007$) were observed. Moreover, evidence of significant moderation was noted: Experimental Condition × Patient Group ($t = -3.38$, $p = .001$) and Experimental Condition × Patient Group × Attachment ($t = 2.67$, $p = .009$). For the purposes of illustrating these conditional effects, coherence was converted into a categorical variable: M, +1 SD, and −1 SD. Figure 3 illustrates this moderated moderation, as follows: When attachment coherence was low, there was a significant negative effect of oxytocin on trust in the healthy control group ($t = -2.33$, $p = .02$) and a significant positive effect of oxytocin on trust in the patient group

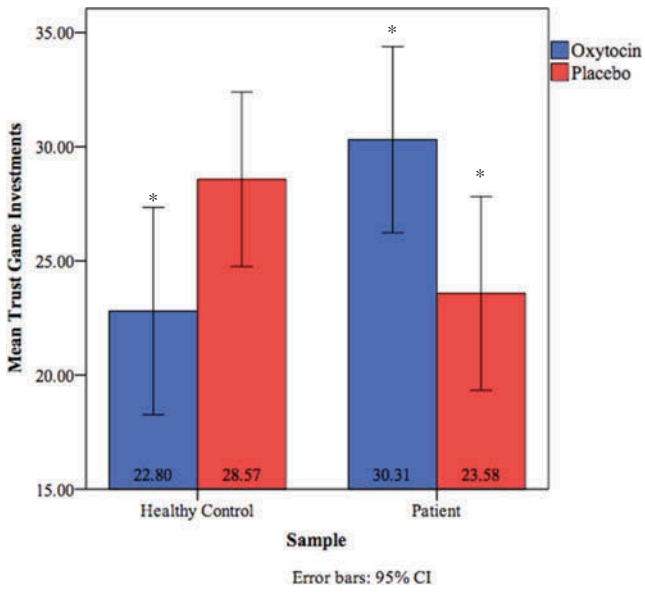

FIGURE 2 Non-attachment-related trust (i.e., mean stranger game investments) by patient group status and experimental condition. *Note*: *Significant differences in mean trust game investments between oxytocin and placebo experimental conditions within the patient group and between the oxytocin patient and healthy control groups ($p \leq .01$). CI = confidence interval.

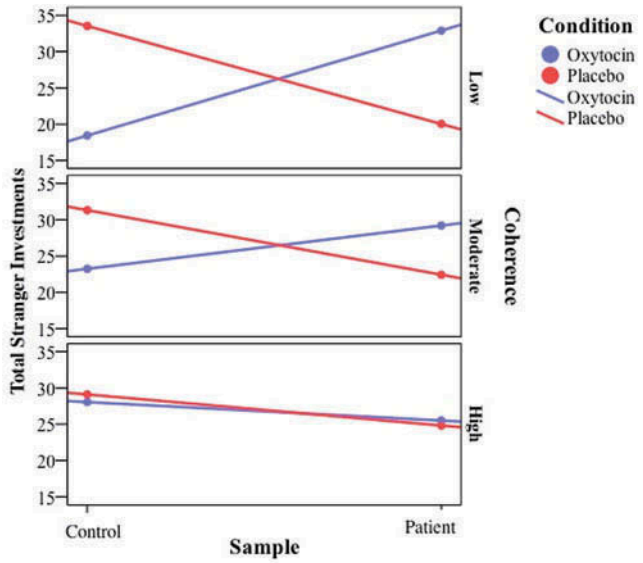

FIGURE 3 Visual illustration of moderated-moderation effect in non-attachment-related trust.

(t = 3.68, p < .001). When coherence was moderate, there was a significant negative effect of oxytocin in the healthy control group (t = −2.10, p = .04) and a significant positive effect of oxytocin in the patient group (t = 2.49, p = .01). When coherence was high, there was no significant effect of oxytocin in either the healthy control (t = −.23, p = .82) or the patient (t = .16, p = .87) groups.

In the second model, attachment-related trust served as the dependent variable. In this model, no significant main effect of experimental condition (t = 1.61, p = .11) was noted, but a significant main effect of patient group was observed (t = 2.51, p = .01). Moreover, evidence of significant moderation was noted: Experimental Condition × Patient Group (t = −2.69, p = .008) and Experimental Condition × Patient Group × Attachment (t = 2.67, p = .009). When attachment coherence was low, there was no significant effect of oxytocin on trust in the healthy control group (t = −1.56, p = .12) and a significant positive effect of oxytocin on trust in the patient group (t = 2.14, p = .04). When coherence was moderate, there was no significant effect of oxytocin in the healthy control group (t = −1.03, p = .30) or the patient group (t = .18, p = .86). When coherence was high, there was no significant effect of oxytocin in either the healthy control (t = .48, p = .63) or the patient (t = −1.53, p = .13) groups.

DISCUSSION

Given controversy around the clinical utility of oxytocin, and the dearth of studies examining this question in typical and atypical adolescents, the present study sought to examine the effect of intranasal oxytocin administration on trust game behavior in the attachment context, determining how this effect differed among inpatient and healthy control adolescents moderated by attachment security. The central hypothesis that oxytocin would raise the level of trust behavior in the patient sample to the level of healthy controls was supported. Results broadly suggested an effect of oxytocin on trust, although effects were mostly moderated and all findings require further scrutiny with more ecologically valid approaches. Specifically, the apparent oxytocin effect was strongest in the non-attachment-related trust game, where a significant main effect of oxytocin was noted. This finding was consistent with the expectation that pre-existing relationships (as in the mother game) would attenuate oxytocin effects. Moderation by patient group status was noted, such that oxytocin significantly increased the investments of inpatient adolescents, consistent with expectations that the largest oxytocin effects would be noted in inpatients. Although the hypothesized main effect of oxytocin was not noted in the attachment-related trust game, significant Experimental Condition × Patient Group status effects emerged across both games such that oxytocin increased the trust game behavior of inpatient adolescents.

Perhaps the most intuitive explanation for this finding is that oxytocin demonstrated a trust-enhancing effect only in the inpatient group because that group has clinical need; indeed, across both games a significant main effect of patient group status was noted. In prior research, oxytocin effects are often conceptualized as mitigating an impairment: decreasing anxiety following stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) or improving emotion recognition impairments (Averbeck, Bobin, Evans, & Shergill, 2012). Psychopathology, generally, is associated with decreased trust (Lester & Gatto, 1990) and insecure attachment (Allen, 2008); thus, the effect of oxytocin in this study was apparent only in mitigating these impairments.

The fact that oxytocin did not increase the investments of healthy controls in this study stands in contrast to prior research indicating that oxytocin increased investments made by healthy adults in a trust game played with an anonymous partner (Kosfeld et al., 2005). This contrast may reflect the broader lack of replicability related to studies of oxytocin (Lane, Luminet, Nave, & Mikolajczak, 2016; Lane et al., 2015; Nave, Camerer, & McCullough, 2015). Indeed, many studies since Kosfeld et al. (2005), including this one, do not document a uniform main effect for intranasal oxytocin across experimental tasks (Lane et al., 2016), and moderated effects are more consistent (Lane et al., 2015; Nave et al., 2015). In addition, developmental variables may be important to consider; given the importance of puberty for the maturation of the oxytocin system (Hostinar et al., 2014). Moreover, normative levels of trust in adolescence are high: Adolescents make large, "overly" fair investments in economic games (Hoffmann & Tee, 2006; Mellick et al., 2015) possibly due to the increased salience of social reward in this developmental stage (Mellick et al., 2015). Thus, normative

adolescent social functioning may impose a ceiling to oxytocin effects, such that effects can be detected only in the presence of clinical need or when normative trust levels decrease, as in adults. Finally, the current study and prior research use varied laboratory-based tasks and, thus, future research utilizing ecologically valid approaches across development is needed. Still, the current study provides preliminary evidence suggesting an unexpected, paradoxical oxytocin effect in healthy controls, though the bivariate difference in investments across placebo and oxytocin conditions in the healthy control sample did not reach statistical significance.

Further evidence of paradoxical oxytocin effects was noted when examining attachment security in moderated-moderation models. Across both trust games, attachment security emerged as a significant moderator of the Oxytocin × Patient Group Status effect. This effect partially supported our hypothesis; indeed, attachment acted as a moderator of oxytocin effects in both games, but the effect was equal in magnitude (contrary to expectations that the effect would be more pronounced for the non-attachment-related game). Regarding non-attachment-related trust, when attachment security was low or moderate, there was a significant negative effect of oxytocin on trust in the healthy control group and a significant positive effect of oxytocin on trust in the patient group. When coherence was high, there was no significant effect of oxytocin in either patient group. These results were partially replicated with regard to attachment-related trust, where a significant, positive effect of oxytocin was noted only in the patient group when attachment coherence was low. These results suggest that the effect of oxytocin depends upon both psychiatric status and attachment security such that no effects are noted, regardless of psychiatric status, unless attachment security is also reduced. As aforementioned, oxytocin is viewed as a biological mechanism underlying affiliation and attachment behaviors. Conversely, deficient oxytocin is associated with reduced attachment behavior. The fact that oxytocin had trust-inducing effects in this study only when attachment coherence was moderate or low suggests that oxytocin may affect trust behavior because it mitigates deficits in baseline oxytocin levels. When no deficit is present (as in high attachment coherence), intranasal oxytocin has no positive effect and rather a paradoxical, trust-reducing effect on healthy control adolescents. To our knowledge, we are the first to document this paradoxical oxytocin effect in adolescents—a finding that warrants replication and tempers enthusiasm based upon simplistic interpretations of oxytocin as a trust-enhancing panacea. Indeed, the current study adds to the research of De Dreu and colleagues (2011), who showed that oxytocin enhances *both* in-group favoritism and out-group derogation, and Declerck, Boone, and Kiyonari (2010), who showed that oxytocin enhanced cooperation only under some conditions. The current study adds to this literature base by suggesting that attachment plays a role in how oxytocin affects interpersonal behaviors toward others.

Several limitations in the current study should be noted. First, the sample sizes, although bigger than most oxytocin studies, provided sufficient power to examine the main study hypotheses but were insufficient to subdivide the sample further by diagnostic category (e.g., major depressive disorder) and conduct sufficiently powered analyses within each diagnostic group. Given that small sample sizes may contribute to inflation of oxytocin effects, the findings of this study should be replicated with larger samples. On the other hand, research domain criteria has identified systems for social processes as a cross-cutting diagnostic variable, and therefore a latent trait approach to psychopathology would be more useful to uncover bottom-up relations of oxytocin response to the behavioral phenotype. Moreover, oxytocin research with youth is difficult to execute, perhaps explaining the dearth of studies in this area. Many parents were hesitant to allow their children to participate, voicing concerns regarding the difference between oxytocin and oxycontin. Indeed, this study's modest sample reflects a 2-year recruitment effort. Second, the inpatient and healthy control groups differed demographically. Specifically, the inpatient sample was characterized by high income and was predominantly Caucasian, limiting generalizability of findings, whereas the healthy control group was more ethnically and socioeconomically diverse. Despite efforts and bearing in mind recruitment challenges, a socioeconomically matched control group was not successfully recruited, and thus these variables were statistically controlled (and did not alter results). Still, future research may seek to recruit more similar samples or examine the role of ethnicity in oxytocin responsiveness. Third, the social setting of inpatients distinguishes the two samples—indeed, the inpatient sample had recently been hospitalized, separated from their parents, and asked to trust a new group of providers, factors that may have influenced their investments. The present study's design cannot disentangle this difference between groups from the psychopathological differences between groups, an important caveat to the findings of the present study. Moreover, research personnel who conducted the CAI were necessarily aware of the patient subgroup status, though the coder of the CAI was unaware of condition and subgroup. In addition, the same researcher who conducted the CAI administered the trust game; experiments are best administered by researchers blinded to any clinical information. Fourth, the trust task used in this study is not only a simplification of true interpersonal interactions but also a simplification of interpersonal trust games as originally conceived. Specifically, in the modified version used in this study, there was no true interaction (or feedback) and, thus, no possibility for learning or reputation development or opportunity to examine how players respond to their partner's behavior (e.g., ruptures in trust associated with low return investment). To understand how oxytocin affects attachment-related social interactions, replication of this study using more complex

variations of the trust task is needed. Still, the present study is strengthened by a design that cuts across multiple levels of analysis; a randomized design, limiting confounding effects; and analytic methods that control for familywise error. In addition, psychopathology and biological confounds were assessed and included in analyses.

In sum, the present study is the first to examine oxytocin response in adolescents with and without emotional-behavior disorders and the first to consider the role of attachment in this context. To that end, this study provides first evidence for the clinical potential of oxytocin among adolescents—that it can increase the level of trust of inpatients to a "healthy control" level and does so to a greater extent at high levels of attachment insecurity. Conversely, this study also adds to the emerging literature questioning the clinical utility of oxytocin. Our findings suggest weaker oxytocin effects with regard to attachment-related trust, no significant effects when attachment security is high, and paradoxical effects in healthy controls with low attachment security. Nonetheless, this study has significant implications for adolescent psychology because it is a first step toward understanding the effects of oxytocin in adolescents and speaks to individual differences in responsiveness by exploring both inpatient and control samples and the moderating role of attachment.

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CONFLICT OF INTEREST

No conflict of interest is noted by any of the listed authors.

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