

# A Randomized Clinical Trial of Oxytocin or Galantamine in Schizophrenia: Assessing the Impact on Behavioral, Lexical, and Self-Report Indicators of Social Affiliation

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**Prior studies examining the impact of oxytocin on negative symptoms in schizophrenia have yielded mixed results. The current study explored whether oxytocin can improve more proximal indicators of social affiliation as indicated by changes in behavior, language and subjective indices of social affiliation among individuals with schizophrenia spectrum disorders during a role-play designed to elicit affiliative responses. We tested the hypothesis that daily intranasal oxytocin administered for 6 weeks would improve social affiliation as manifested by increased social skill ratings, use of positive, affiliative, and social words, and subjective responses from a previously published randomized controlled trial. Forty outpatients with schizophrenia or schizoaffective disorder were randomized to the oxytocin, galantamine, or placebo group and completed affiliative role-plays and self-report questionnaires of affect, reactions to the affiliative confederate, and willingness to interact at baseline and post-treatment. Results demonstrated that oxytocin was not effective at improving behavioral or subjective indicators of social affiliation. This study adds to a growing literature that the prosocial effects of oxytocin in schizophrenia are limited or null.**

*Key words:* psychosis/treatment outcomes/performance-based skills measures

## Introduction

Schizophrenia is characterized by pronounced and enduring deficits in social functioning that are only modestly

responsive to currently available medications.<sup>1,2</sup> These impairments in social functioning are robustly related to negative symptoms reflecting deficits in motivation and pleasure.<sup>3,4</sup> Negative symptoms reflect an unmet therapeutic need, and no medication has been approved with an indication for the treatment of negative symptoms.<sup>5</sup>

Given oxytocin's role in mammalian affiliative behavior, there have been a variety of studies that have sought to examine the potential clinical benefits of oxytocin in schizophrenia.<sup>6-8</sup> In regard to negative symptoms, results have been variable with null results as well as intriguing findings of improvement in negative symptoms.<sup>9-12</sup> A meta-analysis of 7 randomized controlled trial (RCT) studies concluded that for negative symptoms, oxytocin was no different from placebo; however, oxytocin emerged as possibly superior to placebo when focusing on studies with daily administration.<sup>13</sup> A more recent meta-analysis of 8 RCTs concluded that oxytocin does not improve negative symptoms.<sup>14</sup> Consistent with these prior null findings, we recently reported the results of an RCT indicating that the use of oxytocin as adjunctive medication (24 IU twice a day for 6 wk) failed to have any impact on negative symptoms or cognition.<sup>15</sup>

In exploring the potential therapeutic benefits of oxytocin, it may be useful to look beyond clinical ratings of negative symptoms and consider oxytocin's impact on more proximal indicators of changes in social affiliation. Changes in negative symptoms may be difficult to detect in a typical short-term oxytocin study given that improvement in negative symptoms could require alterations in

social networks and social engagement, or in occupational, educational, or recreational activities. Negative symptoms may be slower to respond to treatment as they can reflect both deficits in motivation and desire as well as environmental factors that may impact opportunity. For these reasons, the use of performance-based measures of social behavior (eg, social skill or functional capacity) has been recommended in clinical trial designs.<sup>5</sup> By assessing social behavior through such measures, it is possible to determine changes in behavior regardless of whether these behaviors are performed in the community. Prior studies using performance-based measures of social skill have demonstrated sensitivity to pharmacotherapy with, for example, findings of improved social skill with quetiapine and risperidone.<sup>16</sup>

There have only been 2 studies that have examined oxytocin's impact on performance-based measures of social competence or skill in schizophrenia. In a 6-week RCT of oxytocin, Gibson and colleagues were unable to observe any changes in social skill ratings for the oxytocin treated group.<sup>10</sup> In a larger 12-week RCT of oxytocin conducted by Jarskog and colleagues, no treatment effect was found for skill ratings at either 6- or 12-week assessments.<sup>11</sup> The findings from these 2 studies are discouraging and suggest that oxytocin does not result in the intended changes to interpersonal behavior.

When interpreting these prior null findings, it may be relevant to consider the nature of the social skill tasks being used. In both the Gibson and Jarskog studies, role-plays were based on the Social Skills Performance Assessment (SSPA) developed by Patterson et al, and involved getting to know a new neighbor and consoling an upset friend.<sup>10,11,17</sup> The use of a consoling role-play with an upset confederate expressing negative affect may be useful for looking at empathy in participants, but it may be less relevant for tapping positive affiliative responses. Further, as we have previously noted, traditional role-plays often place the burden of maintaining the conversation on the participant and instruct confederates to minimize expressions and displays of positive affect.<sup>17-20</sup> As a result, these role-plays do not induce positive affect that would be expected from an affiliative interaction.<sup>21</sup> Given these aspects of prior role-play assessments, the behavior elicited in these interactions may be less affiliative and, at least theoretically, less responsive to the affiliation-enhancing effects of oxytocin.

In addition to broad behavioral ratings, it may be informative to examine how oxytocin influences detailed aspects of language. The lexical analysis of word usage could allow for the assessment of changes in affiliation as reflected in an individual's use of positive emotion or social words.<sup>22</sup> Prior research has shown that word use can be related to symptomatology in schizophrenia.<sup>23,24</sup> More importantly, lexical analysis has been shown to be sensitive to pharmacological manipulation that impacts affiliation as demonstrated by changes in the use of social

words following administration of 3,4-methylenedioxymethamphetamine (MDMA).<sup>25</sup>

Given that oxytocin is theorized to modulate sociality through increased affiliative motivation, it is also essential to investigate changes in self-reported affiliative experience to allow for possible detection of subjective changes that may not yet manifest in behavior.<sup>6</sup> Consistent with this, our prior work has demonstrated that, in comparison to controls, individuals with schizophrenia reported similar levels of positive appraisals of their interaction partner, willingness to engage in future interactions, and increased positive affect following an affiliative social interaction task despite being rated as having poorer affiliative social skills.<sup>19</sup> However, negative symptoms can impact self-reported affiliation and affect as they have been associated with diminished positive affect and reduced positive evaluations of social partners, though results have not been consistent.<sup>19,26</sup>

In the current study (conducted as part of an RCT<sup>15</sup>), we examined the impact of oxytocin and galantamine on behavioral ratings of social skill, lexical analysis of speech, and subjective self-reported reactions during affiliative social interactions. Galantamine was investigated in the parent study because of evidence that alpha-7 nicotinic receptor agents could improve cognition and that galantamine may improve cognition.<sup>27-32</sup> Performance-based assessments of social skill were modified in an attempt to increase the elicitation of affiliative behavior. These skill assessments focused on positive affiliative role-plays (eg, making plans for a social activity with a family friend) with confederates trained to display positive affect (ie, facial displays such as smiles and verbal responses that displayed warmth, encouragement, and positive affect). We hypothesized that compared to placebo and galantamine, oxytocin would increase social affiliation as manifested by (1) increased social skill ratings, (2) increases in positive, affiliative, and social word use within these interactions, and (3) increases in self-reported positive affect, positive reactions to the affiliative confederate, and willingness to interact with the confederate.

## Methods

### *Study Design and Participants*

Individuals between ages 18 and 65 years with a diagnosis of schizophrenia or schizoaffective disorder confirmed by the Structured Clinical Interview for DSM-IV (SCID-I) participated in a double-blind RCT between March 2010 and January 2014.<sup>33</sup> Participants completed a 4-week evaluation phase (medical screening and baseline symptom, safety, cognitive, and role-play assessments) and a 6-week double-blind treatment phase. Assessments detailed below were administered at baseline and then repeated 6 weeks later at the end of treatment. Participants were randomized to one of 3 groups: (1) active intranasal oxytocin and placebo galantamine, (2) placebo intranasal

oxytocin and active galantamine, or (3) placebo intranasal oxytocin and placebo galantamine. In the original study, 50 participants were randomized.<sup>15</sup> Due to technical issues with video recordings, data were available for only 40 participants (14 placebo; 12 oxytocin; 14 galantamine). The Institutional Review Boards at the University of Maryland School of Medicine and State of Maryland Department of Mental Health and Hygiene approved all procedures, and the investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. See Buchanan et al<sup>15</sup> for a comprehensive description of study methods, safety assessments, and adverse events.

### *Intervention*

Participants continued established medication regimens and administered intranasal spray and pills twice daily for 6 weeks. The intranasal oxytocin dose was 24 IU twice a day. The galantamine target dose was 12 mg twice a day, and the following titration schedule was used: 4 mg twice a day for 1 week, then 8 mg twice a day for 1 week, then 12 mg twice a day for 4 weeks. Medication compliance was assessed weekly through intranasal bottle weight and pill counts.

### *Measures*

*Affiliative Role-Play Task.* In this task, the participant and an affiliative female confederate who was blind to group status and with whom the participant had not previously interacted completed two 3-minute role-plays, one involving getting to know a new neighbor and the second involving making plans with an old family friend. Participants were read the role-play instructions, asked follow-up questions to assess comprehension (eg, “Can you describe the situation for me?”), and then listened to an audio recording of the instructions a second time before completing each scene. The goal of the role-plays was for the confederate to simulate an affiliative encounter with the participant. Confederates received structured training through manual review with a bachelor’s level trainer, watching 3 recordings of exemplar role-plays while discussing confederates’ strengths in the videos, and completion of a minimum of 2 videotaped practice role-plays (2 scenarios per recording) with a study team member before advancing to role-plays with research participants; they received written and verbal feedback after each videotape was reviewed by the trainer. Confederates were trained to avoid lengthy pauses, display interested and affiliative affect (eg, smiling, nodding, enthusiastic vocal tone), facilitate the conversations through open-ended questions (eg, “What do you like to do in your free

time?”), and focus the conversation on pleasurable and social activities. To ensure that confederates maintained a high level of affiliation during role-plays throughout the study, supervision meetings were held once every 3 months during which the trainer played videotaped participant role-plays with all confederates present and provided feedback on confederates’ strengths and areas for improvement.

*Behavioral Coding Procedure.* Independent Bachelor’s and Master’s level coders blind to group status rated the participants’ social skills during the video-recorded role-plays using a social skills rating manual that was adapted from the Maryland Assessment of Social Competence.<sup>18,20</sup> Each participant’s role-plays were rated by only one coder; however, different coders rated each participant’s baseline and end of treatment role-plays to ensure that rater familiarity with the participant did not impact ratings. Prior to completing participant ratings, coders read the rating manuals and other assigned relevant readings and then watched a training video of 5 role-plays, rated the role-plays, and discussed their ratings with a gold standard criterion rater. Next, each rater independently rated 5 more role-plays to compare their ratings against gold standard ratings, receiving written and verbal feedback regarding their inter-rater reliability after each role-play before advancing to the next one. Coders were required to achieve a high level of inter-rater reliability (ie, ICC > 0.80) before being approved to rate participant role-plays (study ICC = 0.86). To prevent rater drift, coders received regular, structured supervision led by a gold standard criterion rating during which a challenging role-play was reviewed, rated, and discussed as a group. Raters coded social skill components across 4 domains using a 5-point Likert scale ranging from 1 (“very poor”) to 5 (“very good”): (1) Verbal/Conversational domain includes ratings of clarity, spontaneous conversation, positive valence, negative valence, and number of questions asked and word count assessed by totals rather than Likert scale; (2) Nonverbal domain: gaze/eye contact, fluency, meshing, and nonverbal bodily expression; (3) Affiliation: the participant’s engagement, warmth, friendliness, and ability to establish close personal ties coded as an aggregate across verbal and nonverbal behaviors (eg, vocal affective expression, warmth); and (4) Overall Social Skill: a general measure of ability to interact in a meaningful way across verbal and nonverbal domains. The current study examined the Affiliation and Overall Social Skill domains, and ratings were averaged across the 2 role-plays for each assessment visit.

*Linguistic Content Analysis.* Affiliative role-plays were transcribed and linguistic content of the speech of the participant was analyzed using the Linguistic Inquiry and Word Count (LIWC) software.<sup>34</sup> The LIWC contains an

internal dictionary of nearly 6,400 words and calculates the proportion of usage of sets of words that define 80 different linguistic categories, generating an output measure for each of these categories. Category variables of interest in this study were positive emotion (eg, love, nice sweet), negative emotion (eg, hurt, ugly, nasty), social (eg, mate, talk, they), and affiliative (eg, ally, friend, social) words. Output variables were expressed as a percentage of total words spoken by the participant during the role-plays with the exception of the word count which was expressed as the total raw word count. As with the behavioral coding, speech content output variables were averaged across the 2 role-plays for each assessment visit.

*Subjective Responding.* After completing the 2 role-plays, participants completed 3 self-report assessments of their affect and reactions to the role-play. A modified version of the 20-item Positive and Negative Affect Scale (PANAS) assessed present affect using a 5-point Likert scale from 1 (“very slightly or not at all”) to 5 (“extremely”).<sup>35</sup> Four items were added to the PANAS to include positive (sociable, friendly) and negative (rejected, lonely) feelings relating to social interactions, yielding a total of 24 items. Positive and negative affect descriptors were summed separately to form the Positive and Negative Affect Scores. The original PANAS has good convergent and divergent validity.<sup>35</sup> The modified version had excellent internal consistency in our sample for both the Positive (baseline  $\alpha = .86$ ; end of treatment  $\alpha = .93$ ) and Negative (baseline  $\alpha = .88$ ; end of treatment  $\alpha = .89$ ) Affect Scores. A 7-item version of the Positive Reactions to Partner Questionnaire (PRP) measured current social affiliation with the affiliative confederate on a 5-point Likert scale from 1 (“completely agree”) to 5 (“completely disagree”).<sup>36</sup> Items are reverse-coded with higher scores reflecting more positive responses towards the confederate. Although one item from the measure (“I care about how I was perceived by my partner”) was inadvertently dropped in this study, internal consistency in our sample (baseline  $\alpha = .79$ ; end of treatment  $\alpha = .71$ ) was higher than previously published samples using the full 8-item

scale ( $\alpha$  ranged from .64 to .68).<sup>26</sup> The 6-item Willingness to Interact Questionnaire (WIQ) assessed willingness for future social interactions on a 5-point Likert scale from 1 (“definitely willing”) to 5 (“definitely unwilling”).<sup>37</sup> Items are reverse-coded with higher scores reflecting greater willingness to engage in future interactions. The WIQ has high construct validity and evidenced good internal consistency in this study (baseline  $\alpha = .79$ ; end of treatment  $\alpha = .86$ ).<sup>37,38</sup>

*Data Analysis*

Analyses were conducted in SPSS 24. First, characteristics of the sample and group differences were examined. Second, 11 separate 2 (time)  $\times$  3 (treatment group) repeated measures ANOVAs were conducted for each of the behavioral rating (affiliation domain, overall social skill domain), linguistic content (total word count, positive emotion, negative emotion, social, and affiliative words), and subjective responding (PANAS positive, PANAS negative, PRP, WIQ) variables. Given the small sample size, Cohen’s *d* was employed to help interpret the magnitude of change across arms.

**Results**

*Sample Characteristics*

Sample characteristics are presented in [table 1](#). There were no statistically significant differences across treatment arms with regard to sex, ethnicity, age, education, or parental education (*Ps* > .05), and further, characteristics were quite similar. Additionally, there were no group differences on baseline ratings for each of the dependent variables in this study. The sample as a whole was predominantly male, middle-aged, and high-school educated.

*Preliminary Analyses*

Preliminary analyses were conducted to examine the assumption that the affiliative role-plays yielded positive responding as reflected in language and self-reported

**Table 1.** Sample Characteristics

	Oxytocin ( <i>n</i> = 12)	Galantamine ( <i>n</i> = 14)	Placebo ( <i>n</i> = 14)
Age, <i>M</i> (SD)	45.9 (10.7)	49.1 (11.7)	45 (10.8)
Gender			
Male, <i>n</i> (%)	10 (83.3)	11 (78.6)	12 (85.7)
Female, <i>n</i> (%)	2 (16.7)	3 (21.4)	2 (14.3)
Race			
White, <i>n</i> (%)	5 (42)	8 (57.1)	10 (71.4)
Black, <i>n</i> (%)	6 (50)	6 (42.9)	4 (28.6)
American Indian, <i>n</i> (%)	1 (8)	0 (0)	0 (0)
Education (y), <i>M</i> (SD)	13.7 (3.8)	12.4 (2.8)	13.8 (3.0)
Maternal Education (y), <i>M</i> (SD)	13.5 (1.9)	13.1 (2.6)	13.1 (3.3)
Paternal Education (y), <i>M</i> (SD)	12.9 (3.9)	11.8 (2.9)	12.8 (3.9)

affect. Collapsing across groups at baseline, results from the LIWC indicated that participants said more positive ( $M = 5.09\%$ ) than negative ( $M = 0.51\%$ ) words ( $t(39) = 16.22, P < .001$ ), more social ( $M = 7.50\%$ ) than negative words ( $t(39) = 15.21, P < .001$ ), and more affiliative ( $M = 2.22\%$ ) than negative words ( $t(39) = 7.90, P < .001$ ). With regard to mood, collapsing across groups following the baseline role-play, participants reported significantly higher positive ( $M = 40.05\%$ ) than negative ( $M = 19.75\%$ ) affect ( $t(39) = 13.32, P < .001$ ). These results are consistent with the behavior and subjective experiences expected within an affiliative interaction.

*Treatment Effects*

Descriptive statistics between baseline and post-intervention treatment arms for behavioral ratings, linguistic content, and subjective responding are presented

in tables 2–4. With regard to behavioral ratings (table 2), there were no statistically significant treatment group, time, or interaction effects.

Results for linguistic content analyses are presented in table 3. Although there was no significant main effect of group or group by time interaction for word count, there was a moderate effect of treatment on total speech output for the oxytocin group in contrast to small effects for the placebo and galantamine groups. Linguistic content results yielded a significant main effect of time on percentage of positive emotion and social words such that all participants used more positive and social words after treatment. There was also a significant group by time interaction for affiliative words. Post hoc independent sample *t*-tests indicated that participants in the placebo group said more affiliative words during the post-treatment role-plays than those in the galantamine group,  $t(26) = 2.11, P = .04$ , but not the oxytocin group,

**Table 2.** Descriptive Statistics Between Baseline and Post-Intervention Treatment Arms for Behavioral Ratings

	Pre-Treatment	Post-Treatment	Treatment Group	Time	Interaction	Cohen's <i>d</i>
	<i>M</i> (SD)	<i>M</i> (SD)	<i>F</i>	<i>F</i>	<i>F</i>	
Overall social skill						
Oxytocin	3.08 (0.76)	3.21 (0.58)	0.64	0.38	0.21	0.19
Galantamine	3.07 (0.83)	3.06 (0.99)				0.01
Placebo	2.75 (0.91)	2.89 (0.94)				0.15
Affiliation						
Oxytocin	3.41 (0.95)	3.38 (0.95)	0.48	0	2.43	0.03
Galantamine	3.35 (0.95)	3.03 (0.88)				0.35
Placebo	2.85 (1.26)	3.21 (1.07)				0.31

**Table 3.** Descriptive Statistics Between Baseline and Post-Intervention Treatment Arms for Linguistic Content

	Pre-Treatment	Post-Treatment	Treatment Group	Time	Interaction	Cohen's <i>d</i>
	<i>M</i> (SD)	<i>M</i> (SD)	<i>F</i>	<i>F</i>	<i>F</i>	
Word count						
Oxytocin	206.79 (86.82)	237.54 (90.05)	0.71	3.32	0.89	0.35
Galantamine	205.39 (76.02)	211.89 (60.95)				0.09
Placebo	183.92 (84.43)	191.46(75.78)				0.09
Positive Emotion						
Oxytocin	4.96% (2.15)	5.42% (1.94)	0.56	<b>8.85**</b>	0.63	0.22
Galantamine	5.35% (1.69)	6.45% (2.41)				0.52
Placebo	4.97% (1.65)	6.31% (2.12)				0.70
Negative Emotion						
Oxytocin	0.45% (0.60)	0.46% (0.48)	1.50	0.05	0.01	0.02
Galantamine	0.43% (0.57)	0.45% (0.40)				0.04
Placebo	0.65% (0.48)	0.69% (0.74)				0.06
Social						
Oxytocin	7.17% (2.84)	8.18% (3.78)	1.44	<b>4.67*</b>	2.23	0.29
Galantamine	7.56% (2.77)	7.49% (2.64)				-0.03
Placebo	7.74% (3.27)	10.61% (4.53)				0.73
Affiliative						
Oxytocin	2.07% (1.13)	2.08% (1.21)	1.07	0.45	<b>3.68*</b>	0.01
Galantamine	2.58% (1.68)	1.80% (.095)				-0.57
Placebo	1.98% (1.18)	3.44% (2.76)				0.69

Note: Bold values \* $P < .05$ ; \*\* $P < .01$ .

**Table 4.** Descriptive Statistics Between Baseline and Post-Intervention Treatment Arms for Subjective Responses

	Pre-Treatment	Post-Treatment	Treatment Group	Time	Interaction	Cohen's <i>d</i>
	<i>M</i> (SD)	<i>M</i> (SD)	<i>F</i>	<i>F</i>	<i>F</i>	
PANAS Positive						
Oxytocin	39.42 (8.93)	38.67 (12.97)	0.73	0.01	0.04	0.07
Galantamine	38.21 (11.33)	38.50 (11.82)				0.03
Placebo	42.43 (8.74)	42.57 (9.12)				0.02
PANAS Negative						
Oxytocin	20.83 (8.41)	19.92 (8.21)	0.46	0.42	0.02	0.11
Galantamine	18.21 (7.24)	17.64 (6.01)				0.09
Placebo	20.36 (8.67)	19.93 (8.71)				0.05
PRP						
Oxytocin	13.33 (3.96)	13.67 (3.26)	0.84	0.01	0.20	0.09
Galantamine	14.64 (5.99)	14.14 (3.86)				0.09
Placebo	12.36 (4.24)	12.71 (3.69)			0.08	
WIQ						
Oxytocin	12.58 (4.44)	11.92 (3.29)	0.91	1.47	0.33	0.17
Galantamine	13.21 (4.21)	11.79 (4.30)				0.34
Placebo	10.86 (4.29)	10.64 (4.43)				0.05

Note: PANAS, Positive and Negative Affect Scale; PRP, Positive Reactions to Partner Questionnaire; WIQ, Willingness to Interact Questionnaire.

$t(24) = 1.57, P = .13$ . There were no significant differences between the 3 groups at baseline (all  $P$ s > .05), as well as no effect of time within the placebo ( $t(13) = 1.98, P = .07$ ) or oxytocin ( $t(11) = 0.05, P = .96$ ) group with regard to affiliative word use. There was, however, a significant reduction in the percentage of affiliative words spoken in the galantamine group over time,  $t(13) = -3.08, P = .01$ .

Table 4 summarizes self-report responses. There were no statistically significant group, treatment, or interaction effects for self-reported positive or negative affect. Similarly, there were no group, time, or interaction effects for self-reported reactions to the partner or willingness to interact with the partner.

**Discussion**

The present study examined the impact of intranasal oxytocin on social affiliation in schizophrenia. To our knowledge, this is the first study to investigate oxytocin's influence on social skills, linguistic content, and self-reported affiliation and affect during a role-play interaction designed to elicit affiliative behavior. Results indicated that no treatment arm (oxytocin, galantamine, placebo) yielded improvements in social skill, use of social or positive words, self-reported affect, or self-reported affiliative responses towards the role-play confederates. These null results were obtained despite evidence that the affiliative interactions were associated with the intended positive affiliative responses as indicated in language and subjective responding.

Although not significant, there were medium-sized effects of time in the placebo group indicating greater

use of positive, social, and affiliative words during the post-treatment role-play compared to baseline. In contrast, effect sizes within the oxytocin sample were small to negligible with no changes in language. This may suggest that the effect of oxytocin on positive, prosocial linguistic content was not simply null, but that perhaps, compared to placebo, oxytocin even inhibited affiliative expression as measured in language. Of course, caution is required in the interpretation of these effect sizes given the overall null results, but the pattern of results may align with prior research with oxytocin. Research has suggested that person and context variables, such as attachment style, familiarity of partners, and childhood adversity and abuse, can moderate oxytocin's effect on prosocial behavior.<sup>39-42</sup> Declerck and colleagues found that exogenous oxytocin administration actually reduced cooperation and trust among individuals when they were interacting with previously unknown partners during a cooperation game.<sup>41</sup> Similarly, other researchers have reported that oxytocin can strengthen participants' desire to exclude others who are members of an out-group.<sup>43</sup> Taken together, these studies highlight how oxytocin can be beneficial in improving social affiliation during interactions with familiar in-group members (eg, family, friends) but may be counter-productive in forming new relationships. Given that the confederates in this study were previously unknown to the research participants, it is possible that they were viewed as out-group members, and thus oxytocin heightened feelings of distrust and decreased desire to form an affiliative bond. Although not assessed, trait anxiety or an anxious attachment style could have also played a role in our null findings, as Bartz

and colleagues have found that oxytocin decreases agency among individuals with an anxious attachment style.<sup>44</sup> Confederates in this study were trained to respond in ways that displayed warmth and encouragement during the role-plays; however, as being video-recorded and engaging in a role-play can be inherently intimidating, participants may have experienced heightened anxiety, potentially dampening the affiliative effects of oxytocin.

This study had several limitations. First, as detailed in the primary outcomes publication, this study may have been limited by the use of a relatively low dose of oxytocin and inability to monitor proper administration of intranasal oxytocin.<sup>15</sup> Second, the sample size was small, which may have limited our power to detect significant effects. Relatedly, we were underpowered to evaluate possible moderators (eg, the role of antipsychotics, smoking, and sex). Third, all confederates were young women and the participants were primarily middle-aged men, which may have further exacerbated the potential out-group impact on oxytocin's prosocial effect. Future studies may benefit from using confederates who are more similar to participants in regard to age, sex, race, and/or other characteristics. Finally, although the use of structured role-plays is meant to approximate real-world social interactions, there are inherent limitations in regard to their ecological validity. More naturalistic examinations of affiliative interactions may yield different findings.

In summary, this study adds to a growing literature suggesting that oxytocin's therapeutic impact on negative symptoms and social behavior in schizophrenia is limited, if not non-existent. Our study sought to detect a potential signal for oxytocin by utilizing affiliative role-plays to evaluate affiliative social behavior and using other proximal indicators of social affiliation (ie, linguistic content and subjective reporting of affiliative responses); however, results did not support prosocial effects of oxytocin on any of these variables.

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