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A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia

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ABSTRACT

The current study explored whether oxytocin can improve social cognition and social skills in individuals with schizophrenia using a six-week, double-blind design. Fourteen participants with schizophrenia were randomized to receive either intranasal oxytocin or a placebo solution and completed a battery of social cognitive, social skills and clinical psychiatric symptom measures. Results showed within group improvements in fear recognition, perspective taking, and a reduction in negative symptoms in the oxytocin group. These preliminary findings indicate oxytocin treatment may help improve certain components of functioning in schizophrenia. Implications for the treatment of social functioning in schizophrenia are discussed.

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1. Introduction

Individuals with schizophrenia demonstrate difficulties in social cognition, which is associated with poor social functioning (Fett et al., 2011). Given the evidence that antipsychotics do not improve social cognition (Penn et al., 2009), there is a need to explore other potential therapeutic approaches, such as oxytocin (OT).

Studies show intranasal OT treatment has prosocial effects and improves aspects of social cognition (Guastella and MacLeod, 2012; Shahrestani et al., 2013). Plasma OT levels in individuals with schizophrenia are related to some aspects of social cognition, trusting behavior and psychiatric symptoms (Goldman et al., 2008; Keri et al., 2009; Rubin et al., 2010; Walss-Bass et al., 2013). Three recent randomized, placebo-controlled clinical trials all found that intranasal OT treatment significantly decreased psychotic symptoms (Feifel et al., 2010; Pedersen et al., 2011; Modabbernia et al., 2013).

Studies evaluating intranasal OT and social cognition in schizophrenia have demonstrated that a single OT dose is associated with improvements in emotion recognition, specifically accuracy in the recognition and detection of fear (Goldman et al., 2011; Averbeck et al., 2012), social perception (Fischer-Shofty et al., 2013), and higher-order social cognition (Davis et al., 2013). Pedersen et al. (2011) found that two weeks of twice daily OT treatment significantly improved Theory of Mind (ToM) and trended toward increasing trustworthy ratings of untrustworthy faces. The results are promising but their limitations in treatment scope and duration underscore the need to investigate the effects of OT administration for longer periods of time on a broader range of socially relevant measures.

The primary aim of the current study was to evaluate the effects of six weeks of twice daily intranasal OT treatment on social cognition in individuals with schizophrenia. We examined the effect of OT on emotion recognition, Theory of Mind (ToM), empathy, and social perception. Given the preliminary evidence that OT has a beneficial impact on emotion recognition, particularly fear recognition, ToM, empathy and social perception in individuals with schizophrenia, it was hypothesized that OT would lead to improvements in each of these social cognitive domains. We also evaluated the exploratory outcomes of attributional style and social skills (these were considered exploratory given the limited research on OT and these domains). Lastly, we evaluated the effects of OT on clinical psychiatric symptoms. Since the primary aim of the current study was on the impact of OT on social cognition, the evaluation of clinical psychiatric symptoms was considered secondary.

2. Methods

2.1. Participants

The study was approved by the University of North Carolina (UNC) Biomedical Institutional Review Board and conducted in accordance

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with The Code of Ethics of the World Medical Association. Written informed consent was obtained from all participants.

Participants were outpatients recruited from the UNC Department of Psychiatry Schizophrenia Treatment and Evaluation Program outpatient clinics (Chapel Hill, NC), other schizophrenia programs within psychiatry, and the NC Psychiatric Research Center (Raleigh, NC). Seventeen participants completed their baseline visit and fourteen (OT $n = 8$; PL $n = 6$) were retained for six-week analyses. The three dropouts did not differ from retained participants on any of the baseline or demographic variables. Note that for the Interpersonal Reactivity Index, only 5 participants in each group completed the measure since it was added after the study began.

The inclusion criteria for the six-week trial included the following: schizophrenia diagnosis (based on DSM-IV-TR criteria); stability of symptom severity (i.e., no acute psychiatric symptoms); moderate clinical psychiatric symptoms as defined by a total PANSS score greater than 60; social difficulty as defined by a PANSS score of 4 or higher on the suspiciousness/paranoia item, or a 3 on the suspiciousness/paranoia item and 3 or higher on one of the socially relevant PANSS items (e g. hostility, passive social avoidance, active social avoidance or uncooperativeness item); low to moderate depressive symptoms; on the same medication(s) and dose(s) for at least 1-month prior to study participation; and between the ages of 18 and 55. Diagnosis was based on extensive chart review and consultation with the attending psychiatrist. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 2002), Mood Disorders and Psychotic Disorders modules were administered by trained research clinicians or advanced graduate students for participants who were not followed by UNC's Department of Psychiatry or participants whose diagnosis was unclear (e.g., schizophrenia versus schizoaffective disorder).

Exclusion criteria included low literacy as indicated by an inability to read and understand the consent form; positive urine drug screen for illegal substances or drugs that have not been prescribed; dependence on substances other than tobacco or caffeine (based on results from urine drug screen, self-report and chart review); debilitating medical conditions; major surgery or trauma in the past year; pregnancy or breast-feeding; having given birth in the past 6 months or breast-feeding in the past 3 months; abnormalities found during medical evaluation during study participation; and an inability to learn self-administration of intranasal treatments.

Note that the two-week outcome data for 10 participants in the current study were reported in the Pedersen et al. (2011) two-week trial; however, all participants had the same exposure to the measures, so practice effects for those in the Pedersen et al. (2011) two-week trial were not a concern. Similarly, there was no difference in exposure between the experimental and control group.

2.2. Procedures

This was a randomized, double-blind, placebo-controlled six-week treatment trial. Within one week after screening, baseline social cognition, social skills, and clinical psychiatric ratings were assessed. Following instruction by research staff in intranasal self-administration, daily intranasal treatments were initiated after baseline assessments were completed. Social cognition, social skills and clinical psychiatric symptom measures were repeated 50 minutes after the morning dose of study medication at the end of treatment week 6.

The social cognitive measures included: The Emotion Recognition-40 (ER-40; Kohler et al., 2004), Theory of Mind Picture Stories Task (Brune, 2003), The Eyes Test (Baron-Cohen et al., 2001), The Interpersonal Reactivity Index (IRI; Davis, 1983), The Trustworthiness Task (Adolphs et al., 1998), The Ambiguous Intentions Hostility Questionnaire-Abbreviated Version (AIHQ; Combs et al., 2007). Social skills were assessed with a role-play measure administered at the baseline and six-week visits. The current study used two role-play scenarios (meeting a new person and consoling a friend). Social skills were coded in three domains: Global skills (i.e., content, overall social skill item, social anxiety), specific skills (i.e., questions, fluency, clarity, meshing, involvement), and nonverbal skills (i.e., gaze, facial affect, appropriate affect; Pinkham and Penn, 2006). Two independent raters, blind to group status, were trained to reliability. They reached acceptable levels of inter-rater reliability for social skills ratings on the role plays [i.e., ICCs ≥ .60; *Role play 1* (meeting a new person): Global ICC = .70, Specific skills ICC = .94, Nonverbal ICC = .63 and *Role play 2* (consoling a friend): Global ICC = .74, Specific skills ICC = .80, Nonverbal ICC = .60].

Clinical psychiatric symptoms were measured with The Positive and Negative Syndrome Scale (PANSS; White et al., 1997). Trained staff administered the social cognitive, social skills and clinical psychiatric symptom measures. All staff involved in data collection were blind to treatment group.

Participants remained on their pre-study medication regimen and doses throughout the treatment trial. They self-administered intranasal study drug twice daily (before breakfast and before dinner). Each dose consisted of six 0.1 ml insufflations (alternating every 30 seconds between the left and right nostril) of OT spray; the total insufflation at each dose was approximately 24 international units (IU) of OT [Syntocinon Spray, Novartis] or placebo (PL, containing the same ingredients as Syntocinon Spray except for OT). Twenty-four IU is the most commonly used dose in studies that found significant effects of acute intranasal OT treatment (MacDonald and MacDonald, 2010). Outpatient compliance with test treatments was monitored by weighing spray bottles before they were dispensed and after the morning dose during clinic visits at the end of treatment weeks 2, 4 and 6. Participants in the OT and PL groups were evaluated the same number of times and had equal exposure to all study measures.

3. Data analytic plan

Independent t-tests were used to evaluate baseline differences between groups on continuous variables (including primary, secondary and exploratory outcome variables) and chi-square tests were conducted to evaluate baseline differences on categorical variables.

We report within group changes as measured by paired sample- t-tests. Statistical significance was set at an alpha level of .05 or below and SPSS was used for all analyses. Cohen's *d* effect sizes were calculated to measure the magnitude of treatment effects for within group analyses. The baseline and six-week raw means and standard deviations were used in the effect size calculations. The correlation between the baseline and six-week raw mean score was included in the effect size calculations to correct for dependence between these two means (Morris & Deshon, 2002). The following conventions were used to define the magnitude of treatment effects: small, $d = .2$; medium, $d = .5$; large, $d = .8$ (Cohen, 1988). Note that analyses were not adjusted for multiple comparisons.

4. Results

4.1. Descriptive analyses

Treatment groups only differed on the PANSS positive symptom rating [$t(12) = 2.15$, $p = .05$; Table 4] at baseline. Specifically, the PL group had significantly greater positive symptoms at baseline (Table 4). There were no other significant baseline differences on demographic variables, medication compliance (Table 1), primary, exploratory or secondary measures (Tables 2–4).

4.2. Primary analyses

Table 2 shows the baseline and six-week means, standard deviations, and effect sizes for each group on the primary outcome social cognitive variables. Within group analyses revealed a significant improvement in fear recognition in the OT sample [$t(7) = 2.37$, $p = .05$]

Table 1
Demographic information.

	Oxytocin ($n = 8$)		Placebo ($n = 6$)		
Demographic Variable	*n*	%	*N*	%	*p* Value
Male	6	75	5	83.3	.71
Caucasian	4	50.0	3	50.0	1.00
Greater than HS education	5	62.5	4	66.67	.68
	Mean	**SD**	**Mean**	**SD**	
Age in years	38.88	7.22	35.67	9.00	.47
Years since first onset of disorder	15.31	10.28	13.67	9.37	.76
Hospitalizations	3.75	2.92	5.33	2.88	.33
Medication compliance[a] (%)	86.88	38.17	76.50	12.73	.54

Note: chi-square for comparison of proportions; t-test for age, years since first onset of disorder, number of hospitalizations and medication compliance.
[a] The medication compliance for one OT participant was not collected.

and a corresponding large effect size. The PL sample did not show a significant change in fear recognition [$t(5) = -.54$, $p = .61$]; the effect size reflected a small reduction in fear recognition for the PL sample. There were no significant changes over time for recognition of other emotions (angry, sad, happy, neutral) for either group.

Both groups significantly improved on Theory of Mind (ToM) as measured by the Brune total score [OT: $t(7) = 2.82$, $p = .03$; PL: $t(5) = 2.95$, $p = .03$]. Both groups demonstrated trend level improvements for the ToM sub-score, deception detection [OT $t(7) = 2.05$, $p = .08$; PL: $t(5) = 2.24$, $p = .08$]. The OT group showed a trend level improvement for third order ToM [$t(7) = 1.93$, $p = .10$] and the PL group showed a trend level improvement for second order ToM [$t(5) = 2.24$, $p = .08$]. Both groups generally showed large effect size improvements on the Brune indices. Neither group showed significant within group improvements on the Eyes Test (Table 2).

Similarly, there were no significant within group changes on the Trustworthiness Task for either group. Effect sizes on the Trustworthiness Task were inconsistent in direction and in the small range. Finally, the OT group showed a significant increase in self-reported perspective taking (PT) at six weeks [$t(4) = 3.26$, $p = .03$]. The PL group did not show significant within group PT changes [$t(4) = 1.73$, $p = .16$]. The effect size improvement in PT was large for the OT group, while the PL group showed the opposite pattern (worse PT at six weeks). There were no significant within group effects for the other IRI sub-scores.

4.3. Exploratory analyses

In regard to attributional style, both groups showed a significantly reduced hostility bias at six weeks [OT: $t(7) = -2.80$, $p = .03$; PL: $t(5) = -4.34$, $p = .007$]; the magnitude of the change was large for both groups. There were no significant changes for the other AIHQ sub-scores (Table 3).

Regarding social skills, the PL group showed a trend toward worse global [$t(5) = -2.18$, $p = .08$] and nonverbal [$t(5) = -2.22$, $p = .08$] social skills for the second role play. There were no within group changes for the social skill sub-scores for the OT group. See Table 3 for social skills means, standard deviations, and effect sizes.

4.4. Secondary analyses

Finally, within group analyses revealed significant reductions in clinical psychiatric symptoms for both groups. The OT group had a significant decrease on all PANSS sub-scores [positive: $t(7) = -3.64$ $p = .008$; negative: $t(7) = -5.00$, $p = .002$; and general symptom scores: $t(7) = -2.51$, $p = .04$)] at six weeks (Table 4). The PL group showed a significant decrease in PANSS positive [$t(5) = -2.62$ $p = .05$] and general symptoms scores [$t(5) = -3.16$, $p = .025$] and no significant change on negative symptom ratings. The effect sizes for the positive and general symptom reductions were large for both groups, while only the OT group had a large effect size reduction in negative symptoms (Table 4).

Table 2
Primary social cognitive outcomes.

	Oxytocin ($n = 8$)			Placebo ($n = 6$)		
	BL Mean (SD)	Week 6 Raw Mean (SD)	Cohen's *d*[b]	BL Mean (SD)	Week 6 Raw Mean (SD)	Cohen's *d*[b]
ER-40						
Fear	6.25 (1.67)	7.25 (.89)*	1.04	6.83 (2.40)	6.67 (1.86)	−.30
Anger	4.75 (1.28)	4.38 (1.30)	−.35	5.83 (1.60)	6.17 (1.72)	.42
Sad	6.88 (1.36)	7.13 (1.46)	.28	5.33 (1.75)	6.50 (1.64)	.53
Happy	7.88 (.35)	8.00 (.00)	.34	8.00 (.00)	7.83 (.41)	−.42
Neutral	6.25 (1.28)	7.25 (.89)	.79	5.83 (2.14)	7.17 (.98)	.85
Eyes Test	20.63 (3.46)	22.25 (5.29)	.46	21.67 (5.82)	22.17 (7.83)	.08
Brune Tot	18.75 (2.82)	21.13 (1.36)*	1.18	19.50 (2.95)	22.00 (1.27)*	1.88
2nd sum	3.88 (.99)	4.63 (.52)	.67	4.33 (.52)	4.83 (.41)	.92
3rd false	2.00 (.93)	2.63 (.52)	.73	2.50 (.55)	2.83 (.41)	.66
Rec.	2.75 (.46)	2.63 (.52)	−.19	2.83 (.41)	2.83 (.41)	.00
Dec.	2.50 (.76)	2.88 (.35)	1.08	2.17 (.98)	2.67 (.52)	1.66
Trust Tot	−2.00 (57.15)	1.88 (40.98)	.17	12.83 (22.30)	11.33 (34.23)	−.05
Untrust	−12.63 (16.90)	−8.38 (12.66)	.28	−9.67 (8.80)	−13.33 (11.24)	−.25
Trust	10 (11.50)	8.50 (8.25)	−.34	15.00 (5.97)	14.67 (7.20)	−.07
IRI total[a]	86.80 (13.37)	88.00 (13.71)	.13	87.40 (6.91)	87.00 (8.57)	−.17
Fantasy	20.40 (7.44)	21.60 (4.62)	.22	26.20 (6.98)	26.80 (6.26)	.26
Emotion	26.60 (3.65)	23.80 (4.82)	−.88	21.20 (7.40)	23.60 (6.88)	.84
PT	20.60 (1.14)	23.40 (2.51)*	1.93	21.00 (6.63)	19.40 (8.26)	−1.24
Distress	19.20 (3.49)	19.20 (4.09)	.00	19.00 (5.01)	17.20 (4.32)	−1.03

Note: SD = Standard deviation; BL = baseline; ER-40 = Emotion Recognition-40; 2nd sum = Brune 2nd order Theory of Mind sum score; 3rd false = Brune 3rd order Theory of Mind false belief score; Rec. = accurate detection of reciprocity on Brune; Dec. = accurate detection of deception on Brune; Trust overall = overall score on trustworthiness task; Untrust = -score on faces judged as mostly untrustworthy by a normative sample; Trust = score on faces judged as mostly trustworthy by a normative sample; IRI = Interpersonal Reactivity Index; PT = Perspective Taking;
[a] $N = 10$ for participants completing the IRI; 5 participants in each group; IRI items rated on 1–5 Likert scale.
[b] Effect sizes with positive values are in the hypothesized direction (improvement on social cognitive measures, higher scores in OT group); effect size calculation accounts for dependence of baseline and week 6 means (correlation between baseline and week 6 means); raw means and standard deviations at baseline and week 6 used in effect size calculations.
* Indicates significant change from baseline, $p < .05$

Table 3
Exploratory outcomes.

Oxytocin ($n = 8$)				Placebo ($n = 6$)		
Measure	BL Mean (SD)	Week 6 Raw Mean (SD)	Cohen's d[a]	BL Mean (SD)	Week 6 Raw Mean (SD)	Cohen's d[a]
AIHQ						
Hostility	2.24 (.41)	1.66 (.53)*	−1.02	2.38 (.51)	1.85 (.32)*	−2.16
Blame	3.27 (.74)	2.65 (.83)	−.66	3.20 (.84)	2.74 (1.73)	−.95
Agg	1.86 (.28)	1.75 (.32)	−.39	1.78 (.26)	1.80 (.16)	.13
Social Skills: RP1						
Global	11.06 (1.74)	11.69 (.88)	.55	10.75 (2.04)	10.83 (1.72)	.08
Specific	20.56 (2.69)	19.94 (2.37)	−.31	19.17 (2.71)	20.33 (1.21)	.31
Nonverbal	12.13 (1.73)	12.19 (1.00)	.04	11.50 (1.04)	11.17 (1.33)	−.33
Social Skills: RP2						
Global	12.13 (.64)	12.25 (1.77)	.10	11.58 (1.28)	10.33 (2.42)	−1.45
Specific	20.25 (1.75)	21.00 (1.79)	.26	19.83 (1.72)	18.83 (1.94)	−.46
Nonverbal	12.19 (1.31)	11.94 (1.02)	−.23	11.92 (1.11)	10.50 (1.38)	−.92

Note: SD = Standard Deviation; BL = baseline; AIHQ = Ambiguous Intentions Hostility Questionnaire; Agg = Aggression; RP1 = role play 1, "getting to know your neighbor"; RP2 = role play 2 RP1 = role pay 1 (meeting a new friend); RP2 = role play 2 (consoling a friend).
Global = global social skills sub-score; specific = specific social skill sub-score; nonverbal = nonverbal social skill sub-score.
[a] Effect sizes for the AIHQ with a negative sign indicate less hostility, blame and aggression; Positive effect sizes for social skills role play indicate improved social skills; within group effect size accounts for dependence of baseline and week 6 means (correlation between baseline and week 6 means); raw means and standard deviations at baseline and week 6 used in effect size calculations.
* Indicates significant change from baseline, $p < .05$

5. Discussion

This is the first known six-week trial to assess the effects of OT on social cognition and social skills in schizophrenia. The pattern of results showed that participants randomized to the OT condition had significant improvements in fear recognition and perspective taking, as well as reduced negative symptoms. Both the OT and PL conditions showed improvements in Theory of Mind, and reductions in hostility bias, positive symptoms and general symptoms at six weeks.

The improvement observed in fear recognition is consistent with others who have found OT is associated with improved fear recognition in individuals with schizophrenia (Goldman et al., 2011; Averbeck et al., 2012). Improved fear recognition as a function of intranasal OT has supporting neurological correlates. Specifically, Kirsch et al. (2005) found reduced amygdalar response in participants given intranasal OT when they were shown fearful faces. It appears OT may have a particular role in regulating fear recognition, which is interesting given accurate fear recognition has been linked to prosocial behavior (Marsh et al., 2007). Further research is needed to better understand the relationship between OT and the recognition of fear.

The improvement in the perspective-taking component of empathy is promising given that schizophrenia samples have repeatedly shown deficits in self-reported perspective taking as compared to non-clinical samples (e.g., see Montag et al., 2007 and Achim et al., 2011). Additionally, these findings are in accord with previous research showing improved empathy in non-clinical samples administered OT (Bartz et al., 2011); however, the IRI was implemented after the study began and only 10 total participants (5 in each group) completed the measure. Therefore, the IRI results must be interpreted cautiously.

Both groups demonstrated improved overall Theory of Mind and a reduced hostility bias. No other significant social cognitive changes were observed for the OT group. In addition, no significant changes were observed in social skills. These results suggest that OT may differentially affect separate aspects of social cognition, which concurs with a recent review of the literature (Bartz et al., 2011).

Although not a primary outcome, negative symptoms decreased in the OT treatment group and reflected a large treatment effect (both groups showed decreased positive and general symptoms). The relationship between OT and negative symptoms is intriguing given that antipsychotic medications do not significantly ameliorate negative symptoms (Bellack et al., 2004). This is consistent with previous research in the area (MacDonald & Feifel, 2012; Modabbernia et al., 2013). Of note, in the Pedersen et al. (2011) two-week trial, there was a trend toward a within group decrease in negative symptoms for the OT group. Thus duration of OT dosing must be considered. In addition to duration, the amount of OT appears to be another consideration in assessing the efficacy of OT. Modabbernia et al. (2013) found significantly reduced negative symptoms at six and eight weeks after one week of 20 IUs of twice daily OT followed by 40 IUs of twice daily OT for the remaining seven weeks. Feifel et al. (2010) found that OT significantly reduced negative symptoms at three weeks with one week of 20 IUs of twice daily OT and two weeks of 40 IUs of OT sprayed twice daily. Further research is needed to better understand the relationship between dosing, duration and efficacy of OT.

This study has a variety of strengths. The current study is an extended trial (i.e., six weeks of twice daily oxytocin or placebo) rather than a single OT dose. We examined social cognition *and* social skills while the existing OT randomized control trials have typically focused on the

Table 4
Secondary outcomes: clinical psychiatric symptoms.

Oxytocin ($n = 8$)				Placebo ($n = 6$)		
Measure	BL Mean (SD)	Week 6 Raw Mean (SD)	Cohen's d[a]	BL Mean (SD)	Week 6 Raw Mean (SD)	Cohen's d[a]
PANSS						
Positive[b]	16.88 (4.61)	14.00 (3.34)*	−1.55	22.50 (5.17)	18.50 (6.22)*	−1.11
Negative	19.75 (4.10)	17.25 (4.20)*	−1.77	17.50 (4.46)	17.17 (3.66)	−.10
General	34.75 (7.01)	29.88 (4.91)*	−.95	41.00 (9.03)	32.67 (4.13)*	−1.83

Note: SD = Standard Deviation; PANSS = Positive and Negative Syndrome Scale; BL = baseline.
[a] Effect sizes with a negative sign indicate a reduction in symptoms; within group effect size accounts for dependence of baseline and week 6 mean (correlation between baseline and week 6 means); raw means and standard deviations at baseline and week 6 used in effect size calculations.
[b] Significant difference in baseline mean between OT and PL group, $p < .05$.
* Indicates significant change from baseline, $p < .05$.

amelioration of the clinical psychiatric symptoms of schizophrenia. We included a broad range of social cognitive skills to better elucidate the relationship between OT and social cognition in schizophrenia. Moreover, our sample included both men and women (2/8 OT participants were female) whereas the existing OT and schizophrenia literature has not consistently included women.

There are a number of limitations that should be outlined. First, the small sample size precluded making definitive conclusions about the effects of OT treatment on social cognition in schizophrenia, and limited us to examining within group changes rather than between group differences. The small sample additionally limited our ability to evaluate possible moderators (e.g., gender) and mediators. Second, although efforts were made to maintain compliance in the current study, compliance was not 100%. Third, follow-up data were not obtained, so it is unclear whether treatment effects persist after termination of treatment. Lastly, we cannot definitely attribute the social cognitive treatment effects to chronic dosing versus an acute dose (i.e., participants were tested at baseline and 50 minutes after the six-week dose). However, it is important to note that Modabbernia et al. (2013) found that PANSS scores dropped steadily across all time periods so that the decline from baseline was significantly greater for the OT as compared to the PL group for total score at 4 and subsequent weeks and for positive, negative and general scores at six and eight weeks. This result indicates that OT exerts a steadily increasing effect rather than just an acute effect. Regardless, further research should consider waiting a longer period after the last intranasal dose to assess treatment effects in order to clarify this issue.

Overall, the results of the current study indicate that OT may improve fear recognition, perspective taking and negative symptoms in schizophrenia, but has limited impact on other aspects of social cognition and social skills. It remains to be seen if these mixed findings are replicated in larger trials, which underscores the need to continue research in this area.

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Contributors

Authors CMG, CAP, DLP, and KLS collaborated on designing the study; CMG, CAP, DLP, and KLS wrote the protocol and obtained IRB approval. CMG, KLS and TE coordinated execution of the project. CMG and JLS analyzed the data. CMG wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors have a conflict of interest.

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References

Achim, A.M., Ouellet, R., Roy, M.A., Jackson, P.L., 2011. Assessment of empathy in first-episode psychosis and meta-analytic comparison with previous studies in schizophrenia. Psychiatry Res. 190 (1), 3–8.

Adolphs, R., Tranel, D., Damasio, A.R., 1998. The human amygdala in social judgment. Nature 393 (6684), 470–474.

Averbeck, B.B., Bobin, T., Evans, S., Shergill, S.S., 2012. Emotion recognition and oxytocin in patients with schizophrenia. Psychol. Med. 42, 259–266.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42 (2), 241–251.

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. 15 (7), 301–309.

Bellack, A.S., Schooler, N.R., Marder, S.R., Kane, J.M., Brown, C.H., Yang, Y., 2004. Do clozapine and risperidone affect social competence and problem solving? Am. J. Psychiatry 161 (2), 364–367.

Brune, M., 2003. Theory of mind and the role of IQ in chronic disorganized schizophrenia. Schizophr. Res. 60 (1), 57–64.

Cohen, J., 1988. Statistical power analysis for the behavioral sciences, 2nd ed. L. Erlbaum Associates, Hillsdale, NJ.

Combs, D.R., Penn, D.L., Wicher, M., Waldheter, E., 2007. The Ambiguous Intentions Hostility Questionnaire (AIHQ): a new measure for evaluating hostile social-cognitive biases in paranoia. Cogn. Neuropsychiatry 12 (2), 128–143.

Davis, M.H., 1983. Measuring individual differences in empathy: evidence for a multidimensional approach. J. Pers. Soc. Psychol. 44 (1), 113–126.

Davis, M.C., Lee, J., Horan, W.P., Clarke, A.D., McGee, M.R., Green, M.F., Marder, S.R., 2013. Effects of single dose intranasal oxytocin on social cognition in schizophrenia. Schizophr. Res. 147, 393–397.

Feifel, D., Macdonald, K., Nguyen, A., Cobb, P., Warlan, H., Galangue, B., Hadley, A., 2010. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol. Psychiatry 68, 678–680.

Fett, A.K., Gracia-Dominguez, M., Viechtbauer, W., Penn, D.L., van Os, J., Krabbendam, L., 2011. A meta-analytic study on cognition, social cognition, and functional outcome in non-affective psychosis. Neurosci. Biobehav. Rev. 35, 573–588.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J., 2002. Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). Biometrics Research, New York State Psychiatric Institute, New York.

Fischer-Shofty, M., Brune, M., Ebert, A., Shefet, D., Levkovitz, Y., Shamay-Tsoory, S.G., 2013. Improving social perception in schizophrenia: the role of oxytocin. Schizophr. Res. 146 (1–3), 357–362.

Goldman, M., Marlow-O'Connor, M., Torres, I., Carter, C.S., 2008. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr. Res. 98 (1–3), 247–255.

Goldman, M.B., Gomes, A.M., Carter, C.S., Lee, R., 2011. Divergent effects of two different doses of intranasal oxytocin on facial affect discrimination in schizophrenia patients with and without polydipsia. Psychopharmacology 1, 101–110.

Guastella, A.J., Macleod, C., 2012. A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. Horm. Behav. 3, 410–418.

Keri, S., Kiss, I., Kelemen, O., 2009. Sharing secrets: oxytocin and trust in schizophrenia. Soc. Neurosci. 4 (4), 287–293.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Meyer-Lindenberg, A., 2005. Oxytocin modulates neural circuitry for social cognition and fear in humans. J. Neurosci. 25 (49), 11489–11493.

Kohler, C.G., Turner, T.H., Gur, R.E., Gur, R.C., 2004. Recognition of facial emotions in neuropsychiatric disorders. CNS Spectr. 9 (4), 267–274.

MacDonald, K., Feifel, D., 2012. Oxytocin in schizophrenia: a review of evidence for its therapeutic effects. Acta Neuropsychiatr. 24, 130–146.

MacDonald, K., MacDonald, T.M., 2010. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. Harv. Rev. Psychiatry 18, 1–21.

Marsh, A.A., Kozak, M.N., Ambady, N., 2007. Accurate recognition of fear facials expressions predicts prosocial behavior. Emotion 7 (2), 239–251.

Modabbernia, A., Rezaei, F., Salehi, B., Jafarinia, M., Ashrafi, M., Akhondzadeh, S., 2013. Intranasal oxytocin as an adjunct to risperidone in patients with schizophrenia: an 8 week, randomized, double-blind, placebo-controlled study. CNS Drugs 1, 57–65.

Montag, C., Heinz, A., Kunz, D., Gallinat, J., 2007. Self-reported empathic abilities in schizophrenia. Schizophr. Res. 92 (1–3), 85–89.

Morris, S.B., DeShon, R.P., 2002. Combining effect size estimate in meta-analysis with repeated measures and independent-group designs. Psychol. Methods 7, 105–125.

Pedersen, C.A., Gibson, C.M., Rau, S.W., Salimi, K., Smedley, K.L., Casey, R.L…., Penn, D.L., 2011. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr. Res. 132 (1), 50–53.

Penn, D.L., Keefe, R.S., Davis, S.M., Meyer, P.S., Perkins, D.O., Losardo, D., et al., 2009. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. Schizophr. Res. 115 (1), 17–23.

Pinkham, A.E., Penn, D.L., 2006. Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. Psychiatry Res. 143 (2–3), 167–178.

Rubin, L.H., Carter, C.S., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J.A., Maki, P.M., 2010. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr. Res. 124, 13–21.

Shahrestani, S., Kemp, A.H., Guastella, A., 2013. The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38, 1929–1936.

Walss-Bass, C., Fernandes, J.M., Roberts, D.L., Service, H., Velligan, D., 2013. Differential correlations between plasma oxytocin and social cognitive capacity and bias in schizophrenia. Schizophr. Res. 147, 387–392.

White, L., Harvey, P.D., Opler, L., Lindenmayer, J.P., 1997. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathology 30 (5), 263–274.