



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; Averbek 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 $\geq .60$; *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 [$t(7) = 2.37, p = .05$]

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