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A 12-week randomized controlled trial of twice-daily intranasal oxytocin for social cognitive deficits in people with schizophrenia☆

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ABSTRACT

Social cognition is impaired in people with schizophrenia and these deficits are strongly correlated with social functioning. Oxytocin is a hypothalamic peptide that contributes to maternal infant bonding and has diverse pro-social effects in adults. This study tested the hypothesis that 12 weeks of intranasal oxytocin will improve social cognitive function in outpatients with schizophrenia and schizoaffective disorder. Sixty-eight eligible participants were randomized to oxytocin (24 IU twice daily) or placebo. Social cognitive function was assessed using the Emotion Recognition-40, Brüne Theory of Mind, Reading the Mind in the Eyes test, Trustworthiness task and Ambiguous Intentions Hostility Questionnaire at baseline, 6 weeks and 12 weeks. In addition, social function was assessed using the Specific Levels of Functioning Scale and a role-play test, and psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Fifty-five participants completed the 12-week trial. The study found no evidence for a differential advantage of oxytocin over placebo on social cognition. Among secondary outcomes, there was a modest advantage for oxytocin over placebo on a component of social functioning, although there was also evidence that the placebo group outperformed the oxytocin group on the role-play task. No between-group differences emerged on measures of psychopathology in pre-specified comparisons, but oxytocin showed significant within-group reduction in PANSS negative symptoms and significant between-group improvement in negative symptoms in the schizophrenia subgroup. Further testing is needed to clarify whether oxytocin has therapeutic potential for social cognitive deficits and/or negative symptoms in people with schizophrenia.

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1. Introduction

Multiple dimensions of psychopathology contribute to impaired social functioning in people with schizophrenia, including the socially isolating effects of positive symptoms, the lack of social drive associated with negative symptoms, and the disabling impact of cognitive deficits. Among the many cognitive domains that are impaired in people with schizophrenia, social cognition represents a key domain that is strongly

correlated with social functioning (Fett et al., 2011). Social cognition represents the cognitive functions involved in facilitating social decision-making and associated behaviors. It incorporates emotion recognition (identifying other people's emotional states by interpreting their facial expressions), attributional style (beliefs about the causes of events) and theory of mind (inferring the thoughts and feelings of others) (Pinkham et al., 2014). Studies indicate that each of these components of social cognition are impaired in people with schizophrenia (Bora et al., 2009; Kohler et al., 2010); however, antipsychotic medications provide no measurable benefit for social cognitive deficits (Penn et al., 2009).

Given the current limitations of available treatments for impairments in social function in schizophrenia, novel pharmacological options have been sought. The hypothalamic nonapeptide oxytocin has emerged as an intriguing candidate. Oxytocin has diverse pro-social effects including regulation of maternal-infant bonding, social affiliative behavior, social recognition and interpersonal trust (Heinrichs and Domes, 2008; Meyer-Lindenberg et al., 2011). In healthy volunteers,

Abbreviations: AIHQ, Ambiguous Intentions Hostility Questionnaire; ER-40, Emotion Recognition-40 task; Eyes Test, Reading the Mind in the Eyes Test; GSS, Global social skill; IU, International Units; mITT, Modified intention-to-treat; NVSS, Nonverbal social skill; PANSS, Positive and Negative Syndrome Scale; SLOF, Specific Levels of Functioning Scale; SSPA, Social Skills Performance Assessment; VSS, Verbal social skill; WRAT, Wide Range Achievement Test.

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single-dose intranasal oxytocin administration enhances interpersonal trust (Baumgartner et al., 2008; Kosfeld et al., 2005) and improves recognition of internal mental states from subtle facial cues (Domes et al., 2007; Schulze et al., 2011). Similar effects have also been demonstrated in individuals with social deficits including in people with autism. Intravenous oxytocin has improved interpretation of emotional content of speech in people with autism (Hollander et al., 2007) and intranasal oxytocin has improved recognition of affective states from facial cues (Guastella et al., 2010).

There have been several smaller studies on the effects of intranasal oxytocin on social cognitive functioning in people with schizophrenia. For example, our group examined the effects of daily administration of oxytocin for 2 weeks (Pedersen et al., 2011) and 6 weeks (Gibson et al., 2014), while others have explored the impact of twice-weekly oxytocin for 6 weeks (Davis et al., 2014). These studies found modest improvements on several measures of social cognition in adults with chronic schizophrenia.

The current study sought to better understand the therapeutic potential of oxytocin on social cognition in people with schizophrenia and schizoaffective disorder by extending the treatment duration to 12 weeks in a larger cohort of participants than previously studied and examining a broader range of social cognitive assessments. Performance was evaluated on theory of mind, emotion perception and attributional style, as well as on the secondary outcomes of social skills, functional outcome and psychopathology. It was hypothesized that oxytocin will lead to differential improvements in social cognition when compared to placebo from baseline to 12 weeks.

2. Methods

2.1. Study design

The study was conducted between June 2011 and September 2014 in the outpatient research clinics of an academic medical center and an affiliated state psychiatric hospital. The Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill approved the study. In this double-blind, randomized study, stable outpatients with schizophrenia or schizoaffective disorder were randomized to receive 12 weeks of daily intranasal oxytocin or placebo.

2.2. Participants

Eligible subjects were 18–65 years of age; criteria for schizophrenia or schizoaffective disorder were met as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition; duration of illness ≥ 1 year; clinically stable outpatient status and receiving antipsychotic medication with no change in antipsychotic agents or dose for one month prior to entry; concomitant medications were permitted (except as noted in exclusion criteria) if doses were unchanged for one month prior to entry; to enrich baseline deficits in social functioning, participants had to score < 24 on Reading the Mind in the Eyes Test (Eyes Test, a measure of theory of mind and emotion recognition, score < 24 is 0.5 standard deviation (SD) below the mean in a large normative sample) OR score ≥ 3 on two or more of the following Positive and Negative Syndrome Scale (PANSS) items: suspiciousness/persecution, hostility, passive/apathetic social withdrawal, uncooperativeness, active social avoidance; women of childbearing potential and male participants had to use an acceptable method of birth-control; all subjects provided written informed consent.

Exclusion criteria: Manic or hypomanic episode within the past 2 years for subjects with schizoaffective disorder; alcohol or substance abuse or dependence in the past 3 months (except caffeine or nicotine); stimulant or chronic glucocorticoid use; unstable serious medical illness; major surgery/trauma in the past 4 months; pregnancy, childbirth

in the past 6 months, or breast-feeding in the past 3 months; < 5 th grade reading level on the Wide Range Achievement Test (WRAT).

2.3. Intervention

Participants remained on their pre-study medications and doses over the course of the study. Intranasal study drug was self-administered twice daily (before breakfast and before dinner) for 12 weeks. Participants were trained on proper administration technique prior to baseline and administration was also observed at 2 and 6 weeks. Each dose consisted of six 0.1 mL insufflations (alternating every 30 s between the left and right nostril); each dose was approximately 24 international units (IU) of oxytocin (Syntocinon Spray, Novartis) or placebo (containing each ingredient in Syntocinon Spray except oxytocin). This dose was the same as in our pilot studies which suggested efficacy on several measures of social cognition (Gibson et al., 2014; Pedersen et al., 2011). Bottles containing study drug (50 mL solution) were weighed before dispensing to subjects and upon return. Bottle weights and a daily medication diary were used to assess adherence to study drug.

2.4. Randomization

Eligible subjects were randomly assigned in blocks of four, stratified by gender, to receive oxytocin or placebo in a 1:1 ratio. Randomization was performed using PROC PLAN in SAS Version 9.2. An interim analysis, which was performed after 19 subjects had completed the trial, revealed significantly uneven distribution in baseline PANSS scores between the two treatment groups. Given the target sample size ($N = 60$), there was concern that the uneven distribution in baseline PANSS scores would not have time to even out over the remainder of enrollment. Therefore, subsequent randomization was also stratified by low (< 63) versus high (≥ 63) baseline PANSS score based on a median split of total PANSS scores.

2.5. Primary outcome measures:

Ratings of social cognitive function were administered at baseline, 6 and 12 weeks, as follows:

Emotion Recognition-40 Task (ER-40) – consists of 40 faces presented sequentially on a computer screen along with the choices of rating the face as happy, sad, anger, fear or no emotion (Kohler et al., 2004). It uses racially and ethnically diverse face images. Performance is indexed as the total number of correct responses.

Brüne Theory of Mind Stories Task – consists of a series of 6 sets of 4 cartoon pictures that illustrate interactions between two or more individuals (Brüne, 2003). The subject is asked to rearrange the pictures, initially presented in an illogical sequence, in an order that conveys a logical story. The duration of time the subject takes to complete the task and the accuracy of the sequencing is recorded. The subject is then asked questions about the characters' own beliefs and beliefs of other characters in the cartoons. The subject's interpretations of the characters' beliefs are scored as correct or incorrect.

Reading the Mind in the Eyes Test (Eyes Test) – consists of 36 photographs and participants are asked to guess the mental state from among 4 choice words (Baron-Cohen et al., 2001). Each eye region is presented on a computer screen with the four-choice mental states shown in the four corners of the card or computer screen (one target word and three foil words). Performance is measured by the number of faces correctly discriminated.

Trustworthiness Task – comprises 42 faces of unfamiliar people (Adolphs et al., 1998). Participants are shown each picture individually on a computer screen and are asked to rate how much they would trust that person (i.e., with their money or their life) on a 7-point scale, ranging from -3 (very untrustworthy) to $+3$ (very trustworthy). Performance was indexed as the average rating for trustworthy and untrustworthy faces separately.

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