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Effects of single dose intranasal oxytocin on social cognition in schizophrenia ☆

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ABSTRACT

Deficits in social cognition are common in schizophrenia and predict poor community functioning. Given the current limitations of psychosocial treatments and the lack of pharmacological treatments for social cognitive deficits, the development of novel therapeutic agents could greatly enhance functional recovery in schizophrenia. This study evaluated whether a single dose of intranasal oxytocin acutely improves social cognitive functioning in schizophrenia. Twenty-three male veterans with schizophrenia completed baseline assessments of social cognition that were divided into lower-level (facial affect perception, social perception, detection of lies) and higher-level (detection of sarcasm and deception, empathy) processes. One week later, patients received the same battery after being randomized to a single dose of 40 IU intranasal oxytocin or placebo. Though the groups did not differ significantly on the social cognition composite score, oxytocin improved performance for the higher-level social cognitive tasks (Cohen's $d = 1.0$, $p = 0.045$). Subjects were unable to accurately guess which treatment they had received. The improvements found in higher-level social cognition encourage further studies into the therapeutic potential of oxytocin in schizophrenia.

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1. Introduction

Schizophrenia is a serious mental illness associated with substantial social and occupational dysfunction (Tandon et al., 2008). While positive psychotic symptoms of schizophrenia often respond to antipsychotic medications, negative symptoms and cognitive impairments are difficult to treat, necessitating novel interventions. In this work, we focus on social cognition, which can be defined as the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others (Mortimer, 2009; Grant et al., 2012).

Impairments in social cognition predict multiple aspects of community functioning in schizophrenia (Fett et al., 2011). There are currently two broad approaches to improve social cognition in schizophrenia: psychosocial and pharmacological interventions. While psychosocial interventions (training exercises that target domains of social cognition) have shown some benefit, improvements have typically been limited to a narrow subset of social cognitive processes (most notably, facial affect recognition) (Andreasen, 1982). Pharmacological trials have yielded mixed results, and no medication has consistently improved social cognition schizophrenia (Gray and Roth, 2007). Thus, further treatment development is clearly needed in this area.

One potential therapeutic target for enhancing social cognition is the oxytocin (OT) system. OT is a nine-amino acid peptide that, in addition to its role in the periphery for regulating lactation and uterine contractions, functions centrally as a neurotransmitter involved in multiple aspects of social behavior (Heinrichs et al., 2009; Meyer-Lindenberg et al., 2011). Given the role of OT in social behavior, and the prominent deficits in social functioning in schizophrenia, a handful of studies have examined the OT system in schizophrenia.

Patients with schizophrenia may have altered baseline levels of OT that correlate with symptoms. Specifically, it has been found that lower levels of baseline plasma OT predict negative symptoms (Keri et al., 2009) and also predict the ability of patients with schizophrenia to identify facial expressions (Goldman et al., 2008).

OT has also been evaluated as a potential treatment for schizophrenia. For example, regular administration of intranasal OT, added on to antipsychotic therapy, significantly reduced psychotic symptoms of schizophrenia (Feifel et al., 2010; Pedersen et al., 2011; Modabbernia et al., 2013). Beyond symptoms, several groups have also examined the effects of OT on domains of social cognition in schizophrenia, in both acute (single dose) and chronic dosing paradigms. In the two single-dose studies, one found low doses of intranasal OT (10 IU) worsened scores on the Ekman facial affect discrimination task, while a higher 20 IU dose improved scores in patients with polydipsia (Goldman et al., 2011), and the other found a 24 IU dose improved facial affect discrimination (Averbeck et al., 2011). In the study using a

☆ Clinical trial registration: Does acute oxytocin administration enhance social cognition in individuals with schizophrenia? http://clinicaltrials.gov/ ClinicalTrials.gov identifier: NCT01312272.

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chronic dosing paradigm, 14 days of intranasal OT administration significantly improved scores on one test of theory of mind, but not other social cognitive measures (Pedersen et al., 2011). Altogether, there is some evidence that OT administration may have therapeutic benefit in the treatment of schizophrenia, but the effects on social cognition are unclear.

One important question, arising from the heterogeneity of prior study results, is whether the potential effects of OT on social cognition are specific to particular social cognitive domains. Our current study examined whether a single dose of intranasal OT improved performance across key subdomains of social cognition in schizophrenia. Prior research identified two levels of social cognitive impairment in schizophrenia that are significantly associated with functional capacity and real-world social and work functioning: 1) low-level social cue detection and 2) high-level inferential and regulatory processes (Mancuso et al., 2011). The former factor comprised tasks in which minimal inferential processes are necessary to interpret the presented social information, while the latter factor comprised tasks which required higher-level cognitive processing incorporating knowledge not directly presented in the stimuli.

Using a randomized, double-blind, placebo-controlled design, patients completed a social cognitive assessment battery. The primary outcome measure was a composite social cognition score, with secondary analyses examining the low-level and high-level composites separately. In addition to our primary goal of assessing changes in social cognition, our secondary goals included assessing: 1) the subjective experience of intranasal OT treatment; and 2) acute changes in clinical symptoms following intranasal OT treatment.

2. Experimental methods and materials

2.1. Participants

Twenty-four male outpatients between the ages of 18 and 56 were recruited from the VA Greater Los Angeles Healthcare System (VAGLAHS). Patients met DSM-IV-TR criteria for schizophrenia, based on clinical interview and medical records. Subjects were clinically stable as indicated by: no psychiatric hospitalizations in the past 6 months; adherent to antipsychotic medication with dosages not varying by >25% over 3 months prior to participation; at least 6 months since any indication of potential danger to self or others; no acute medical problems; and chronic medical conditions consistently treated and stable for >3 months. Exclusion criteria were mental retardation; treatment with electroconvulsive therapy within 6 months prior to participation; history of stroke, traumatic brain injury, or epilepsy; history of substance abuse or dependence within 6 months prior to participation; history of hyponatremia within 6 months prior to participation; or allergic rhinitis or other inflammation of nasal mucosa. Antipsychotic medication type and dose were clinically determined. All participants had the capacity to give informed consent and provided written informed consent in accordance with procedures approved by the Institutional Review Board at VAGLAHS.

2.2. Pharmacological treatment

OT nasal spray (50 IU/ml) was compounded by Inland Compounding Pharmacy (Loma Linda, CA). A placebo nasal spray was prepared that was otherwise identical to the active treatment. Nasal sprays were prepared in 3 ml single use vials, calibrated to dispense 0.1 ml per puff. Subjects were instructed to spray 4 puffs into each nostril, for a total dose of 40 IU OT (or equivalent volume of placebo spray).

2.3. Study design

At an initial screening visit, informed consent was obtained and demographic data and medical histories were obtained. Brief physical examinations were performed. If subjects were eligible, they were scheduled for a second visit for baseline assessment. At baseline, subjects were assessed with the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI), and the social cognition assessment battery, with no pharmacological intervention. The order of administration for social cognitive tests was counter-balanced across subjects. On the third visit, one week later, subjects were randomized (double-blind) to receive either intranasal OT or placebo. Thirty minutes after treatment, each subject completed the same assessments in the same order as in their baseline visit. At the conclusion of the visit, participants were interviewed regarding their subjective experiences of the treatment.

2.4. Social cognition assessments

Social cognition was assessed by 4 tests that represented 4 social cognitive domains. The tests are briefly described here and more complete descriptions about the tests and their use in schizophrenia are available elsewhere.

2.4.1. Theory of mind

Theory of mind was assessed using Part III of The Awareness of Social Inference Test (TASIT Part III: Social Inference—Enriched) (McDonald et al., 2003), as described previously (Mancuso et al., 2011). This test provides a total score (maximum 64) and subscale scores for lies and sarcasm scenes (maximum 32 each).

2.4.2. Empathy

Empathy was assessed using the Emotional Perspective Taking Task (EPTT) (Derntl et al., 2009). In this task, subjects are presented with 60 digital images depicting two individuals in a social interaction, with one individual's face masked. Subjects are asked to infer the emotional expression of the masked face, selecting between two choices. Scenes portray 5 basic emotions as well as neutrality and each image is displayed for 4 s each. The score is the total number correct (maximum = 60).

2.4.3. Social perception

Social perception was assessed using the Half Profile of Nonverbal Sensitivity (Half-PONS) (Rosenthal et al., 1979; Ambady et al., 1995), as described previously (Mancuso et al., 2011). The score is the total number correct (maximum = 110).

2.4.4. Facial affect recognition

Facial affect recognition was assessed by asking participants to identify facial expressions of emotion in still images from the standardized stimulus set developed by Ekman (2004), as described previously (Mancuso et al., 2011). The score is the total number correct (maximum = 56).

2.5. Clinical assessments

Positive and Negative Syndrome Scale (*PANSS*) for Schizophrenia (Kay et al., 1987): This instrument assesses 30 different symptoms on a scale from 1 to 7 based on clinical interview. For the current study, total scores as well as positive, negative, and general psychopathology subscores were examined.

Clinical Global Impression (*CGI-S and CGI-I*) (Guy, 1976): For the CGI-S (severity scale) the clinician rates the severity of the subject's mental illness, relative to their past experience with patients with the same diagnosis, from 1 (=normal, not at all ill) to 7 (=extremely ill). The CGI-I (improvement scale) requires the clinician to rate on a scale from 1 to 7 how much the mental illness has improved or worsened, relative to a baseline.

MIRECC Global Assessment of Functioning (*MIRECC GAF*): This is a version (Niv et al., 2007) of the Global Assessment of Functioning