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# A single dose of oxytocin nasal spray improves higher-order social cognition in schizophrenia

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ABSTRACT

Schizophrenia is associated with significant impairments in both higher and lower order social cognitive performance and these impairments contribute to poor social functioning. People with schizophrenia report poor social functioning to be one of their greatest unmet treatment needs. Recent studies have suggested the potential of oxytocin as such a treatment, but mixed results render it uncertain what aspects of social cognition are improved by oxytocin and, subsequently, how oxytocin might best be applied as a therapeutic. The aim of this study was to determine whether a single dose of oxytocin improved higher-order and lower-order social cognition performance for patients with schizophrenia across a well-established battery of social cognition tests. Twenty-one male patients received both a single dose of oxytocin nasal spray (24 IU) and a placebo, two weeks apart in a randomized within-subjects placebo controlled design. Following each administration, participants completed the social cognition tasks, as well as a test of general neurocognition. Results revealed that oxytocin particularly enhanced performance on higher order social cognition tasks, with no effects on general neurocognition. Results for individual tasks showed most improvement on tests measuring appreciation of indirect hints and recognition of social faux pas. These results suggest that oxytocin, if combined to enhance social cognition learning, may be beneficial when targeted at higher order social cognition domains. This study also suggests that these higher order tasks, which assess social cognitive processing in a social communication context, may provide useful markers of response to oxytocin in schizophrenia.



## 1. Introduction

Schizophrenia is characterized by a heterogeneous presentation of positive, negative, and disorganized symptoms, cognitive and motor impairments, and restricted affective expressions (APA, 2000). Among these characteristic clinical features, cognitive deficits have been argued to be at least partially independent of other symptoms in schizophrenia, present before the diagnosis of the illness and stable over time (Fett et al., 2011).

Social cognition is a specialized neurocognitive domain that facilitates social communication and social skill (Green et al., 2012). Social cognition can be described as an ability to understand the thoughts and intentions of others and is often argued to include a range of higher order (reflective, controlled and integrative) and lower order (automatic, fast) skills. For example, 'theory of mind' is regarded as a higher order social cognition skill. It refers to the cognitive ability to attribute mental states such as thoughts, beliefs and intentions that are separate from reality to the self or others, and in doing so, to explain, manipulate and predict behavior (Sprong et al., 2007). It requires one to reflect upon, deliberate and to make complex social inferences (Woolley et al., 2014). Alternatively, lower order social cognition processes are relatively automatic and typically involve fast cue detection (e.g., eye gaze detection) and judgments (e.g., emotion recognition). These differing social cognitive processes are believed to be underpinned by different underlying brain structures (Lieberman, 2007). Despite this, there is a wealth of evidence demonstrating deficits across both lower and higher order social cognition in schizophrenia (Mehta et al., 2013).

Recent evidence has highlighted a critical role for the neuropeptide and hormone oxytocin in the regulation of social behavior (Meyer-Lindenberg et al., 2011; Guastella and MacLeod, 2012; Bakermans-Kranenburg and van I Jzendoorn, 2013). Across a variety of mammalian models, the administration of oxytocin enhances social recognition and

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bonding, and reduces anxiety associated with social threat. In schizophrenia, single-dose administration studies have shown effects of oxytocin on social cognition, including lower order facial emotion recognition (Averbeck et al., 2011; Goldman et al., 2011) and higher order social cognitive task performance (such as detection of sarcasm, deception and empathy) (Davis et al., 2013; Woolley et al., 2014). However, currently, a wide variety of tests have been used and a lack of consistency across studies, including failures to replicate (Horta de Macedo et al., 2014), has resulted in debate about the specific benefits from oxytocin treatment across different social cognitive domains in people with schizophrenia.

Understanding how oxytocin influences social cognition is important for a number of reasons. First these studies provide important information regarding the biology underlying social cognitive deficits in schizophrenia. Second, they provide guidance as to how oxytocin could be employed for therapeutic purposes to improve social cognitive functioning. For example, oxytocin influences lower order social cognition in healthy adults and this may suggest a combinatorial strategy of delivering oxytocin with emotion recognition training for therapeutic purposes in clinical conditions. This is particularly important in light of recent debate that in Schizophrenia specifically, the effect of oxytocin may be only beneficial for a limited number of tests assessing very specific higher order, rather than lower order (Horta de Macedo et al., 2014), social cognitive processes (Davis et al., 2014). Such an argument has also been used to explain why some longer term administration studies that included lower-order social cognition skill training found no additional benefit of oxytocin in psychosis (Cacciotti-Saija et al., 2015). Finally, it would be useful to identify reliable markers of response to oxytocin in different clinical populations, to be able to predict who is receiving adequate dosing and likely to respond to treatment (Guastella and MacLeod, 2012). Currently, there is little understanding as to what constitutes a reliable response to oxytocin, although some social cognitive tests, such as emotion recognition, have shown promise as potential markers in healthy populations (Guastella and MacLeod, 2012; Shahrestani et al., 2013).

Thus, the aim of this study was to further explore the different domains of social cognition in patients with schizophrenia following intranasal administration of oxytocin. We utilized well-known and established tests of higher order and lower order social cognition to further test recent claims (Davis et al., 2013) that oxytocin has specific effects on higher order in comparison to lower order social cognition tasks.

## 2. Experimental materials and methods

### 2.1. Study design

Participants were enrolled in a within-subjects crossover, double-blind, randomized controlled trial at the Brain & Mind Research Institute (BMRI), University or Sydney. Participants were recruited from specialized tertiary referral services for the assessment and intervention of mental health problems (Youth Mental Health Clinic at the BMRI, and the Mental Health Service, Liverpool Hospital) and from the Australian Schizophrenia Research Bank. The study was approved by the Human Research Ethics Committee at the University of Sydney (11268) and the South Western Sydney Local Health District (10/051) was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 1260 9000528257). After a complete description of the study to the participants, written informed consent was obtained.

### 2.2. Participants

Eligible participants were male adults over the age of 16 years with a confirmed current diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria. Exclusion criteria included female sex due to likely interactions of treatment with menstrual cycle and contraceptive pill control, a verbal IQ lower than 75, experiencing acute exacerbation of psychiatric symptoms (including severe suicidal thoughts and/or actions), recurrent substance abuse problems within the last six months causing significant impairment, current physical health conditions (for example, cardiovascular disease, kidney disease) or hypersensitivity to preservatives in the nasal spray (in particular E 216, E 218, or chlorobutanol hemihydrates). Concurrent medication use was stabilized for at least eight weeks prior to entering the study and maintained over the course of participation in the trial (See Consort diagram; Fig. 1).

### 2.3. Interventions and adverse reporting

Nasal sprays were developed and randomized by a local compounding chemist with an identical placebo containing all ingredients except the active oxytocin (all sprays contained sorbitol, benzyl alcohol glycerol, and distilled water, contained within an amber 7 ml glass nasal spray with metered dose pump). Participants received either 24 international units (IU) of oxytocin or placebo (4 IU per spray, 3 sprays per nostril) at each administration (Phases A and B). Nasal sprays were labeled with sequential numbers and Phase A or Phase B; blocking was in sets of 6 (3 active and 3 placebo sprays) in a randomly generated order. All research staff members conducting assessments and participants were blind to treatment allocation and unaware of randomization.

To assess for any potential adverse effects from the nasal spray, participants were asked to report any side effects and what drug they thought they had taken by free response at the end of each visit. A safety monitoring board (comprising of IBH; PBW and others) was involved to oversee any adverse events.

### 2.4. Diagnostic assessments

Diagnostic tests included the Diagnostic Interview for Psychoses (DIP), assessing occurrence of relevant symptoms and signs across the patient's lifetime to confirm diagnosis (Castle et al., 2006) and the Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS), to rate positive and negative symptoms experienced over the past month (Andreasen, 1983, 1984). To estimate IQ, we used the verbal subscale of the Wechsler Abbreviated Scale of Intelligence (Weschler, 1999) due to its lower susceptibility to the impact of psychosis (O'Connor et al., 2012).

### 2.5. Outcome measures

#### 2.5.1. Lower order social cognition

The paralanguage and face subtasks of the Diagnostic Analysis of Non-Verbal Accuracy (DANVA: (Nowicki and Duke, 1994)). The DANVA measures individual differences in nonverbal emotion recognition accuracy. We used the adult stimuli. In the paralanguage subtask, the ability to correctly process nonverbal information about affect from tones of voice is assessed, while the faces subtask tests the ability to correctly process nonverbal information about affect from photographs of faces. Facial Expressions of Emotions Task (FEEST, (Young et al., 2002)): In this task, accuracy in emotion recognition from a standardized set of photos of faces (Ekman and Friesen, 1976) is assessed. Finally, we included the Reading the Mind in the Eyes Task (RMET(Baron-Cohen et al., 2001)). This test requires participants to identify the best emotion descriptor that matches the expression displayed by the eye region of 36 faces. It has well established reliability and validity, and was included as previous studies have demonstrated sensitivity to oxytocin administration on this task in healthy (Domes et al., 2007) and autistic samples (Guastella et al., 2010).

#### 2.5.2. Higher order social cognition

False Belief Picture Sequencing Task (FBPSTL) (Langdon et al., 1997): This task assesses theory of mind by requiring individuals to sequence a

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