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Oxytocin administration selectively improves olfactory detection thresholds for lyral in patients with schizophrenia

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Summary
Background: Olfaction plays an important role in mammalian social behavior. Olfactory deficits are common in schizophrenia and correlate with negative symptoms and low social drive. Despite their prominence and possible clinical relevance, little is understood about the pathological mechanisms underlying olfactory deficits in schizophrenia and there are currently no effective treatments for these deficits. The prosocial neuropeptide oxytocin may affect the olfactory system when administered intranasally to humans and there is growing interest in its therapeutic potential in schizophrenia.
Methods: To examine this model, we administered 40 IU of oxytocin and placebo intranasally to 31 patients with a schizophrenia spectrum illness and 34 age-matched healthy control participants in a randomized, double-blind, placebo-controlled, cross-over study. On each test day, participants completed an olfactory detection threshold test for two different odors: (1) lyral, a synthetic fragrance compound for which patients with schizophrenia have specific olfactory detection threshold deficits, possibly related to decreased cyclic adenosine 3′,5′-monophosphate (cAMP) signaling; and (2) anise, a compound for which olfactory detection thresholds change with menstrual cycle phase in women.
Results: On the placebo test day, patients with schizophrenia did not significantly differ from healthy controls in detection of either odor. We found that oxytocin administration significantly and selectively improved olfactory detection thresholds for lyral but not for anise in patients with schizophrenia. In contrast, oxytocin had no effect on detection of either odor in healthy controls.

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Discussion: Our data indicate that oxytocin administration may ameliorate olfactory deficits in schizophrenia and suggest the effects of intranasal oxytocin may extend to influencing the olfactory system. Given that oxytocin has been found to increase cAMP signaling *in vitro* a possible mechanism for these effects is discussed.
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1. Introduction

Patients with schizophrenia have significant olfactory impairments including difficulties with odor identification, detection threshold sensitivity, discrimination, and memory (Moberg et al., 2014). These deficits are associated with smaller olfactory bulbs, worsen over the course of the illness, and are present in unaffected family members (Moberg et al., 2014). Because of these findings, olfactory deficits have been proposed as an endophenotype of schizophrenia. Additionally, olfaction plays a critical role in social behavior, such as emotion contagion, bonding, and mate selection in mammals, including humans (Stevenson, 2010); and deficits in odor identification correlate with negative symptoms in schizophrenia, in particular with low social drive (Malaspina and Coleman, 2003). Despite their prominence and possible clinical importance, little is understood about the pathological mechanisms underlying olfactory deficits in schizophrenia and there are currently no effective treatments for these deficits.

Few studies have investigated odor detection threshold deficits in schizophrenia, and findings have been inconsistent, perhaps due to the diverse nature of the disease symptomology (Moberg et al., 1999). Additionally, because odor identification involves higher cognitive processes, odor identification is generally more impaired in schizophrenia than odor detection threshold (Moberg et al., 2014). One study found that while controlling for odor identification, worse odor detection levels correlated with lack of spontaneity in males and emotional withdrawal in females, factors that contribute to social isolation. Better odor detection levels were associated with blunted affect in males and better emotional expression in females (Malaspina et al., 2012). Clearly, more research needs to be conducted to elucidate the role of odor detection deficits in schizophrenia.

The neuropeptide oxytocin is involved in many aspects of social behavior including mother-child bonding and trust, and animal work has implicated oxytocin in olfactory-based social processing (Wacker and Ludwig, 2012). For example, in rodents and sheep, oxytocin receptors are present in the olfactory bulb, and oxytocin is required for retaining olfactory social memories (Wacker and Ludwig, 2012). Additionally, in rats, vaginocervical stimulation-induced improvement in recognition of conspecifics requires oxytocin release in the olfactory bulb (Larrazolo-López et al., 2008). These studies link oxytocin signaling in the olfactory bulb with olfactory and social functions. Finally, there is growing evidence that oxytocin administration to patients with schizophrenia improves emotion recognition and higher-level social cognition and decreases both positive and negative symptoms (Gumley et al., 2014). Additionally, a recent study that administered 20 IU of oxytocin or placebo twice daily for three weeks to patients with schizophrenia found that oxytocin improved patients' ability to identify pleasant, but not neutral or unpleasant odors (Lee et al., 2013). Taken together, this evidence suggests that oxytocin administration may reduce olfactory deficits in schizophrenia.

Due to oxytocin's involvement in the olfactory system and the prominence of olfactory deficits in schizophrenia, we hypothesized that administration of intranasal oxytocin would improve olfactory deficits in schizophrenia. In order to minimize the confounding effects of higher order cognitive processes on the task, we focused on odor detection thresholds, which do not require subjects to engage in memory retrieval or verbal labeling of the odor. We focused on odor detection thresholds for two compounds, lyral and anise oil. We selected lyral (4-[4-hydroxy-4-methylpentyl]-3-cyclohexene-1-carboxyaldehyde), a synthetic fragrance compound, as patients with schizophrenia are known to show specific deficits in olfactory detection thresholds for lyral, and these deficits have been hypothesized to be due to cyclic adenosine 3′,5′-monophosphate (cAMP) signaling dysregulation in schizophrenia (Turetsky and Moberg, 2009). We selected anise oil, distilled from the anise plant, as previous work has found that women's olfactory detection threshold for anise changes with their menstrual cycle (Caruso et al., 2001) and as oxytocin has been proposed to change with the menstrual cycle (Salonia et al., 2005), we wished to examine whether intranasal oxytocin would alter olfactory detection thresholds to this compound. The addition of healthy comparison subjects allowed us to investigate if any effects of oxytocin were specific to schizophrenia and to document normal response patterns in healthy adults.

2. Methods

2.1. Subjects

Twenty-five men and six women with a schizophrenia spectrum illness (SZ, twenty-one with schizophrenia, nine with schizoaffective disorder, and one with schizophreniform disorder) in outpatient care, and thirty-two male and two female healthy control (HC) subjects matched as a group in age to the SZ group participated in the study. All diagnoses were established with the Structured Clinical Interivew for DSM-IV (First et al., 2002) administered by trained clinical interviewers that consisted of doctoral clinical psychology students and research staff with Bachelor's degrees. They attended extensive training sessions on administering clinical interviews, conducted mock interviews, observed experienced clinicians, and were observed by experienced clinicians. Exclusion criteria included: (1) history of a psychiatric disorder (except for a schizophrenia spectrum illness in the patient group), (2) brain trauma with loss of consciousness, (3) substance dependence or recent illicit substance