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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

use, (4) history of seizures, (5) conditions that could alter olfactory functioning (e.g., congestion, sinus infection), and (6) pregnancy. Patients were on a stable dose of psychiatric medications for at least one month and throughout the study. Trained raters administered the Positive and Negative Syndrome Scale (PANSS) once at baseline before nasal spray administration. Written informed consent was obtained from each participant, and the Committee on Human Research at the University of California, San Francisco approved study protocols. A urine toxicology test was administered on each testing day to ensure that participants had no recent illicit substance use.

2.2. Design and procedures

We used a randomized, double-blind, cross-over design with the two testing days separated by at least one week. At each testing session, 40 IU of oxytocin (Novartis, Switzerland) was self-administered intranasally by alternating insufflations every 20 s between nostrils. This dose of oxytocin has been used in previous clinical trials of oxytocin in schizophrenia (Gumley et al., 2014). Mean time from drug administration to olfactory testing was 139 min (SD = 19 min, range: 111—206 min).

2.3. Olfactory testing

We used the Munich olfaction test (Kruggel, 1989) with serial dilutions of lyral and anise odors to assess olfactory detection thresholds (for detailed methods see Supplementary Materials). Briefly, starting with a single odor at the lowest concentration, we measured detection threshold using an ascending triple-forced choice procedure. Three bottles were presented in random order, two with pure mineral oil (the diluent) and one with the diluted oil (lyral or anise), and the participant identified the bottle that smelled different from the other two. To minimize correct choices occurring by chance, threshold was defined as the lowest concentration that subjects could correctly identify on three consecutive trials. After incorrect trials, the procedure continued with the next higher concentration of the odor. After threshold or the highest available concentration was reached for a single odor, the next odor was tested with the same procedure. The other nostril was tested with the same procedure after testing of both odors in the initial nostril. Similar methods have been used to determine olfactory thresholds in healthy individuals (Hummel et al., 1997) and in individuals with schizophrenia (Purdon and Flor-Henry, 2000).

2.4. Data analysis

Differences between groups in demographic factors were examined using independent samples *t*-tests for continuous variables and chi-square tests for categorical variables. Olfactory detection threshold data for lyral and anise were not normally distributed so non-parametric statistical tests were used. To assess whether SZ patients had abnormal olfactory detection thresholds, placebo-day detection thresholds for each odor were compared between groups using a Mann—Whitney *U* test. The effects of oxytocin on detection thresholds were compared between groups for each odor by first calculating oxytocin-induced olfactory detection threshold differences for each subject (i.e., oxytocin day—placebo day thresholds). The detection-threshold difference scores for each odor were then compared between groups (SZ vs. HC) using a Mann—Whitney *U* test. Follow-up Wilcoxon signed-rank tests were then performed within each group to compare oxytocin- and placebo-day detection thresholds separately for each odor.

In secondary analyses, we examined whether SZ patients showed differential abnormalities between their baseline detection thresholds for the two odors, and between the effects of oxytocin on the two odors. To accomplish this, patient detection thresholds were transformed to *z*-scores separately for each odor based on normative data provided by the HC group on the placebo day (i.e., z = [patient threshold − HC threshold mean]/HC threshold SD]. These *z*-scores expressed the patient detection thresholds for each odor and each test day as deviations, in standard units, from the detection thresholds exhibited by HC on the placebo day. *z*-Scoring controlled for scale differences between the detectability thresholds of lyral and anise, allowing them to be directly compared in patients. For baseline comparisons, patient *z*-scores for lyral and anise from the placebo day were directly compared using a Wilcoxon signed rank-tests. For comparison of oxytocin effects, patient *z*-score differences between the oxytocin-day and placebo-day were calculated for lyral and for anise, followed by direct comparison of these *z*-difference scores in the patients using a Wilcoxon signed-rank test.

For details concerning manipulation checks and exploratory analysis of possible moderators of oxytocin's effects on olfactory detection thresholds, see Supplementary data.

3. Results

3.1. Sample characteristics

Demographic and clinical data for SZ and HC are presented in Table 1. Patients were significantly less educated than HC, but the groups were similar on age, smoking habits, and ethnicity.

3.2. Group differences in olfaction

We found no significant differences in olfactory detection thresholds between SZ and HCs for lyral ($U = 524$, $Z = =0.04$, $p = 0.97$) or anise ($U = 419$, $Z = -1.23$, $p = 0.22$) on the placebo day, indicating that the groups did not differ in their ability to detect these odors.

3.3. Oxytocin effects on olfaction

We found that oxytocin induced significantly greater improvement in detection of lyral in the SZ than in the HC group ($U = 374$, $Z = -2.01$, $p = 0.04$, Fig. 1, Supplemental Table 2). Follow-up within-group analyses revealed a significant oxytocin-induced improvement in detection thresholds

Table 1 Demographics and clinical information.

	Schizophrenia patients ($N = 31$)		Healthy controls ($N = 34$)		
	Mean (N)	SD (%)	Mean (N)	SD (%)	p-Value
Demographics					
Age (years)	44.0	9.7	43.3	12.7	0.82
Range	23—61	—	20—64	—	—
Education Level	13.6	2.4	15.3	1.9	0.003**
Current Smoker	11	35.5%	7	20.6%	0.27
Race					0.13
Caucasian	6	19.4%	17	50.0%	
African American	8	25.8%	7	20.6%	
Latino/Hispanic	3	9.7%	3	8.8%	
Asian American	12	38.7%	7	20.6%	
Other	2	6.5%	0	0.0%	
Clinical symptoms ($N = 21$)					
Positive	16.1	4.2	—	—	—
Negative	15.1	5.4	—	—	—
General	31.4	9.6	—	—	—
Medication Equivalents					
Cogentin	0.4	0.6	—	—	—
Chlorpromazine	308	318	—	—	—
	Placebo	Oxytocin	Placebo	Oxytocin	
Olfaction compounds	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	
Anise detection threshold	1.1E − 4[9.1E − 6, 1.5E − 3]	6.5E − 5[1.3E − 5, 4.3E − 4]	4.3E − 4[2.5E − 5, 2.2E − 3]	8.2E − 5[4.4E − 6, 1.5E − 3]	
Lyral detection threshold	4.8E − 4[1.0E − 5, 3.8E − 2]	5.3E − 5[1.1E − 6, 4.3E − 3]	1.1E − 3[1.8E − 5, 6.7E − 2]	2.2E − 4[1.0E − 5, 4.6E − 2]	
	Placebo	Oxytocin—placebo	Placebo	Oxytocin—placebo	
z-Score	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	
Anise	−0.34(0.12)	0.28(0.94)	—	—	
Lyral	0.09(1.09)	−0.33(0.83)	—	—	

** $p \leq 0.01$.
* $p \leq 0.05$.
IQR = inter-quartile range.

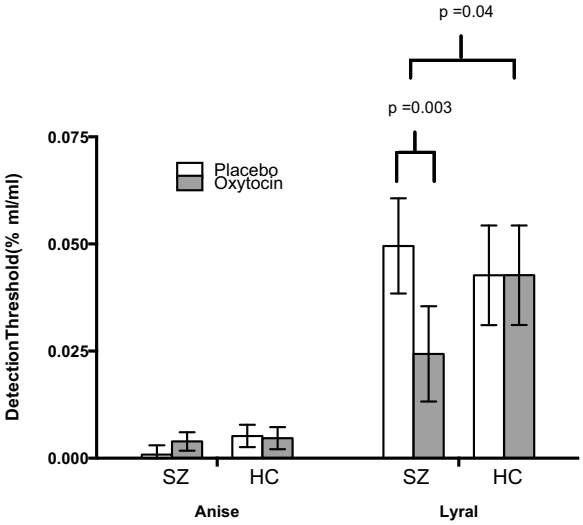

Fig. 1 *Oxytocin effects on olfaction detection thresholds.* SZ = schizophrenia patients, HC = healthy controls. Graph represents mean concentration levels detected on different drug days separated by group. Lower concentrations denote better olfactory ability. Error bars indicate within-subject error. Compared to healthy controls, oxytocin significantly improves detection of lyral in patients with schizophrenia ($U = 374$, $Z = -2.01$, $p = 0.04$). Compared to placebo, oxytocin significantly improves detection of lyral in patients with schizophrenia ($Z = -3.01$ $p = 0.003$).

for lyral in SZ ($Z = -3.0$, $p = 0.003$) but not in HCs ($Z = -0.21$, $p = 0.84$). Oxytocin-induced changes in detection of anise were not significantly different between groups ($U = 434$, $Z = -1.03$, $p = 0.30$) and follow-up within-group analyses revealed no effect of oxytocin on detection thresholds for anise in SZ ($Z = -0.22$, $p = 0.83$) or in HC ($Z = -1.67$, $p = 0.10$).

In our secondary analyses of HC-normed detection threshold *z*-scores, we found that patient *z*-scores for the two odors did not significantly differ on the placebo day (*z*-score mean (SD); lyral: 0.09 (1.09), anise: −0.34 (0.12); $Z = -0.61$, $p = 0.54$). In terms of the oxytocin vs. placebo *z*-difference scores in patients (normed to the HC placebo day thresholds), the effect of oxytocin was significantly greater for lyral than for anise (*z*-difference score mean (SD); lyral: −0.33 (0.83), anise: 0.28 (0.94)); $Z = -3.01$, $p = 0.003$).

Given the small number of women in the current study, we repeated all analyses excluding women to explore any effects of gender. Results were unchanged. Furthermore, our blinding procedure was adequate and the order of drug administration was not significantly different between groups or from chance and did not significantly interact with our results (for details and analyses see Supplementary data).

4. Discussion

We found that administration of a single dose of oxytocin selectively improves olfactory detection ability for lyral in patients with schizophrenia, but not in healthy participants. Our findings extend those of other studies (Lee et al., 2013), and suggest that the oxytocin system plays a role in some aspects of the olfactory deficits in schizophrenia. However, oxytocin did not improve participants' ability to detect anise, suggesting some specificity to its olfaction-enhancing effect.

Different odor molecules induce different levels of cAMP in the nasal epithelium via activation of a G-protein signaling cascade. Patients with schizophrenia show a deficit in detecting odors that release low levels of cAMP (e.g., lyral), but their ability to detect compounds associated with high release of cAMP (e.g., citralva) is intact (Turetsky and Moberg, 2009). Interestingly, *in vitro* work suggests that oxytocin can increase cAMP, suggesting that this may be the mechanism by which it enhances olfactory detection of lyral in patients with schizophrenia (Cassoni et al., 1997). Due to citralva's high cAMP release, we hypothesize that oxytocin would have little effect on patients' detection threshold for citralva (Turetsky and Moberg, 2009). Unfortunately, we do not know whether anise odor is a strong or weak inducer of cAMP. Patients were not impaired in detecting lyral on the placebo-testing day compared to healthy controls, consistent with previous studies that find within-subject deficits in detection of lyral compared to detection of citralva, but no between-group differences in lyral detection ability (Turetsky and Moberg, 2009).

There are several limitations of our study. First, our sample size was small and contained few women. Therefore, results must be interpreted with caution. Second, we did not employ a strong cAMP-activating odor such as citralva, limiting the interpretation of our findings. Finally, we only administered a single dose of oxytocin. Future studies should investigate the effects of gender and the effects of repeated intranasal oxytocin administration on detection of a greater number of odors, in a larger sample, as well as examine any associated improvements in socially-mediated behavior related to improved olfaction.

Contributors

Josh Woolley designed the study and supervised all data collection and analysis and manuscript writing. Olivia Lam helped manage various aspects of the study including data collection and recruitment of participants and assisted with manuscript writing. Brandon Chuang assisted with data collection, data management, statistical analyses, and manuscript writing. Judith Ford consulted with the team about data analysis and helped edit the manuscript. Dan H. Mathalon assisted with study design and data analysis. Sophia Vinogradov assisted with study design and data analysis. All authors contributed to and have approved the final manuscript.

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Conflict of interest statement

Dan Mathalon is a consultant to Bristol Myers Squibb Inc. Sophia Vinogradov is a consultant to Brain Plasticity Institute. The remaining authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2014.12.018.

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