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Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: Results from a randomized double blind placebo controlled pilot study

Mary R. Lee [a,*], Heidi J. Wehring [b], Robert P. McMahon [b], Jared Linthicum [b], Nicola Cascella [c], Fang Liu [b], Alan Bellack [d], Robert W. Buchanan [b], Gregory P. Strauss [b], Carlo Contoreggi [e], Deanna L. Kelly [b]

[a] Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD, United States
[b] Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, United States
[c] Sheppard Pratt Health System, Baltimore, MD, United States
[d] Veterans Affairs Medical Center VISN5, University of Maryland School of Medicine, United States
[e] Chemical Biology Research Branch, National Institute on Drug Abuse, Intramural Research Program, Rockville, MD, United States

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ABSTRACT

Background: Deficits in olfactory identification have been widely reported in patients with schizophrenia (SZ) and are associated with negative symptomatology. Adjunctive oxytocin delivered intranasally has been shown to improve some aspects of social cognition as well as positive and negative symptoms in patients with schizophrenia. Given the intranasal delivery route of oxytocin to olfactory pathways and that olfactory abnormalities are a potential endophenotype in SZ, we investigated the effect of intranasal oxytocin on olfactory identification as well as positive and negative symptoms in people with schizophrenia.
Methods: Individuals with schizophrenia or schizoaffective disorder (n = 28; 16 outpatients, 12 inpatients) were randomized to receive adjunctive intranasal oxytocin 20 IU BID or placebo for 3 weeks.
Results: All 28 participants completed the clinical trial. Odor identification performance significantly improved on the University of Pennsylvania Smell Identification Test (UPSIT) total score and subscore for pleasant smells. UPSIT score ($F = 5.20$, $df = 1,23$, $p = 0.032$) and subscore for pleasant smells ($F = 4.56$, $df = 1,23$, $p = 0.044$), in patients treated with oxytocin were compared to placebo from baseline to endpoint. Global symptomatology as well as positive and negative symptoms were not improved by intranasal oxytocin. In fact, global symptoms, not positive or negative symptoms, improved in the placebo group. Secondary analysis shows that intranasal oxytocin improved negative symptoms in the small group of inpatients. Intranasal oxytocin was well tolerated during the three week trial.
Conclusion: Adjunctive intranasal oxytocin may improve olfactory identification, particularly in items of positive valence. Larger studies are needed to determine the effects of oxytocin on negative symptoms in SZ. (NCT00884897; http://www.clinicaltrials.gov).

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1. Introduction

Negative symptoms are largely refractory to standard treatment with first and second generation antipsychotics and contribute to the increasing social withdrawal and avolition, as well as the functional and vocational impairments that characterize the deteriorating clinical course in people with schizophrenia (SZ) (Kirkpatrick et al., 2006). Given this, there has been considerable interest in developing treatments to ameliorate negative symptoms and enhance social functioning in people with SZ. Recently, there have been reports of small clinical studies using repeated intranasal oxytocin as an adjunctive treatment for people with SZ. These studies have reported improvement in positive and negative symptoms as well as improvement in some domains of emotional processing and cognitive processing (Bakharev et al., 1984; Feifel et al., 2010; Pedersen et al., 2011; Feifel et al., 2012; Wacker and Ludwig, 2012). There is a large literature of animal and human studies showing that oxytocin enhances a wide range of social behaviors including pair-bonding, maternal behavior, emotional memory, trust and social approach (Meyer-Lindenberg et al., 2011).

Negative symptoms are a multi-dimensional construct, with consistent support for 2 factors reflecting on the one hand, motivation–pleasure such as measures of asociality, avolition and anhedonia, and on the other hand, diminished emotional expressivity such as measures of alogia and blunted affect (Blanchard and Cohen, 2006). Overall, given the animal and human literature on the impact of oxytocin on social affiliation, social

* Corresponding author at: Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, 251 Bayview Blvd. #200, Baltimore, MD 21224, United States.
E-mail address: leemary@mail.nih.gov (M.R. Lee).

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approach and pair bonding, oxytocin's effect, if any, might be expected to be apparent particularly in the domain of motivation and pleasure.

In the animal literature, social affiliation or pair-bonding is mediated via olfactory sensory signals to limbic structures where oxytocin and dopamine interact to facilitate olfactory learning and memory (Young and Wang, 2004). Oxytocin receptors are highly expressed on olfactory neurons as well as limbic structures (Loup et al., 1991) and recent reviews suggest that oxytocin modulates social recognition and behavior at the level of the olfactory system (Wacker and Ludwig, 2012). In people with SZ, dysfunction in olfactory processes, including identification (Stedman and Clair, 1998), discrimination (Dunn and Weller, 1989), memory (Wu et al., 1993) and detection threshold sensitivity (Turetsky and Moberg, 2009) for odors, has been well described. Of these, deficits in smell identification have been most frequently described in people with SZ (Cascella et al., 2007). Using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984), Moberg et al. (1999) report that up to 80% of people with SZ have deficits in odor identification compared to 15% of the general population. The deficits are present early in the disorder and correlate with the duration of the disorder (Moberg et al., 1997; Ugur et al., 2005) apart from aging effects (Kopala et al., 1995). Further findings suggesting that deficits in odor identification might constitute an endophenotype for SZ are that deficits in odor identification are not associated with gender, or state measures such as medication use, smoking, olfactory hallucinations, or clinical symptoms at the onset of illness (Kopala et al., 1989; Kopala et al., 1994; Brewer et al., 2001, 2003; Malaspina and Coleman, 2003; Corcoran et al., 2005; Rupp et al., 2005; Roalf et al., 2006). In addition, several studies have shown that youth who are at high risk for psychosis have olfactory dysfunction (Brewer et al., 2003; Keshavan et al., 2009; Woodberry et al., 2010; Kamath et al., 2011c) and these deficits predict progression to psychosis (Brewer et al., 2003; Corcoran et al., 2005). Further, studies of monozygotic twins discordant for SZ (Kopala et al., 1998; Ugur et al., 2005) and of first and second degree relatives of SZ (Kopala et al., 2001; Roalf et al., 2006; Kamath et al., 2011b,c) also find deficits in odor identification in unaffected relatives of SZ patients. Lastly, odor identification deficits in SZ are not attributable to reduced olfactory sensitivity (Brewer et al., 2001; Rupp et al., 2005).

Importantly, there are several studies that report a relationship between dysfunction in odor identification and negative symptoms in SZ (Brewer et al., 1996; Stedman and Clair, 1998; Brewer et al., 2001; Coleman et al., 2002; Malaspina and Coleman, 2003; Corcoran et al., 2005; Good et al., 2006; Moberg et al., 2006). Specifically, the deficit syndrome (Carpenter et al., 1988) has been found to be associated with poor performance on the UPSIT (Malaspina et al., 2002; Malaspina and Coleman, 2003; Moberg et al., 2006; Strauss et al., 2010). In particular, subscales of the Scale for Assessment of Negative Symptoms (SANS); (Buchanan et al., 2007) such as blunted affect, apathy and anhedonia have been found to be predicted by lower UPSIT scores (Ishizuka et al., 2010). With regard to anhedonia, people with SZ, compared to controls, have impaired performance on the UPSIT that is specific for positive and neutral-valenced odors, (Kamath et al., 2011d) and rate pleasant odors as less so (Crespo-Facorro et al., 2001; Moberg and Turetsky, 2003; Plailly et al., 2006).

Given the potential of oxytocin as a treatment for disorders of social affiliation such as SZ and autism (Young and Wang, 2004; Hammock and Young, 2006; Meyer-Lindenberg et al., 2011), and the intranasal delivery route of oxytocin to olfactory pathways, abnormalities in the latter being a potential endophenotype in SZ, we investigated the effect of intranasal oxytocin on olfactory identification using the UPSIT in a double blind placebo controlled randomized 3 week clinical trial. We also investigated concomitant changes in negative and positive symptoms, as well as their relationship to performance on the UPSIT as a consequence of oxytocin administration.

2. Subjects and methods

2.1. Participants

Between January 2010 and February 2012 we conducted a double blind randomized clinical trial (Clinical Trials.gov NCT00884897) of three week treatment with adjunctive intranasal oxytocin vs. placebo in people with SZ. Those included in the study met the DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician version (SCID-IV); (First and S.R.G.M.a.W.J., 2002) were male or female between 18 and 60 years old, on stable antipsychotic treatment (no change in medication in previous 6 weeks and no change in dose for past 30 days), were inpatient or outpatient, and were capable of passing the Evaluation to Sign Consent (ESC) (DeRenzo et al., 1998). Additional information is provided in the supplementary materials on patient exclusion and enrollment. There was no change in antipsychotic medication or dosage throughout the 3 week trial.

2.2. Medication dosing and blinding

Each participant was instructed to administer 20 IU oxytocin or placebo intranasally twice daily. Each 20 IU oxytocin dose consisted of five puffs, each containing 4 IU of oxytocin. No unblinded staff was involved in clinical ratings for participants. Subjects were randomized to oxytocin (20 IU BID) or matching placebo and were stratified by inpatient and smoking status. All patients went a two week lead in stabilization period prior to randomization in the 3 week study.

2.3. Olfactory identification

Olfactory identification ability was assessed using the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984) at baseline and end of treatment. The UPSIT is a standardized measure that requires identification of 40 common microencapsulated odors by selecting one of four multiple-choice answers consisting of various odor names after birhinal administration. We also calculated valence-specific UPSIT scores based upon other published studies using the UPSIT in schizophrenia (Strauss et al., 2010; Kamath et al., 2011a,d). The 40 odorants were divided into pleasant, neutral, and unpleasant categories using pleasantness ratings from the UPSIT manual (Doty et al., 1984):16 pleasant, 15 neutral and 9 unpleasant items.

2.4. Symptom assessment

The Brief Psychiatric Rating Scale (BPRS) total score (18 items, each scored 1–7) (Overall and Gorham, 1962; Doty et al., 1984) assessed general psychopathology. The BPRS 4-item positive symptom score measured changes in positive symptoms. The modified Scale for the Assessment of Negative Symptoms (SANS) (Buchanan et al., 2007) total score measured negative symptom change. The average of the SANS avolition and anhedonia/asociality global items was measured to examine the motivation–pleasure dimension of negative symptoms that has been found to be separable from diminished emotional expressivity (restricted affect and alogia) (Blanchard and Cohen, 2006). The Clinical Global Impression (CGI) severity of illness item measured global changes (Guy, 1976). The BPRS, SANS, and CGI were obtained at baseline, week 1 and after the last dose of study medication. Intraclass correlation coefficients for these instruments ranged from 0.76 to 0.90. All raters were blind to treatment assignment. Information on side effect ratings and laboratory tests and results are provided in the supplementary materials.

2.5. Data analysis

A mixed model for repeated measures ANCOVA was used to compare the changes between treatment groups for symptom scores and for the total UPSIT score. A mixed model was used controlling for age and baseline values: outcome = baseline primary outcome variable + age + treatment group + time + time × treatment. Pleasant, neutral and unpleasant odors were examined separately. Pearson's correlations coefficients were used to examine the relationship between change in symptoms and UPSIT performance. For symptom measures (BPRS, SANS), we examined inpatient status in an exploratory analysis and found a significant treatment × inpatient status interaction of the SANS total score and the SANS dimension of motivation and pleasure. Thus, post hoc analyses examined independent effects of oxytocin on inpatients and outpatients. For additional information on data analysis, see the supplementary information.

3. Results

There were 28 participants randomized to either adjunctive oxytocin nasal spray (N = 13) or matching placebo nasal spray (N = 15) for a 3 week study (see Fig. 1 for study flow).

Age was included as a covariate in all analyses as mean age was older in the oxytocin group (44.7 ± 11.7 versus 35.1 ± 8.2 years). Table 1 shows the baseline demographic and clinical variables for the two groups.

Table 1
Baseline demographic and clinical information.

	Oxytocin (N = 13)	Placebo (N = 15)
Age (years)* ± SD	44.74 ± 11.74	35.07 ± 8.21
Sex (male)	9 (69%)	11 (73%)
Race (White)	10 (77%)	8 (53%)
Education level (years)	12.08 ± 2.84	11.86 ± 1.70
Marital status (never married)	11(92%)	14 (93%)
Outpatient/inpatient	7/6	9/6
Smoker	9 (69%)	10 (67%)
CGI (Global)	3.77 ± 0.63	3.57 ± 0.46
Total BPRS	37.31 ± 7.24	34.00 ± 7.78
SANS total score	31.19 ± 7.85	36.00 ± 8.54
BMI (mean) ± SD (kg/m^2)	30.77 ± 6.34	32.64 ± 5.08
Type II Diabetes	5(38%)	2(13%)
RBANS	79.3 ± 12.9	75.0 ± 13.0

* p = 0.03.

3.1. Symptom changes

Table 3 shows symptom changes from baseline to endpoint by treatment group for the BPRS, SANS and CGI. For the total BPRS, there was a significant treatment × time interaction favoring placebo during the study in the repeated measures analysis (F = 14.19, df = 1,26, p = 0.0009). With respect to SANS total score there was a treatment × time interaction for the SANS total scores (F = 2, df = 1,26, p = 0.17, effect size d = 0.01). However, on exploratory analysis of treatment setting, there was a treatment group × setting interaction (F = 5.51, df = 1,22, p = 0.028) favoring oxytocin in the inpatient setting. Thus, at week 3, there was a significant difference between treatment groups for the inpatient mean total SANS scores only: oxytocin: 25.5 ± 7.2, placebo: 38.7 ± 7.4, difference = −8.0 ± 3.4, t = −2.3, df = 33.8, p = 0.025. At week 3 there was no significant difference between treatment groups for the outpatient mean total SANS scores: oxytocin: 34.86 ± 5.64, placebo: 33.00 ± 8.93, difference = 4.8 ± 3.0, t = 1.6, df = 33.7, p = 0.11. Fig. 2 shows the total and the motivation–pleasure dimension of the SANS scores by treatment and setting. The latter SANS subscore also showed significant improvement in the oxytocin group in the inpatient setting (F = 4.65, df = 1,22, p = 0.042). The effect size for the improvement in the total SANS in the inpatient group was d = 0.85 and for the pleasure and motivation dimension, d = 0.74.

3.2. Smell identification

Table 2 shows the UPSIT baseline and endpoint total scores and subscores for pleasant, neutral and unpleasant odors. There was a significant treatment group × time interaction such that there was a significant improvement in total UPSIT score in the oxytocin group relative to placebo from baseline to endpoint (F = 5.20, df = 1,23, p = 0.032). There was also a treatment group × time interaction for

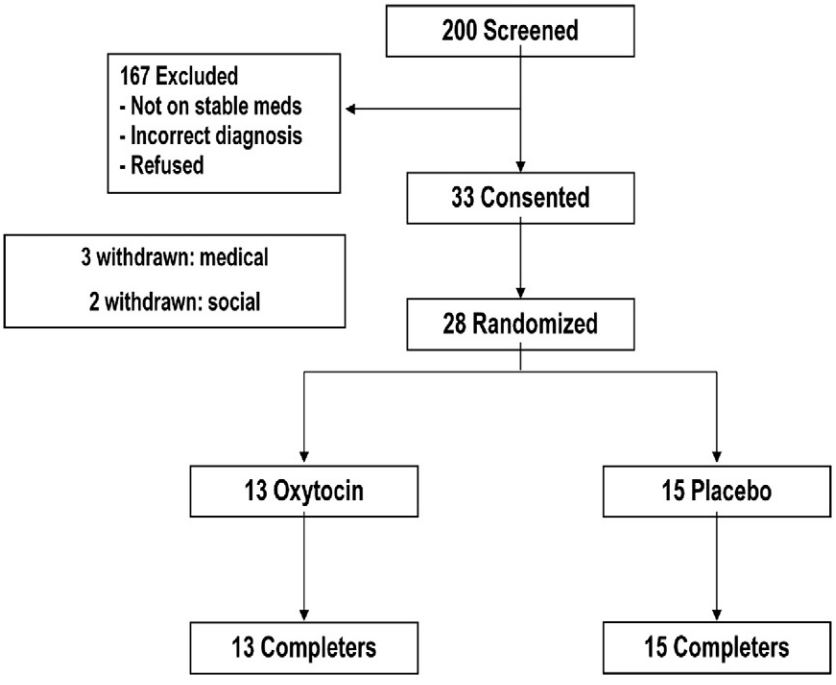

Fig. 1. Study flow diagram.

Table 2
University of Pennsylvania Smell Identification Test (UPSIT).

	Oxytocin (N = 13)	Placebo (N = 15)	Statistic[a]
Total score baseline	31.31 ± 5.63	32.07 ± 3.00	
Total score endpoint	32.46 ± 3.60	31.79 ± 5.15	F = 5.20, df = 1,23, p = 0.032
Pleasant odor baseline	12.15 ± 2.79	12.86 ± 1.35	
Pleasant odor endpoint	13.00 ± 1.68	12.57 ± 2.59	F = 4.56, df = 1,23, p = 0.044
Neutral odor baseline	12.46 ± 2.37	12.50 ± 1.70	
Neutral odor endpoint	12.39 ± 2.50	12.50 ± 2.31	F = 1.79, df = 1,23, p = 0.194
Unpleasant odor baseline	6.69 ± 1.31	6.64 ± 0.84	
Unpleasant odor endpoint	7.15 ± 0.80	6.71 ± 1.20	F = 1.38, df = 1,23, p = 0.253

[a] ANCOVA treatment assignment, controlling for age and baseline.

pleasant smell UPSIT subscore only such that the oxytocin group improved significantly (F = 4.56, df = 1,23, p = 0.044) with no significant treatment effects found for neutral or unpleasant smells. The effect sizes for the between group difference in change of the UPSIT total score and the pleasant odor score were d = 0.32 and d = 0.52, respectively. There was no inpatient/outpatient interaction for the UPSIT. We did not find any significant correlation between changes in UPSIT score and changes in symptom scores for the total or inpatient or outpatient groups.

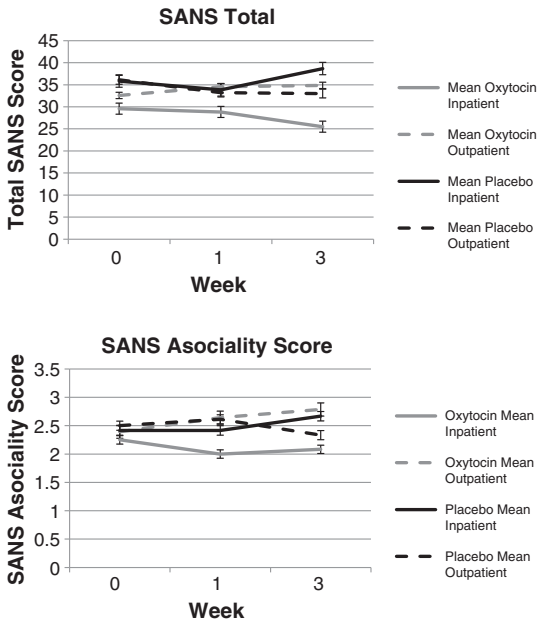

Fig. 2. SANS scores by treatment setting and medication. SANS total setting × treatment interaction: F = 5.51, df = 1,22, p = 0.028. Week 3: treatment difference inpatients, p = 0.025, outpatients, p = 0.120. SANS total avolition/anhedonia/asociality setting × treatment interaction: F = 4.65, df = 1,22, p = 0.042. There were N = 6 inpatients on oxytocin, N = 7 outpatients on oxytocin. There were N = 6 inpatients on placebo, N = 9 outpatients on placebo.

4. Discussion

In summary, adjunctive intranasal oxytocin (20 IU BID) given over 3 weeks significantly improved odor identification on the UPSIT in people with schizophrenia relative to placebo and this improvement was driven largely by improvement in the identification of pleasant odors. Global symptomatology was improved significantly in the placebo group, while secondary analysis showed improvements on the SANS for intranasal oxytocin but only in the inpatient group.

Performance deficits on the UPSIT in SZ have been shown to be related to negative symptoms (Brewer et al., 1996; Stedman and Clair, 1998; Brewer et al., 2001; Malaspina and Coleman, 2003; Corcoran et al., 2005; Good et al., 2006; Moberg et al., 2006; Ishizuka et al., 2010) and to be valence-dependent. Kamath et al. (2011d) report that odor identification accuracy on the UPSIT in people with SZ patients is impaired due to errors in identifying pleasant and neutral odors compared to controls, with no group difference in ability to correctly identify unpleasant odors. Indeed, accuracy for pleasant odors on the UPSIT in the Kamath et al. study and at baseline in ours is almost identical, 76 and 75% respectively. Kamath et al. (2011d) also reports a positive correlation between identification of unpleasant odors and the SANS anhedonia subscale. People with SZ rate the subjective experience or "hedonicity" of pleasant odors as less pleasant compared to control subjects with no difference in hedonicity ratings for unpleasant odors (Crespo-Facorro et al., 2001; Moberg and Turetsky, 2003; Plailly et al., 2006). Taken together, these findings have lead to speculation that the abnormalities in neural circuitry for odor processing in SZ may overlap with those underlying anhedonia.

Oxytocin, we report here, improved performance on the UPSIT in a valence-dependent manner, that is, specifically for pleasant odors. In human studies using intranasal oxytocin, mostly in healthy control populations, there is a well described context-dependent effect for oxytocin over multiple domains, showing some evidence for oxytocin having a stronger effect on the perception of positive stimuli across a range of stimulus types e.g., faces, words (Guastella and MacLeod, 2012). In people with schizophrenia single doses of intranasal oxytocin have been shown to improve emotion recognition equally for positive and negatively valenced facial expressions (Averbeck et al., 2011). Other recent studies using adjunctive intranasal oxytocin over several weeks in SZ report improvement in verbal memory (Feifel et al., 2012), as well as positive and negative symptoms (Feifel et al., 2010; Pedersen et al., 2011). We are the first to examine smell identification with intranasal oxytocin and report its context-dependent effect in this domain in people with SZ, selectively improving the specific deficit in olfactory identification on the UPSIT found by Kamath et al. (2011d). It is, of course, unclear how this improvement in olfactory identification overall and

Table 3
Symptom changes during the three week study.

	Oxytocin (N = 13)		Placebo (N = 15)		ANCOVA
	Baseline	Endpoint	Baseline	Endpoint	
BPRS (total)	37.31 ± 7.24	36.51 ± 7.96	34.00 ± 7.78	29.87 ± 6.44	F = 14.19, df = 1,26, p = 0.0009
BPRS subscores:					
Psychosis	11.58 ± 4.53	11.61 ± 4.59	8.17 ± 4.29	7.40 ± 3.92	F = 0.76, df = 1,26, p = 0.392
Anxiety/Depression	6.00 ± 1.71	5.38 ± 1.61	6.33 ± 2.49	5.20 ± 2.45	F = 1.64, df = 1,26, p = 0.211
Hostility	4.88 ± 1.29	5.07 ± 1.89	4.37 ± 1.48	3.73 ± 1.38	F = 2.96, df = 1,26, p = 0.0973
Activation	4.77 ± 1.80	4.23 ± 1.74	4.40 ± 1.21	4.40 ± 1.40	F = 0.08,df = 1,26, p = 0.7815
SANS (total)[a]	31.19 ± 7.85	30.54 ± 7.81	36.00 ± 8.53	35.27 ± 8.57	F = 2, df = 1,26, p = 0.17
SANS motivation–pleasure subfactor[a]	2.33 ± 0.63	2.46 ± 0.83	2.47 ± 0.58	2.47 ± 0.48	F = 1.15, df = 1,26, P = 0.29
CGI	3.85 ± 0.38	3.77 ± 0.60	3.87 ± 0.51	3.80 ± 0.41	F = 0.04, df = 1,26, p = 0.846

[a] Treatment by setting interaction noted. See Fig. 2 below.

improvement of identification of pleasant odors relates to the symptom improvement (positive and negative symptoms) seen in the small studies to date using adjunctive intranasal oxytocin in SZ.

In general, intranasal oxytocin has not been studied with respect to odor processing in humans, despite the large body of literature on the role of oxytocin (and vasopressin) on social odor processing in animal models (Wacker and Ludwig, 2012), although there are possible species differences that might render olfactory processing less important in human social interactions. The proximity of olfactory pathways to this intranasal route of delivery, as well as the known expression of oxytocin receptors on olfactory neurons, in the hypothalamus as well as in the frontal, temporal cortices and the striatum (Loup et al., 1991), areas known to be involved in odor identification (Kjelvik et al., 2012) and to be dysfunctional in SZ (Nguyen et al., 2010), warrants further investigation of this drug on olfactory processing in this population.

We did not find that adjunctive intranasal oxytocin improved negative symptoms relative to placebo in the full sample as others have found (Feifel et al., 2010; Pedersen et al., 2011). We did, however, find a significant improvement in total and motivation–pleasure SANS subscore negative symptoms in the group treated with oxytocin in the inpatient setting (N = 6), in the absence of a main effect of treatment setting on negative symptoms. The inpatient environment provides more opportunity for social interaction and in this setting adherence to treatment is guaranteed. That a drug effect was limited to a socially-enriched context is a finding that has also been reported in other studies using intranasal oxytocin in healthy controls (Heinrichs et al., 2003; Kosfeld et al., 2005).

Although performance deficits on the UPSIT have been shown to be associated with negative symptoms, we found no correlation overall at baseline or, for either treatment group, between negative symptom change and UPSIT total score change or for subscore changes. However, this pilot study might have lacked the power to give any convincing evidence for or against the idea that changes in the SANS and UPSIT are correlated as a function of oxytocin administration. A larger study is needed to more appropriately identify if indeed a relationship exists. Also, the use of oxytocin used in a subgroup with significant olfactory impairments may be ideal to study the relationship of improvements to symptom improvements such as negative symptoms.

There are several limitations to our study. First, the dose used in this study was lower than used in the other published studies to date using 80 IU (Feifel et al., 2010) and 48 IU (Pedersen et al., 2011). It is intriguing, however, that for the entire sample (n = 28), the largest effect from the dose used in our study was on olfaction which is mediated by neural structures most proximate to the delivery of the drug, the olfactory epithelium and primary olfactory cortex. Using larger doses of oxytocin, might impact negative and or positive symptoms, that are mediated by more distant, complex neurocircuitry. Second, our small, pilot study did not recruit for high levels of paranoia at baseline as did the two other studies of adjunctive intranasal oxytocin reporting improvements in positive symptoms (Feifel et al., 2010; Pedersen et al., 2011). Third, while baseline cognitive function did not differ between groups, we are not sure if neurocognitive measures were affected by oxytocin in the study. Lastly, our study was only a 3 week intervention and negative symptoms often take much longer to improve (Fleischhacker, 2000). Thus, longer term studies with adjunctive intranasal oxytocin may allow for more improvement in this symptom domain.

In conclusion, this pilot study provides evidence that intranasal oxytocin, 20 mg IU BID, given to people with schizophrenia is well tolerated and is associated with improvements in smell identification, particularly for pleasant odors. It also may be effective for a domain of negative symptoms that is difficult to treat: avolition and anhedonia, particularly in the context of social support. This data suggests that adjunctive intranasal oxytocin warrants further study for its impact on symptoms and olfaction in people with schizophrenia.

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Contributors

MRL, DLK, and HJW designed the study and wrote the protocol. MRL and DLK managed the literature searches and analyses. FL and RPM undertook the statistical analysis, and MRL wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Kelly receives grant support from Bristol Meyers Squibb and Ameritox.

Dr. McMahon serves on the advisory board of Amgen.

Dr. Buchanan serves on the following advisory boards: Abbott; Amgen; Astellas; Cypress Bioscience; Janssen Pharmaceuticals Inc.; Merck; NuPathe; Pfizer; Roche; Solvay Pharmaceuticals, Inc.; Takeda. He serves as Consultant for Abbott; Amgen; Astra-Zeneca; Bristol-Meyer-Squibb; EnVivo; Glaxo-Smith-Kline; Pfizer; Takeda. He is also a DSMB member for Pfizer, Cephalon, and Otsuka.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.01.001.

References

Averbeck, B.B., Bobin, T., Evans, S., Shergill, S.S., 2011. Emotion recognition and oxytocin in patients with schizophrenia. Psychol. Med. 1–8.

Bakharev, V.D., Tikhomirov, S.M., Lozhkina, T.K., 1984. Psychotropic properties of oxytocin. Probl. Endokrinol. (Mosk) 30, 37–41.

Blanchard, J.J., Cohen, A.S., 2006. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr. Bull. 32, 238–245.

Brewer, W.J., Edwards, J., Anderson, V., Robinson, T., Pantelis, C., 1996. Neuropsychological, olfactory, and hygiene deficits in men with negative symptom schizophrenia. Biol. Psychiatry 40, 1021–1031.

Brewer, W.J., Pantelis, C., Anderson, V., Velakoulis, D., Singh, B., Copolov, D.L., McGorry, P.D., 2001. Stability of olfactory identification deficits in neuroleptic-naive patients with first-episode psychosis. Am. J. Psychiatry 158, 107–115.

Brewer, W.J., Wood, S.J., McGorry, P.D., Francey, S.M., Phillips, L.J., Yung, A.R., Anderson, V., Copolov, D.L., Singh, B., Velakoulis, D., Pantelis, C., 2003. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am. J. Psychiatry 160, 1790–1794.

Buchanan, R.W., Javitt, D.C., Marder, S.R., Schooler, N.R., Gold, J.M., McMahon, R.P., Heresco-Levy, U., Carpenter, W.T., 2007. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. Am. J. Psychiatry 164, 1593–1602.

Carpenter Jr., W.T., Heinrichs, D.W., Wagman, A.M., 1988. Deficit and nondeficit forms of schizophrenia: the concept. Am. J. Psychiatry 145, 578–583.

Cascella, N.G., Takaki, M., Lin, S., Sawa, A., 2007. Neurodevelopmental involvement in schizophrenia: the olfactory epithelium as an alternative model for research. J. Neurochem. 102, 587–594.

Coleman, E., Goetz, R.R., Leitman, D., Yale, S., Stanford, A., Gorman, J.M., Malaspina, D., 2002. Odor identification impairments in schizophrenia: relationship with demographic measures, clinical variables, and diagnostic subtypes. CNS Spectr. 7, 43–48.

Corcoran, C., Whitaker, A., Coleman, E., Fried, J., Feldman, J., Goudsmit, N., Malaspina, D., 2005. Olfactory deficits, cognition and negative symptoms in early onset psychosis. Schizophr. Res. 80, 283–293.

Crespo-Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 2001. Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. JAMA 286, 427–435.

DeRenzo, E.G., Conley, R.R., Love, R., 1998. Assessment of capacity to give consent to research participation: state-of-the-art and beyond. J. Health Care Law Policy 1, 66–87.

Doty, R.L., Shaman, P., Kimmelman, C.P., Dann, M.S., 1984. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 94, 176–178.

Dunn, T.P., Weller, M.P., 1989. Olfaction in schizophrenia. Percept. Mot. Skills 69, 833–834.

Feifel, D., Macdonald, K., Nguyen, A., Cobb, P., Warlan, H., Galangue, B., Minassian, A., Becker, O., Cooper, J., Perry, W., Lefebvre, M., Gonzales, J., Hadley, A., 2010. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol. Psychiatry 68, 678–680.

Feifel, D., Macdonald, K., Cobb, P., Minassian, A., 2012. Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. Schizophr. Res. 139, 207–210.

First, M.B., S.R.G.M.a.W.J., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). Biometrics Research, New York.
Fleischhacker, W., 2000. Negative symptoms in patients with schizophrenia with special reference to the primary versus secondary distinction. Encephale 26 (Spec No. 1), 12–14.
Good, K.P., Whitehorn, D., Rui, Q., Milliken, H., Kopala, L.C., 2006. Olfactory identification deficits in first-episode psychosis may predict patients at risk for persistent negative and disorganized or cognitive symptoms. Am. J. Psychiatry 163, 932–933.
Guastella, A.J., MacLeod, C., 2012. A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. Horm. Behav. 61, 410–418.
Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology Revised Edition. US Department of Health Education and Welfare, Washington, D.C.
Hammock, E.A., Young, L.J., 2006. Oxytocin, vasopressin and pair bonding: implications for autism. Philos. Trans. R. Soc. Lond. B Biol. Sci. 361, 2187–2198.
Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54, 1389–1398.
Ishizuka, K., Tajinda, K., Colantuoni, C., Morita, M., Winicki, J., Le, C., Lin, S., Schretlen, D., Sawa, A., Cascella, N.G., 2010. Negative symptoms of schizophrenia correlate with impairment on the University of Pennsylvania smell identification test. Neurosci. Res. 66, 106–110.
Kamath, V., Bedwell, J.S., Compton, M.T., 2011a. Is the odour identification deficit in schizophrenia influenced by odour hedonics? Cogn. Neuropsychiatry 16, 448–460.
Kamath, V., Turetsky, B.I., Moberg, P.J., 2011b. Identification of pleasant, neutral, and unpleasant odors in schizophrenia. Psychiatry Res. 187, 30–35.
Kamath, V., Moberg, P.J., Kohler, C.G., Gur, R.E., Turetsky, B.I., 2011c. Odor hedonic capacity and anhedonia in schizophrenia and unaffected first-degree relatives of schizophrenia patients. Schizophr. Bull.
Kamath, V., Turetsky, B.I., Calkins, M.E., Kohler, C.G., Conroy, C.G., Borgmann-Winter, K., Gatto, D.E., Gur, R.E., Moberg, P.J., 2011d. Olfactory processing in schizophrenia, non-ill first-degree family members, and young people at-risk for psychosis. World J. Biol. Psychiatry.
Keshavan, M.S., Vora, A., Montrose, D., Diwadkar, V.A., Sweeney, J., 2009. Olfactory identification in young relatives at risk for schizophrenia. Acta Neuropsychiatr. 21, 121–124.
Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 32, 214–219.
Kjelvik, G., Evensmoen, H.R., Brezova, V., Haberg, A.K., 2012. The human brain representation of odor identification. J. Neurophysiol. 108, 645–657.
Kopala, L., Clark, C., Hurwitz, T.A., 1989. Sex differences in olfactory function in schizophrenia. Am. J. Psychiatry 146, 1320–1322.
Kopala, L.C., Good, K.P., Honer, W.G., 1994. Olfactory hallucinations and olfactory identification ability in patients with schizophrenia and other psychiatric disorders. Schizophr. Res. 12, 205–211.
Kopala, L.C., Good, K., Honer, W.G., 1995. Olfactory identification ability in pre- and postmenopausal women with schizophrenia. Biol. Psychiatry 38, 57–63.
Kopala, L.C., Good, K.P., Torrey, E.F., Honer, W.G., 1998. Olfactory function in monozygotic twins discordant for schizophrenia. Am. J. Psychiatry 155, 134–136.
Kopala, L.C., Good, K.P., Morrison, K., Bassett, A.S., Alda, M., Honer, W.G., 2001. Impaired olfactory identification in relatives of patients with familial schizophrenia. Am. J. Psychiatry 158, 1286–1290.
Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435, 673–676.
Loup, F., Tribollet, E., Dubois-Dauphin, M., Dreifuss, J.J., 1991. Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. Brain Res. 555, 220–232.
Malaspina, D., Coleman, E., 2003. Olfaction and social drive in schizophrenia. Arch. Gen. Psychiatry 60, 578–584.
Malaspina, D., Coleman, E., Goetz, R.R., Harkavy-Friedman, J., Corcoran, C., Amador, X., Yale, S., Gorman, J.M., 2002. Odor identification, eye tracking and deficit syndrome schizophrenia. Biol. Psychiatry 51, 809–815.
Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci. 12, 524–538.
Moberg, P.J., Turetsky, B.I., 2003. Scent of a disorder: olfactory functioning in schizophrenia. Curr. Psychiatry Rep. 5, 311–319.
Moberg, P.J., Doty, R.L., Turetsky, B.I., Arnold, S.E., Mahr, R.N., Gur, R.C., Bilker, W., Gur, R.E., 1997. Olfactory identification deficits in schizophrenia: correlation with duration of illness. Am. J. Psychiatry 154, 1016–1018.
Moberg, P.J., Agrin, R., Gur, R.E., Gur, R.C., Turetsky, B.I., Doty, R.L., 1999. Olfactory dysfunction in schizophrenia: a qualitative and quantitative review. Neuropsychopharmacology 21, 325–340.
Moberg, P.J., Arnold, S.E., Doty, R.L., Gur, R.E., Balderston, C.C., Roalf, D.R., Gur, R.C., Kohler, C.G., Kanes, S.J., Siegel, S.J., Turetsky, B.I., 2006. Olfactory functioning in schizophrenia: relationship to clinical, neuropsychological, and volumetric MRI measures. J. Clin. Exp. Neuropsychol. 28, 1444–1461.
Nguyen, A.D., Shenton, M.E., Levitt, J.J., 2010. Olfactory dysfunction in schizophrenia: a review of neuroanatomy and psychophysiological measurements. Harv. Rev. Psychiatry 18, 279–292.
Overall, J.E., Gorham, D.R., 1962. The Brief Psychiatric Rating Scale. Psychol. Rep. 10, 812.
Pedersen, C.A., Gibson, C.M., Rau, S.W., Salimi, K., Smedley, K.L., Casey, R.L., Leserman, J., Jarskog, L.F., Penn, D.L., 2011. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr. Res. 132, 50–53.
Plailly, J., d'Amato, T., Saoud, M., Royet, J.P., 2006. Left temporo-limbic and orbital dysfunction in schizophrenia during odor familiarity and hedonicity judgments. NeuroImage 29, 302–313.
Roalf, D.R., Turetsky, B.I., Owzar, K., Balderston, C.C., Johnson, S.C., Brensinger, C.M., Gur, R.E., Siegel, S.J., Moberg, P.J., 2006. Unirhinal olfactory function in schizophrenia patients and first-degree relatives. J. Neuropsychiatry Clin. Neurosci. 18, 389–396.
Rupp, C.I., Fleischhacker, W.W., Kemmler, G., Oberbauer, H., Scholtz, A.W., Wanko, C., Hinterhuber, H., 2005. Various bilateral olfactory deficits in male patients with schizophrenia. Schizophr. Bull. 31, 155–165.
Stedman, T.J., Clair, A.L., 1998. Neuropsychological, neurological and symptom correlates of impaired olfactory identification in schizophrenia. Schizophr. Res. 32, 23–30.
Strauss, G.P., Allen, D.N., Ross, S.A., Duke, L.A., Schwartz, J., 2010. Olfactory hedonic judgment in patients with deficit syndrome schizophrenia. Schizophr. Bull. 36, 860–868.
Turetsky, B.I., Moberg, P.J., 2009. An odor-specific threshold deficit implicates abnormal intracellular cyclic AMP signaling in schizophrenia. Am. J. Psychiatry 166, 226–233.
Ugur, T., Weisbrod, M., Franzek, E., Pfuller, U., Sauer, H., 2005. Olfactory impairment in monozygotic twins discordant for schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 255, 94–98.
Wacker, D.W., Ludwig, M., 2012. Vasopressin, oxytocin, and social odor recognition. Horm. Behav. 61, 259–265.
Woodberry, K.A., Seidman, L.J., Giuliano, A.J., Verdi, M.B., Cook, W.L., McFarlane, W.R., 2010. Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. Schizophr. Res. 123, 188–198.
Wu, J., Buchsbaum, M.S., Moy, K., Denlea, N., Kesslak, P., Tseng, H., Plosnaj, D., Hetu, M., Potkin, S., Bracha, S., 1993. Olfactory memory in unmedicated schizophrenics. Schizophr. Res. 9, 41–47.
Young, L.J., Wang, Z., 2004. The neurobiology of pair bonding. Nat. Neurosci. 7, 1048–1054.