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# Plasma oxytocin levels predict olfactory identification and negative symptoms in individuals with schizophrenia

Gregory P. Strauss [a,*], William R. Keller [b], James I. Koenig [b], James M. Gold [b], Kathryn L. Ossenfort [a], Robert W. Buchanan [b]

[a] Department of Psychology, State University of New York at Binghamton, Binghamton, NY, USA
[b] Maryland Psychiatric Research center and Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

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ABSTRACT

Basic neuroscience research provides strong evidence for the role of oxytocin in olfactory processes and social affiliation in rodents. Given prior indication of olfactory impairments that are linked to greater severity of asociality in schizophrenia, we examined the association between plasma oxytocin levels and measures of olfaction and social outcome in a sample of outpatients with schizophrenia ($n = 39$) and demographically matched healthy controls ($n = 21$). Participants completed the 40-item University of Pennsylvania Smell Identification Test (UPSIT), and rated each odor for how positive and how negative it made them feel. Results indicated that individuals with schizophrenia had higher plasma oxytocin levels and lower overall accuracy for UPSIT items than controls. Individuals with schizophrenia also reported experiencing more negative emotionality than controls in response to the olfactory stimuli. Lower plasma oxytocin levels were associated with poorer accuracy for pleasant and unpleasant odors and greater severity of asociality in individuals with schizophrenia. These findings suggest that endogenous oxytocin levels may be an important predictor of olfactory identification deficits and negative symptoms in schizophrenia.



## 1. Introduction

Basic neuroscience research provides strong evidence for the role of oxytocin in olfactory processes and social affiliation. For example, the olfactory bulb is rich in oxytocin receptors and ablation of the olfactory bulb impairs social recognition and affiliative bonding between mothers and their offspring (Dickinson and Keverne, 1988; Dantzer et al., 1990). Conversely, bulbar administration of oxytocin enhances social discrimination and social memory (Dluzen et al., 1998). Thus, studies in rodents and other mammals provide evidence for a link between social behavior and oxytocin functioning in the olfactory bulb (Wacker and Ludwig, 2012).

Individuals with schizophrenia display a range of olfactory processing abnormalities, including deficits in odor identification, discrimination, detection threshold sensitivity, hedonic judgments, and memory (for review see Moberg et al., 2014). These impairments are evident as early as the prodromal and first-episode periods and may worsen throughout the course of illness (Brewer et al., 2003; Woodberry et al., 2010; Kamath et al., 2014). Importantly, poor olfactory identification and lower hedonic judgments for pleasant odors have been associated with greater severity of negative symptoms, especially reduced social drive (Hudry et al., 2002; Malaspina et al., 2002; Malaspina and Coleman, 2003; Moberg et al., 2003; Strauss et al., 2010). It has yet to be determined whether endogenous oxytocin levels mediate the association between social functioning and olfactory processing in schizophrenia, as might be expected based on the basic neuroscience literature.

To date, relatively few studies have examined endogenous oxytocin levels in schizophrenia. There is inconsistency among findings, with some studies reporting that people with schizophrenia who are polydipsic have lower endogenous oxytocin levels than healthy controls (Goldman et al., 2008, 2011), some reporting higher levels in people with schizophrenia (Beckmann et al., 1985), and others reporting no group differences (Rubin et al., 2010, 2011, 2013, 2014). Furthermore, lower endogenous oxytocin has been associated with greater severity of positive and negative symptoms, poor social functioning, impaired facial affect perception, abnormal judgment of gaze direction, and impaired theory of mind (Goldman et al., 2008; Keri et al., 2009; Rubin et al., 2010, 2011; Walss-Bass et al., 2013). Acute challenge and multidose clinical trials have produced inconsistent results (Lee et al., 2013; Horta de Macedo et al., 2014); however, there is some evidence that intranasal administration of oxytocin improves psychiatric symptoms and social cognition (Feifel et al., 2010; Pedersen et al., 2011; Averbeck et al.,

* Corresponding author at: University of New York at Binghamton, Department of Psychology, PO Box 6000, Binghamton, New York, USA, 13902-6000. Tel.: +1 607 777 5408; fax: +1 607 777 4890.
*E-mail address:* gstrauss@binghamton.edu (G.P. Strauss).

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2012; Davis et al., 2013; Fischer-Shofty et al., 2013a,b; Davis et al., 2014; Gibson et al., 2014; Woolley et al., 2014), as well as olfactory identification (Lee et al., 2013).

The current study aimed to extend this literature by directly examining the association between plasma oxytocin, social functioning, symptoms, olfactory identification, and olfactory hedonic judgments. We hypothesized that people with schizophrenia would have lower plasma oxytocin levels than healthy controls, and that lower endogenous oxytocin would be associated with poor olfactory identification accuracy, lower hedonic ratings for pleasant stimuli, greater severity of negative symptoms, and poor community-based social outcome.

## 2. Methods

### 2.1. Participants

Participants included 39 individuals meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for schizophrenia and 21 healthy controls.

Participants with schizophrenia (SZ) were recruited from the outpatient research program at the Maryland Psychiatric Research Center and evaluated during periods of clinical stability. Consensus diagnosis was established via a best-estimate approach based on psychiatric history and multiple interviews and subsequently confirmed using the Structured Clinical Interview for DSM-IV (SCID: First et al., 1997). All participants in the SZ group met DSM-IV lifetime diagnostic criteria for schizophrenia or schizoaffective disorder were assessed after a minimum period of 4 weeks of stable treatment and prescribed an antipsychotic medication at the time of testing.

Control subjects (CN) were recruited through random-digit dialing and word of mouth among enrolled participants. All CN underwent a screening interview, including the SCID-I and SCID-II (Pfohl et al., 1997), and did not meet criteria for any current Axis I or II disorder or lifetime criteria for a psychotic disorder. CN also had no family history of psychosis. No participants met criteria for substance dependence in the last 6 months, and all denied lifetime history of neurological disorders associated with cognitive impairment (e.g., traumatic brain injury, epilepsy). Lack of substance use in the week prior to the study was confirmed by urine toxicology. Female participants completed a pregnancy screen, as this can affect oxytocin levels; no participants were pregnant.

Individuals with SZ and CN did not significantly differ in age, parental education, sex, or ethnicity. People with schizophrenia had lower personal education than controls.

### 2.2. Procedures

Participants completed a standard clinical interview that was performed by a clinical psychologist (GPS) trained to MPRC reliability standards (reliability > 0.80). After this interview, patients were rated on the Brief Negative Symptom Scale (BNSS: Kirkpatrick et al., 2011; Strauss et al., 2012,ab), the Brief Psychiatric Rating Scale (BPRS: Overall & Gorham, 1962), and the Level of Function Scale (LOF: Hawk et al., 1975).

The University of Pennsylvania Smell Identification Test (UPSIT: Doty et al., 1984) is a standardized olfactory perception measure that requires identification of 40 common microencapsulated odors by selecting one of four multiple-choice answers consisting of various odor names. The UPSIT was administered birhinally by a trained technician. After identifying the odor of each item, participants reported how positive and how negative the odor made them feel using separate unipolar rating scales. Each rating scale ranged from 1 (not at all) to 9 (extremely). Separate rating scales were used for positive and negative emotions, rather than a bipolar valence scale (i.e., ranging from extremely unpleasant to extremely pleasant), because emotional stimuli can induce co-activations of positive and negative emotion.

Several UPSIT score calculations were derived. In addition to calculating the global UPSIT total accuracy score, we also calculated valence-specific accuracy scores based upon procedures established by other published studies using the UPSIT in schizophrenia (Strauss et al., 2010; Kamath et al., 2014). Using these procedures, the 40 odorants were divided into pleasant, neutral, and unpleasant valence categories using published pleasantness ratings from the UPSIT manual (Doty et al., 1984):16 items were categorized as pleasant, 15 items were categorized as neutral, and 9 items were categorized as unpleasant. Separate accuracy scores for pleasant, unpleasant, and neutral items were calculated. Additionally, ratings of self-reported positivity and negativity were calculated separately for the pleasant, unpleasant, and neutral items.

Plasma oxytocin levels were determined by radioimmunoassay using a magnetic bead kit from Phoenix Pharmaceuticals, Inc. Samples were assayed in duplicate; the average of these samples was taken as the final oxytocin value. Assay sensitivity was 5 pg/ml, with minimal cross reactivity with vasopressin. The coefficient of variation averaged 5-8% across the assay.

## 3. Results

### 3.1. Endogenous oxytocin levels

One-way ANOVA indicated that people with schizophrenia had significantly higher plasma oxytocin levels than controls, $F(1, 59) = 6.93$, $p < 0.01$ (see Table 1).

### 3.2. Olfactory identification

MANOVA investigating accuracy across valence conditions indicated a significant overall effect, $F(1, 59) = 6.16$, $p < 0.001$, as well as significant individual effects for pleasant: $F(1, 59) = 15.22$, $p < 0.001$ and unpleasant odors: $F(1, 59) = 8.46$, $p < 0.01$. There was a trend toward participants with schizophrenia being less accurate than controls for neutral odors: $F(1, 59) = 3.75$, $p = 0.058$ (see Fig. 1, panel A). Thus, people with schizophrenia had poorer olfactory identification than controls.

### 3.3. Olfactory emotional experience ratings

Using self-reports of how positive participants felt in relation to pleasant, unpleasant, and neutral odors, MANOVA revealed a

**Table 1**
Participant demographic and clinical characteristics.

| | Schizophrenia ($n = 39$) | Controls ($n = 21$) | Test statistic, $p$-value |
|---|---|---|---|
| Age | 43.9 (11.7) | 42.6 (9.3) | $F = 0.2$, $p = 0.65$ |
| Participant education | 13.1 (2.1) | 15.1 (1.9) | $F = 14.3$, $p < 0.001$ |
| Parental education | 13.6 (2.5) | 14.3 (2.4) | $F = 0.99$, $p = 0.33$ |
| % Male | 72% | 67% | $\chi^2 = 0.68$, $p = 0.33$ |
| Ethnicity | | | $\chi^2 = 1.2$, $p = 0.77$ |
| Caucasian | 89.7% | 95.2% | |
| African American | 5.1% | 4.8% | |
| Native American | 2.6% | 0.0% | |
| Bi-racial | 2.6% | 0.0% | |
| Plasma oxytocin (pg/ml) | 24.5 (7.5) | 19.7 (5.9) | $F = 6.9$, $p < 0.02$ |
| CPZ equivalent dosage (mg) | 610.0 (394) | – | – |
| Symptoms | | | |
| BNSS total | 24.8 (17.5) | – | – |
| BPRS total | 38.1 (9.6) | – | – |
| BPRS positive | 2.4 (1.1) | – | – |
| BPRS negative | 2.2 (1.1) | – | – |
| BPRS disorganized | 1.5 (0.5) | – | – |
| Functional outcome | | | |
| LOF total | 19.1 (7.7) | – | – |
| LOF social | 4.7 (2.6) | – | – |
| LOF work | 2.1 (2.8) | – | – |

Note. CPZ = chlorpromazine equivalent dosage; BNSS = Brief negative Symptom Scale; BPRS = Brief Psychiatric Rating Scale; LOF = Level of Function Scale.