# Peripheral oxytocin is associated with reduced symptom severity in schizophrenia

Leah H. Rubin [a],[*], C. Sue Carter [b], Lauren Drogos [a], Hossein Pournajafi-Nazarloo [b], John A. Sweeney [a], Pauline M. Maki [a]

[a] Departments of Psychiatry, Center for Cognitive Medicine, University of Illinois at Chicago, Chicago, IL, USA
[b] Department of Psychiatry, Brain Body Center, University of Illinois at Chicago, Chicago, IL, USA

## ARTICLE INFO

## ABSTRACT

*Background:* Emerging evidence from clinical trials suggests that oral estrogen and intranasal oxytocin might reduce symptom severity in schizophrenia. Whether increases in endogenous hormones are similarly associated with improved symptoms is unknown. We investigated the effects of menstrual cycle phase and related fluctuations in peripheral hormone levels on clinical symptoms in women with chronic schizophrenia.
*Method:* Twenty-three women with schizophrenia were administered the Positive and Negative Syndrome Scale (PANSS), a measure of clinical symptom severity, at two menstrual cycle phases: 1) early follicular (Days 2–4; low estrogen/progesterone) and 2) midluteal (Days 20–22; high estrogen/progesterone). Twenty-seven males with schizophrenia and 58 controls (31 female) completed testing at comparable intervals. Men were included to examine whether the relationships between clinical symptoms and hormone levels in women generalize to men. Plasma hormone assays of estrogen, oxytocin, progesterone, and testosterone were obtained.
*Results:* Female patients showed less severe symptoms during the midluteal versus early follicular phase ($p$'s < 0.01). Oxytocin did not fluctuate across phases, but in female patients ($p$'s < 0.01) higher oxytocin levels were associated with less severe positive symptoms and overall psychopathology. In both sexes, higher oxytocin levels were associated with more prosocial behaviors ($p < 0.05$).
*Conclusion:* Consistent with previous findings in acutely ill patients, our results suggest that clinical symptoms vary across the menstrual cycle in patients with chronic schizophrenia. Similar to recent findings regarding benefits of intranasal oxytocin, these new findings indicate that high levels of endogenous oxytocin might improve positive symptom severity and general psychopathology in women and social behaviors in both sexes.

© 2010 Elsevier B.V. All rights reserved.

## 1. Introduction

Sex modulates the clinical presentation and course of schizophrenia. The course of the disease is more benign in women than in men; females generally have a later age of onset, shorter and less frequent acute episodes of psychosis, less severe negative symptoms, better premorbid functioning, and a better treatment response to antipsychotic medication compared to males (Riecher-Rossler and Hafner, 2000; Halbreich and Kahn, 2003; Rao and Kolsch, 2003). These sex differences suggest involvement of hormonal factors. In this study, we use a menstrual cycle paradigm to explore changes in clinical symptoms in relation to fluctuating peripheral hormone levels.

* Corresponding author. University of Illinois at Chicago, Department of Psychiatry, 912 S. Wood St. (MC 913), Chicago, Illinois 60612, USA. Tel.: +1 312 355 5017; fax: +1 312 413 7856.
E-mail address: lrubin@psych.uic.edu (L.H. Rubin).

Patients with schizophrenia show reduced levels of estrogen and other sex hormones such as progesterone and testosterone (Oades and Schepker, 1994; Goyal et al., 2004; Huber et al., 2004; Bergemann et al., 2005a; Huber et al., 2005; Howes et al., 2007; Ko et al., 2007), and alterations in neurohormones such as oxytocin (Linkowski et al., 1984; Beckmann et al., 1985; Legros et al., 1992; Mai et al., 1993, cf., Glovinsky et al., 1994; Goldman et al., 2008; Keri et al., 2009). Impressively, four (Kulkarni et al., 2002; Akhondzadeh et al., 2003; Louza et al., 2004; Ko et al., 2006; Kulkarni et al., 2008) of five (Bergemann et al., 2005b) randomized, placebo-controlled clinical trials (RCT) demonstrate beneficial effects of short-term adjunctive estrogen treatment on clinical symptoms including overall, positive, negative, and/or general psychopathology in premenopausal women with chronic schizophrenia. The one neutral trial differed from the other four positive trials in its use of high-dose oral estrogen (Bergemann et al., 2005b).

Following promising findings from open label studies (Bujanow, 1972; Bakharev et al., 1984), intranasal oxytocin is now being examined in RCTs as a therapy for schizophrenia. A randomized clinical trial of short-term adjuvant intranasal oxytocin (versus placebo) demonstrated therapeutic effects on clinical symptoms in a small sample of predominantly male schizophrenia patients with residual symptoms (Feifel et al., 2010). Oxytocin has widespread effects beyond its characteristic roles in pregnancy and lactation, including effects on behaviors that are impaired in schizophrenia such as emotional processing, stress management, affiliative behavior, and certain aspects of cognition (Carter et al., 2008; Heinrichs et al., 2009). Whether natural changes in endogenous estrogen or oxytocin influence clinical symptoms in women with schizophrenia is unknown.

Menstrual cycle paradigms provide insights into how clinical symptoms might change in relation to physiological changes in estrogen and progesterone (which reliably change across cycle phases) and oxytocin (which changes in some studies) (Salonia et al., 2005; Liedman et al., 2008). These paradigms allow for assessment of symptoms in relation to significant change in hormone levels across specific menstrual phases as well as average hormone levels across different phases. Four (Hallonquist et al., 1993; Riecher-Rossler et al., 1994; Choi et al., 2001; Bergemann et al., 2007) of six (Harris, 1997; Thompson et al., 2000) studies in premenopausal women with schizophrenia demonstrate improved clinical symptoms in relation to natural fluctuations across the menstrual cycle; specifically, symptom improvement was evident in the midluteal (high estrogen/progesterone) versus the early follicular (low estrogen/progesterone) phase. In two of these studies, higher estradiol levels were associated with improved clinical symptoms and in particular positive symptoms (Riecher-Rossler et al., 1994; Bergemann et al., 2007). Of the two studies finding no cycle-related changes, one did not validate menstrual cycle phase with hormone assays (Harris, 1997) and the other did not tightly control menstrual cycle phase (Thompson et al., 2000), allowing for a wide range of estradiol and progesterone levels. Animal studies suggest that estrogen can upregulate the synthesis of oxytocin (Young et al., 1998; Patisaul et al., 2003), but the relationship between oxytocin and clinical symptoms has not been investigated in a menstrual cycle study, and no previous study has examined endogenous oxytocin levels over time in relation to clinical symptom severity.

The purpose of this study was to investigate the effects of menstrual phase and hormone levels on clinical symptom severity in women with chronic schizophrenia. We hypothesized that like acutely ill women with schizophrenia, women with chronic schizophrenia would show improvements in clinical symptoms during the midluteal versus early follicular phase, and that these improvements would relate to increases in estradiol. We also extended previous studies by including measures of oxytocin. We predicted that oxytocin levels would be inversely related to clinical symptom severity in patients with schizophrenia. We examined progesterone and testosterone because metabolites of both hormones as well as testosterone can influence clinical symptom expression in schizophrenia (Ko et al., 2008; Marx et al., 2009; Ritsner et al., 2010). We also evaluated relationships between clinical symptoms and hormone levels in men with schizophrenia and included male controls. Male patients were included to examine whether the relationships between hormone levels and clinical symptoms in female patients generalize to men.

## 2. Methods

### 2.1. Participants

The sample included 108 participants, including 50 patients (23 women, 27 men) and 58 controls (31 women, 27 men). Inclusion criteria for all participants were: (1) age 18–40; (2) English as first language; (3) for patients, Structured Clinical Interview for DSM (SCID; First et al., 1995) diagnosis of schizophrenia or schizoaffective disorder depressed type; (4) for patients, reported medication compliance and consistency in treatment medication for 2 months prior to the study; and (5) for women, regular menstrual cycles ($28 \pm 5$ days). Additional inclusion criteria for women helped to validate menstrual phase based on the normal range for the estradiol assay (Diagnostic Products, Los Angeles, CA), including (6) early follicular levels $\leq 90$ pg/ml and (7) midluteal levels between 27–246 pg/ml. Exclusion criteria for all participants were: (1) history of moderate/severe head trauma or other neurological disorder; (2) history of substance abuse/dependence, excluding cigarettes; (3) high intake of phytoestrogens ($3 \geq$ servings of soy/day or supplements); (4) conditions resulting in abnormal gonadal hormone secretion; (5) significant medical illness; (6) use of hormone treatments; and (7) for women, pregnancy/lactation within the last year. Controls were also excluded if they (8) currently used medications known to influence the central nervous system or (9) had an Axis I psychiatric disorder (based on SCID interview).

Controls were recruited from the community, and patients from outpatient clinics and residential facilities in the Chicago metropolitan area. Patients were diagnosed with schizophrenia (68%) or schizoaffective disorder—depressed type (32%), were clinically stable, and self-reported stable medication regimens for the prior 2 months. Most patients (84%) were prescribed second generation antipsychotics. Antipsychotic medication dosages ranged from 40–1133 mg chlorpromazine equivalents (Woods, 2003; Lehman et al., 2004) per day (median dosage, 400 mg/day). Forty-six percent of patients were taking antidepressants, 4% were taking mood stabilizers,

and 38% met criteria for hyperprolactinemia (>20 ng/mL). Written informed consent was obtained from all participants. Study procedures were approved by the UIC Institutional Review Board.

Table 1 shows demographic and clinical information for the 108 participants. The sample had high body mass index scores (BMI; 42% obese; 21% overweight according to standard criteria (1998)). Compared to controls, patients were older by 3–4 years and had higher BMIs (*p*'s<0.05). Controlling for age and BMI did not affect the significance of the results. Male and female patients were similar across most clinical variables, but male patients received higher doses of antipsychotic medication (*p*<0.05).

### 2.2. Measures

#### 2.2.1. Clinical symptoms

The Positive and Negative Symptom Scale (PANSS; Kay et al., 1987) was administered to patients at each study visit to generate measures of positive symptoms, negative symptoms, general psychopathology, and a total score. A PANSS prosocial factor derived from an exploratory factor analysis in a sample of outpatients with SCID diagnoses within the schizophrenia spectrum was also examined (Purnine et al., 2000). Items in this subscale were active social avoidance, emotional withdrawal, passive social withdrawal, stereotyped thinking, hallucinatory behavior, and suspiciousness/paranoia.

#### 2.2.2. Serum hormone assays

To account for circadian rhythm effects (Brambilla et al., 2009), blood samples were drawn once at the same time of day during both sessions. Samples were stored in plain tubes, centrifuged (2400×*g* for 15 min at 4 °C), placed into −80 °C freezers, and assayed in duplicate. Batched samples (placed in dry ice; shipped overnight) were sent to the University of Alabama at Birmingham's General Clinical Research Center for analysis (Gower and Nyman, 2000). Serum concentrations were analyzed using commercial kits: estradiol by double-antibody radioimmunoassay (RIA; Diagnostic Products, Los Angeles, CA) (sensitivity 1.61 pg/ml, intra-assay CV=4.01%), progesterone by "Coat-a-Count" coated tube RIA (Diagnostic Products, Los Angeles, CA) (sensitivity 0.05 ng/ml, intra-assay CV=2.33%), prolactin (for determination of possible hyperprolactinemia, >20 ng/mL) by a two-site immunoenzymometric assay (TOSOH Bioscience, CA) (sensitivity=1 ng/mL, intra-assay CV=1.5%), and sex hormone binding globulin by immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX) (sensitivity=3 nmol/L; intra-assay CV=1.37%). Free testosterone was calculated using the method of Stephen J. Winters (University of Louisville; Louisville, KY) (sensitivity 0.82 ng/dl; intra-assay CV=2%). Oxytocin was quantified at UIC with an EIA kit (Assay Designs, Ann Arbor, MI) (sensitivity 16 pg/mL, intra-assay CV<11%) that is highly specific for oxytocin versus other peptides, as determined by HPLC (Carter et al., 2007). Samples were initially run undiluted. Twenty of 203 samples showed values greater than 600 pg/ml. Dilution (1:2 ratio) was subsequently used to confirm the accuracy of those samples.

### 2.3. Procedures

Women were evaluated once during the early follicular phase (Day 2–4; low estradiol/progesterone) and once during

**Table 1**
Demographics and other descriptive information.

| | Women | | Men | |
|---|---|---|---|---|
| | Patients (*n*=23) | Healthy controls (*n*=31) | Patients (*n*=27) | Healthy controls (*n*=27) |
| Variables | M (SD) | M (SD) | M (SD) | M (SD) |
| Age[G] | 30.65 (5.73) | 27.55 (6.67) | 31.19 (6.60) | 27.93 (5.99) |
| Parental SES | 3.00 (0.95) | 3.13 (1.34) | 3.14 (1.08) | 3.33 (1.30) |
| Race | | | | |
|   Caucasian | 31% | 29% | 15% | 44% |
|   African–American | 48% | 45% | 59% | 30% |
|   Asian | 4% | 16% | 4% | 15% |
|   Hispanic or Latino | 17% | 10% | 15% | 4% |
|   Other/unknown | – | – | 7% | 7% |
| Parous | 30% | 19% | – | – |
| Past oral contraceptive use | 57% | 39% | – | – |
| Body mass index[G] | 33.28 (8.52) | 28.17 (9.18) | 32.24 (7.55) | 27.20 (7.03) |
| Test sessions in afternoon (after 12 pm) | 70% | 55% | 63% | 52% |
| SCID diagnosis | | | | |
|   Schizophrenia | 57% | | 78% | |
|   Schizoaffective (depressed type) | 43% | | 22% | |
| Duration of illness in years[†] | 12.96 (5.50) | | 11.39 (7.89) | |
| Antipsychotics (on second generation) | 87% | | 82% | |
| Risperidone[‖] | 26% | | 33% | |
| Chlorpromazine mg equivalents[S] | 320 (255) | | 484 (288) | |
| Antipsychotic + antidepressant | 56% | | 37% | |
| Antipsychotic + mood stabilizer | 4% | | 4% | |
| Hyperprolactinemia, >20 ng/ml (%) | 38% | | 33% | |

Note. Parental SES higher scores reflect higher SES; SCID = Structured Clinical Interview for DSM. [†] In years since initial treatment for psychosis. [‖] Higher propensity to elevate prolactin levels compared to other second generation antipsychotics. [G] Main effect of group was significant at *p*<0.05. [S] Main effect of sex was significant at *p*<0.05.

the midluteal phase (Day 20–22; high estradiol/progesterone). Phase at first session was counterbalanced across participants. Sessions were held during two separate cycles about 42 days apart. Menstrual phase was initially estimated by counting back to Day 1 of the last menstrual cycle, and was later validated with estradiol and progesterone levels. Examiners were blinded to menstrual cycle status. Men were tested in separate sessions approximately 42 days apart. Given that half of the women were randomly assigned to follicular phase first and half to luteal phase first, half of the men were randomly assigned to have their second session data reversed with that of the first session. This counterbalancing reduces confounds related to carry over effects (e.g., change in symptom ratings due to increased comfort with the examiner).

### 2.4. Statistical analyses

Our hypotheses were tested using multilevel random coefficient models in which the two measurement time points (i.e., follicular and midluteal) were nested within individuals. The first analyses examined changes in hormone levels across the menstrual cycle (follicular and midluteal), with menstrual phase as a within-subjects variable (Level 1 in model) and group (patients, controls) as a between-subjects variable (Level 2 in model). The second analyses (benchmark model) examined the effect of menstrual phase (Level 1 in model) on clinical symptoms (primary outcome) in female patients. Next, we examined the degree to which individual variations in hormone levels that fluctuate across the menstrual cycle (i.e., estradiol, progesterone) were associated with clinical symptoms that change across the menstrual cycle in female patients. To accomplish this, we added estradiol and progesterone levels as time-varying covariates (Level 1 in model) to our benchmark model. These models provide an estimate of how individual variation in a specific hormone (e.g., estradiol) is associated with changes in clinical symptoms while controlling for variations in other hormones (e.g., progesterone). Finally, we examined the degree to which hormone levels that did not change across the menstrual cycle (e.g., testosterone) predicted average symptom presentation in female patients. This was accomplished by adding these hormones as time-invariant covariates to the model (Level 2 in model). Parallel analyses were conducted in male patients to examine changes in hormones and clinical symptoms across sessions spaced at equivalent time inter-vals. Analyses in patients examined the following covariates: BMI, primary SCID diagnosis (schizophrenia versus schizoaffective), type of antipsychotic medication (first versus second generation) and dosage, use of SSRI or mood stabilizer, and hyperprolactinemia (>20 ng/ml). Non-significant covariates were eliminated from the models. Regression coefficients are presented as unstandardized beta weights (standard errors). Only $p$ values<0.10 are reported (so that trend-level effects are noted). Multilevel models were analyzed with SAS (v.9.02 for Windows; SAS, Cary, NC).

## 3. Results

### 3.1. Hormone levels in women and men

Table 2 shows average hormone levels for female participants. As expected for females overall, estradiol and progesterone levels were significantly higher during the midluteal versus early follicular phase, ($p$'s<0.001). Testosterone and oxytocin levels did not change significantly across the cycle. Progesterone levels were lower in patients compared to controls ($p$<0.01), but levels of estradiol, free testosterone, and oxytocin did not differ between female groups. Both groups showed similar progesterone levels during the early follicular phase, but patients showed lower progesterone levels compared to controls during the midluteal phase ($p$<0.001). Patients and controls showed a similar magnitude of change in estrogen, testosterone, and oxytocin across phase.

Table 3 presents hormone levels for men. Free testosterone levels were lower in male patients compared to controls ($p$<0.05), but estradiol and oxytocin levels did not differ between the two groups. As expected, no hormone levels differed as a function of test session, and there were no Group by Session interactions.

### 3.2. Changes in clinical symptoms in women with schizophrenia across the menstrual cycle

Table 4 shows PANSS ratings for female patients at each cycle phase as well as the change score. Scores on the positive (Cohen's $d = 0.15$) and general psychopathology (Cohen's $d = 0.50$) subscales and the total symptom score (Cohen's $d = 0.34$) were lower during the midluteal versus early follicular phase ($p$'s<0.01), whereas scores on the negative symptom subscale and prosocial factor did not change.

**Table 2**
Endogenous serum hormone levels (M and SD) in a function of menstrual cycle phase (early follicular, midluteal) in female patients and healthy controls.

| Phase | Group | | | | | |
| | Patients ($n=23$) | | | Controls ($n=31$) | | |
| | Early follicular | Midluteal | Average | Early follicular | Midluteal | Average |
| | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) |
| 17-β-Estradiol (pg/ml)[P] | 42.47 (21.95) | 120.82 (57.04) | 81.64 (7.15) | 42.48 (21.64) | 121.67 (48.63) | 82.08 (27.39) |
| Progesterone (ng/ml)[P,G,I,†] | 0.78 (0.48) | 5.69 (4.77) | 3.23 (2.45) | 0.77 (0.40) | 11.19 (7.21) | 5.99 (3.66) |
| Free testosterone (pm/L) | 17.02 (17.19) | 16.91 (13.86) | 16.77 (13.46) | 15.68 (19.74) | 13.59 (8.60) | 14.25 (10.50) |
| Oxytocin (pg/ml) | 284.35 (187.50) | 321.88 (229.45) | 299.45 (192.04) | 327.75 (231.76) | 316.16 (174.70) | 322.93 (187.05) |

Note. [P] Menstrual phase significant at $p$<0.05. [G] Significant group differences $p$<0.05. [I] Subject group x menstrual phase interaction significant at $p$<0.05. [†] Patients had lower values than controls during the midluteal phase.

**Table 3**
Endogenous serum hormone levels (M and SD) in male patients and controls over two study sessions (A, B).

| | Group | | | | | |
|---|---|---|---|---|---|---|
| | Patients ($n=27$) | | | Controls ($n=27$) | | |
| | Session A | Session B | Average | Session A | Session B | Average |
| | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) |
| 17-β-estradiol (pg/ml) | 46.14 (20.91) | 42.75 (20.61) | 44.45 (18.81) | 40.31 (14.85) | 38.63 (12.50) | 39.47 (11.95) |
| Free testosterone (pm/L)[G] | 314.06 (121.90) | 326.74 (115.56) | 320.40 (99.55) | 383.16 (153.02) | 385.26 (134.84) | 384.21 (133.08) |
| Oxytocin (pg/ml) | 277.56 (243.14) | 265.82 (225.24) | 273.52 (228.85) | 293.19 (210.46) | 310.87 (241.89) | 302.03 (219.10) |

Note. [G] Significant group differences $p<0.05$.

Clinical symptoms in male patients did not differ significantly from Session A and B.

### 3.3. Relationships between clinical symptoms and hormone levels in women and men with schizophrenia

Individual variation in estradiol and progesterone levels did not significantly account for changes in clinical symptom scores. Average levels of oxytocin, which was very consistent over time (test-retest reliability $r=0.81$, $p<0.001$), were associated with average symptom presentation in female patients (Table 5). Specifically, higher levels of oxytocin were associated with lower scores on the total symptom, and positive, general psychopathology, and prosocial measures ($p$'s$<0.01$; see Fig. 1). There was a trend for higher oxytocin levels to be related to lower negative symptom scores in women ($p=0.06$). In men, higher oxytocin levels were associated with better prosocial scores ($p<0.05$). Testosterone did not relate to symptoms in either sex.

Exploratory analyses on individual PANSS items indicated that in female patients, higher levels of oxytocin were significantly associated with better clinical symptoms on delusions, hallucinatory behavior, suspiciousness/paranoia, passive social withdrawal, and tension ($p$'s$<0.05$). Trends were also noted on blunted affect, emotional withdrawal, and depression ($p<0.10$). In male patients, trends were noted on active social avoidance and hostility ($p<0.10$).

## 4. Discussion

The primary goal of this study was to examine the effects of menstrual cycle phase and peripheral hormone levels on clinical symptom severity in women with schizophrenia. In women, menstrual cycle-related changes on the PANSS were observed, with lower positive symptoms, total symptoms, and general psychopathology in the midluteal compared to early follicular phase. Individual variations in hormone levels across the cycle were not related to these cycle-related changes in symptoms. Although oxytocin did not vary significantly across the menstrual cycle, higher average levels of oxytocin predicted less severe positive, general, and prosocial symptoms in women. In men, higher levels of oxytocin predicted better prosocial symptom scores. These findings in chronic patients extend previous work in acutely ill patients showing that symptoms fluctuate across the menstrual cycle. Additionally, our findings support continued investigation of hormones in relation to symptom severity in schizophrenia, and continued investigation of exogenous oxytocin as an adjunctive treatment in schizophrenia.

### 4.1. Clinical symptoms, menstrual cycle, and hormones in women with schizophrenia

Our finding that clinical symptoms improve during the midluteal versus follicular phase is consistent with previous studies (Hallonquist et al., 1993; Riecher-Rossler et al., 1994; Bergemann et al., 2007). We observed small to medium improvements (i.e., according to Cohen's $d$ effect sizes) in positive, general, and total symptoms in the midluteal versus follicular phase. This finding is similar to that of Bergemann et al. (2007) who studied changes in symptoms across the menstrual cycle in 125 premenopausal women with schizophrenia. The negative symptom subscale was only marginally affected by menstrual cycle in the Bergemann et al. (2007)

**Table 4**
The effects of menstrual cycle phase in female patients and test session in male patients on the Positive and Negative Syndrome Scale ratings (PANSS).

| | Female patients ($n=23$) | | | Male patients ($n=27$) | | |
|---|---|---|---|---|---|---|
| | Early follicular | Midluteal | Change | Session A | Session B | Change |
| Outcomes | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) | M (SD) |
| Total score | 63.00 (9.31) | 60.02 (8.06) | −2.98 (4.16)[**] | 65.67 (13.67) | 64.93 (11.04) | −0.74 (10.10) |
| Positive scale | 15.35 (4.34) | 14.70 (4.06) | −0.65 (0.92)[**] | 14.89 (2.91) | 15.26 (3.63) | 0.37 (2.27) |
| Negative scale | 14.91 (3.87) | 14.57 (3.27) | −0.35 (1.70) | 18.67 (6.37) | 17.48 (4.38) | −1.19 (4.36) |
| General psychopathology | 32.74 (4.13) | 30.76 (3.84) | −1.98 (2.85)[**] | 32.11 (6.90) | 32.19 (5.52) | 0.07 (5.47) |
| Prosocial factor | 15.30 (4.11) | 14.65 (3.65) | −0.65 (2.54) | 16.00 (4.54) | 15.59 (3.75) | −0.41 (4.23) |

Note. [**]$p<0.01$.

**Table 5**
The effects of menstrual cycle change, fluctuating and non-fluctuating hormones in female patients on the Positive and Negative Syndrome Scale ratings (PANSS).

| Predictors | Scales | | | | |
|---|---|---|---|---|---|
| | Total score | Positive | Negative | General | Prosocial factor |
| | $\hat{\beta}$ (SE) | $\hat{\beta}$ (SE) | $\hat{\beta}$ (SE) | $\hat{\beta}$ (SE) | $\hat{\beta}$ (SE) |
| *Covariates*[a] | | | | | |
| SSRI | −5.67 (2.09)[*] | −3.02 (0.84)[**] | – | −2.78 (1.23) | – |
| Second generation antipsychotic | 6.02 (2.75)[*] | 3.78 (1.14)[**] | – | – | – |
| SCID diagnosis of schizophrenia | −7.28 (2.11)[**] | −2.76 (0.86)[**] | – | −3.61 (1.26)[*] | −2.92 (1.09) |
| Change (Δ) from follicular to midluteal | −3.27 (0.92)[**] | −0.64 (0.20)[**] | −0.45 (0.39) | −2.17 (0.62)[**] | −1.00 (0.53) |
| *Fluctuating hormones (hormone change predicts symptom change)* | | | | | |
| Estradiol | −0.0002 (0.02) | −0.002 (0.004) | – | 0.004 (0.01) | – |
| Progesterone | −0.06 (0.20) | −0.04 (0.05) | – | −0.10 (0.13) | – |
| *Non-fluctuating hormones (average levels predicts average symptoms)* | | | | | |
| Oxytocin | −0.03 (0.005)[***] | −0.01 (0.002)[**] | −0.01 (0.004)[T] | −0.01 (0.003)[**] | −0.01 (0.003)[*] |
| Free testosterone | −0.15 (0.08) | −0.05 (0.03) | −0.03 (0.05) | −0.05 (0.05) | −0.04 (0.04) |

Note. [***]$p < 0.001$, [**]$p < 0.01$, [*]$p < 0.05$, [T]$p > 0.05$ and $p < 0.10$. [a]Only significant covariates ($p < 0.05$) were included in the models. For symptom Δ, a negative sign preceding a coefficient refers to symptom improvement. For hormone levels, a negative sign preceding a coefficient refers to higher levels of a hormone relating to better symptom presentation.

study and was not significantly related to menstrual cycle in our study, possibly because our study was underpowered to detect a subtle change. Our study did not replicate previous reports that estrogen levels related to clinical symptoms (Riecher-Rossler et al., 1994; Bergemann et al., 2007). This difference may reflect different characteristics of our patient populations; in earlier studies, patients showed reduced estrogen levels across the entire menstrual cycle and were either acutely ill or tested following recent hospitalization. In contrast, our study involved an outpatient female sample with similar estradiol compared to controls, regular menstrual cycles, stable drug therapy, and comparatively low and stable psychopathology scores. Thus, our study provides evidence that menstrual cycle fluctuations in symptoms are evident not only in acutely ill women with high levels of symptoms, but also in chronically ill stable women with lower levels of symptoms.

In this study, we also related clinical symptoms to endogenous levels of oxytocin, progesterone, and testosterone.

Progesterone levels in female patients were not significantly associated with changes in clinical symptoms. However, we found reduced midluteal progesterone levels, as in other studies (Bergemann et al., 2005a; Bergemann et al., 2007) and reduced overall progesterone levels in women with schizophrenia, similar to some (Riecher-Rossler et al., 1994; Howes et al., 2007) but not all studies (Huber et al., 2004). Reduced levels of progesterone may indicate anovulatory cycles and insufficient follicular maturation (Bergemann et al., 2007) or could be due to stress or nutritional deficiencies (Huber et al., 2004).

Consistent with previous studies, we found indications of reduced free testosterone levels in men with schizophrenia (Goyal et al., 2004; Huber et al., 2005; Akhondzadeh et al., 2006; Ko et al., 2007; Konarzewska et al., 2009). There are a number of factors reported to affect testosterone level in both men with and without schizophrenia including obesity (Zumoff et al., 1990; Jensen et al., 2004) and over half of the male patients in our sample were overweight (56% with BMI
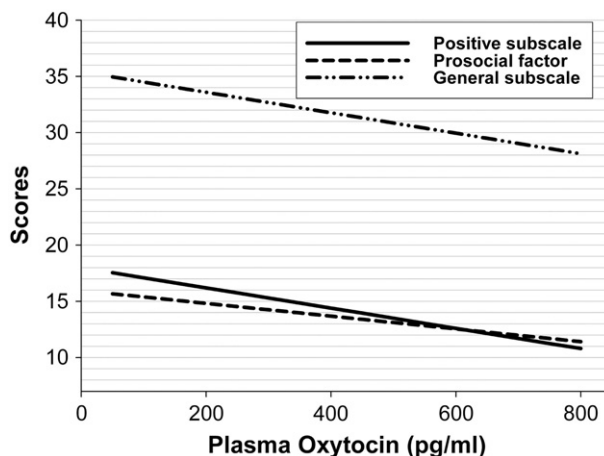


**Fig. 1.** Fitted subscale scores on the Positive and Negative Syndrome Scale (PANSS) using multilevel random coefficient models as a functions of plasma oxytocin levels in female patients for three scales: positive subscale ($p < 0.001$), general psychopathology subscale ($p < 0.01$), and the prosocial factor ($p < 0.05$).

scores>30). Further work is needed to examine the impact of idiopathic or drug-induced obesity factors in hormone-psychopathology relationships in schizophrenia patients.

### 4.2. Oxytocin and clinical symptoms in men and women with schizophrenia

High oxytocin levels were associated with reduced prosocial symptoms in both sexes. The relationship between oxytocin and prosocial behaviors may reflect the well-established role of oxytocin in affiliative behaviors (Carter et al., 2008). There are several neurobiological mechanisms by which oxytocin might influence prosocial behaviors in schizophrenia. Oxytocin/glutamate interactions have been documented in two preclinical studies involving prepulse inhibition (PPI), a widely used measure of sensorimotor gating. PPI is impaired in schizophrenia and is used to test the efficacy and action of antipsychotic drugs in preclinical models. In one study, oxytocin treatment in male rats reversed deficits in PPI induced by dizocilpine, a non-competitive NMDA antagonist. Oxytocin had smaller benefits following PPI induced by amphetamine, and was ineffective in reversing apomorphine-induced deficits in PPI (Feifel and Reza, 1999). In the second study, oxytocin knock-out mice show disrupted PPI following treatment with phencyclidine, a non-competitive NMDA antagonist, but not following treatment with amphetamine or apormorphine (Caldwell et al., 2009). Oxytocin also reversed social deficits in male rats caused by chronic phencyclidine (Lee et al., 2005).

Oxytocin was also associated with positive, general, and overall symptoms in female but not male patients. The novel of finding of oxytocin relating to positive symptoms was in part due to decreasing suspiciousness/paranoia, hallucinations, and delusions, as indicated by the exploratory item analysis. Intranasal oxytocin given to healthy individuals increases trust (Kosfeld et al., 2005; Theodoridou et al., 2009), and peripheral oxytocin levels are associated with increased trustworthiness (Zak et al., 2005). The relationship between oxytocin and lower levels of general symptoms in women was in part due to decreasing depression and tension. Oxytocin may have a more global effect on general psychopathology due to its role in emotional processing, stress management, affiliative behavior, and depression (Scantamburlo et al., 2007; Carter et al., 2008; Heinrichs et al., 2009; Parker et al., 2010).

The relationship between oxytocin and positive symptoms in particular might be influenced by dopamine/neuropeptide interactions (Shahrokh et al.; Rosenfeld et al., 2010). Mesolimbic dopamine projections are thought to be hyperactive, especially in the acute phase of schizophrenia (Abi-Dargham and Moore, 2003). Peripheral administration of oxytocin has been shown to inhibit dopamine transmission in mesolimbic pathways (Sarnyai and Kovacs, 1994). Animal and clinical studies demonstrate that antipsychotic medication increases both central (Beckmann et al., 1985) and peripheral (Uvnas-Moberg et al., 1992) oxytocin levels, suggesting that enhancing endogenous oxytocin may play a role in the therapeutic effects of antipsychotic drugs.

In men, oxytocin levels were not related to most symptom domains. Our analytic model examined the relationship between oxytocin and symptoms while controlling for the effects of other hormones, including estrogen. When estrogen

was taken out of the model, a significant relationship between oxytocin levels and positive and overall symptoms was evident in men ($p<0.05$). This pattern suggests that the relationship between oxytocin and symptoms in men may be influenced by estradiol levels.

### 4.3. Limitations

One limitation to our study is that statistical controls for medication effects (antipsychotic type, SSRIs, mood stabilizers) only partially adjust for the diverse neurochemical effects of different antipsychotic drugs. Studies suggest that antipsychotic medications may impact oxytocin (Beckmann et al., 1985; Uvnas-Moberg et al., 1992), particularly clozapine and olanzapine (20% on these medications in current study) and less by risperidone and haloperidol (36% on these medications in current study) (Kiss et al. 2009); (Beckmann et al., 1985; Uvnas-Moberg et al., 1992). Future studies should examine untreated acutely ill first episode patients where biology/symptom associations can be examined early in the course of illness without confounding influence of psychiatric medications. Second, the EIA measurement of oxytocin was done in unextracted samples, which is associated with higher levels of this peptide. However, earlier work separating samples with HPLC prior to assay revealed that this assay is highly specific for oxytocin (Carter et al., 2007). Also, in the present study oxytocin samples showed comparable values when rerun after dilution; within and between assay coefficients of variation were less than 11%. Third, we measured oxytocin once at each of two menstrual phases. Although, test–retest reliabilities were high ($r = 0.81$), oxytocin secretion may be pulsatile and measurement at multiple time points during each cycle phase might yield a more fine-grained understanding of oxytocin secretion. However, we were only able to measure oxytocin at one point at each phase of the menstrual cycle due to funding limitations. Fourth, neuropeptides do not readily cross the blood–brain barrier. However, most endogenous oxytocin is synthesized within the brain, and there is some evidence in animals that central and peripheral oxytocin are correlated (Landgraf and Neumann, 2004). Peripheral administration of oxytocin as well as peripheral levels may influence behavior by bypassing the brain through circumventricular organs. Furthermore, peptide effects on mood and behavior may result from effects on peripheral receptors, which are abundant in visceral organs, including organs innervated by the vagus. Finally, while the prosocial factor has been used in two additional studies (Loebel et al., 2004; Docherty et al., 2010) it has not been revalidated.

### 4.4. Conclusions

In summary, the present study examined the effect of menstrual cycle phase and hormones on clinical symptoms in women with schizophrenia. Earlier studies involving acutely ill patients demonstrated that clinical symptoms fluctuate across the menstrual cycle (Riecher-Rossler et al., 1994; Bergemann et al., 2007). Here we show the same pattern of findings in chronically ill, clinically stable female patients. Peripheral hormone levels did not account for these cycle-related changes but peripheral measures are an imperfect

index of CNS levels, and secondary effects of hormones or other cycle-related factors were not measured. Endogenous oxytocin levels, which had not been examined in previous menstrual cycle studies, were significantly associated with improvements in positive symptoms in female patients and prosocial symptoms in male and female patients. This work supports the general hypothesis that endogenous hormones can modulate symptoms in chronically-treated men and women with schizophrenia. It may be important to consider sex when evaluating oxytocin in the management of schizophrenia.

## References

Abi-Dargham, A., Moore, H., 2003. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. Neuroscientist 9, 404–416.

Akhondzadeh, S., Nejatisafa, A.A., Amini, H., Mohammadi, M.R., Larijani, B., Kashani, L., Raisi, F., Kamalipour, A., 2003. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. Prog. Neuropsychopharmacol. Biol. Psychiatry 27, 1007–1012.

Akhondzadeh, S., Rezaei, F., Larijani, B., Nejatisafa, A.A., Kashani, L., Abbasi, S.H., 2006. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr. Res. 84, 405–410.

Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch. Intern. Med. 158, 1855–1867.

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

Beckmann, H., Lang, R.E., Gattaz, W.F., 1985. Vasopressin–oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls. Psychoneuroendocrinology 10, 187–191.

Bergemann, N., Mundt, C., Parzer, P., Jannakos, I., Nagl, I., Salbach, B., Klinga, K., Runnebaum, B., Resch, F., 2005a. Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics. Schizophr. Res. 73, 357–366.

Bergemann, N., Mundt, C., Parzer, P., Pakrasi, M., Eckstein-Mannsperger, U., Haisch, S., Salbach, B., Klinga, K., Runnebaum, B., Resch, F., 2005b. Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study. Schizophr. Res. 74, 125–134.

Bergemann, N., Parzer, P., Runnebaum, B., Resch, F., Mundt, C., 2007. Estrogen, menstrual cycle phases, and psychopathology in women suffering from schizophrenia. Psychol. Med. 37, 1427–1436.

Brambilla, D.J., Matsumoto, A.M., Araujo, A.B., McKinlay, J.B., 2009. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J. Clin. Endocrinol. Metab. 94, 907–913.

Bujanow, W., 1972. Hormones in the treatment of psychoses. Br. Med. J. 4, 298.

Caldwell, H.K., Stephens, S.L., Young 3rd, W.S., 2009. Oxytocin as a natural antipsychotic: a study using oxytocin knockout mice. Mol. Psychiatry 14, 190–196.

Carter, C.S., Pournajafi-Nazarloo, H., Kramer, K.M., Ziegler, T.E., White-Traut, R., Bello, D., Schwertz, D., 2007. Oxytocin: behavioral associations and potential as a salivary biomarker. Ann. NY Acad. Sci. 1098, 312–322.

Carter, C.S., Grippo, A.J., Pournajafi-Nazarloo, H., Ruscio, M.G., Porges, S.W., 2008. Oxytocin, vasopressin and sociality. Prog. Brain Res. 170, 331–336.

Choi, S.H., Kang, S.B., Joe, S.H., 2001. Changes in premenstrual symptoms in women with schizophrenia: a prospective study. Psychosom. Med. 63, 822–829.

Docherty, J.P., Baker, R.A., Eudicone, J., Mathew, S., Marcus, R.N., McQuade, R.D., Mankoski, R., 2010. Effect of aripiprazole versus haloperidol on PANSS Prosocial items in early-episode patients with schizophrenia. Schizophr. Res. 120, 199–203.

Feifel, D., Reza, T., 1999. Oxytocin modulates psychotomimetic-induced deficits in sensorimotor gating. Psychopharmacology (Berl) 141, 93–98.

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.

First, M., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P). New York State Psychiatric Institute, New York.

Glovinsky, D., Kalogeras, K.T., Kirch, D.G., Suddath, R., Wyatt, R.J., 1994. Cerebrospinal fluid oxytocin concentration in schizophrenic patients does not differ from control subjects and is not changed by neuroleptic medication. Schizophr. Res. 11, 273–276.

Goldman, M., Marlow-O'Connor, M., Torres, I., Carter, C.S., 2008. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr. Res. 98, 247–255.

Gower, B.A., Nyman, L., 2000. Associations among oral estrogen use, free testosterone concentration, and lean body mass among postmenopausal women. J. Clin. Endocrinol. Metab. 85, 4476–4480.

Goyal, R.O., Sagar, R., Ammini, A.C., Khurana, M.L., Alias, A.G., 2004. Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann. NY Acad. Sci. 1032, 291–294.

Halbreich, U., Kahn, L.S., 2003. Hormonal aspects of schizophrenias: an overview. Psychoneuroendocrinology 28 (Suppl 2), 1–16.

Hallonquist, J.D., Seeman, M.V., Lang, M., Rector, N.A., 1993. Variation in symptom severity over the menstrual cycle of schizophrenics. Biol. Psychiatry 33, 207–209.

Harris, A.H., 1997. Menstrually related symptom changes in women with schizophrenia. Schizophr. Res. 27, 93–99.

Heinrichs, M., von Dawans, B., Domes, G., 2009. Oxytocin, vasopressin, and human social behavior. Front. Neuroendocrinol. 30, 548–557.

Howes, O.D., Wheeler, M.J., Pilowsky, L.S., Landau, S., Murray, R.M., Smith, S., 2007. Sexual function and gonadal hormones in patients taking antipsychotic treatment for schizophrenia or schizoaffective disorder. J. Clin. Psychiatry 68, 361–367.

Huber, T.J., Borsutzky, M., Schneider, U., Emrich, H.M., 2004. Psychotic disorders and gonadal function: evidence supporting the oestrogen hypothesis. Acta Psychiatr. Scand. 109, 269–274.

Huber, T.J., Tettenborn, C., Leifke, E., Emrich, H.M., 2005. Sex hormones in psychotic men. Psychoneuroendocrinology 30, 111–114.

Jensen, T.K., Andersson, A.M., Jorgensen, N., Andersen, A.G., Carlsen, E., Petersen, J.H., Skakkebaek, N.E., 2004. Body mass index in relation to semen quality and reproductive hormones among 1558 Danish men. Fertil. Steril. 82, 863–870.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keri, S., Kiss, I., Kelemen, O., 2009. Sharing secrets: oxytocin and trust in schizophrenia. Soc. Neurosci. 4, 287–293.

Ko, Y.H., Joe, S.H., Cho, W., Park, J.H., Lee, J.J., Jung, I.K., Kim, L., Kim, S.H., 2006. Effect of hormone replacement therapy on cognitive function in women with chronic schizophrenia. Int. J. Psychiatry Clin. Pract. 10, 97–104.

Ko, Y.H., Jung, S.W., Joe, S.H., Lee, C.H., Jung, H.G., Jung, I.K., Kim, S.H., Lee, M.S., 2007. Association between serum testosterone levels and the severity of negative symptoms in male patients with chronic schizophrenia. Psychoneuroendocrinology.

Ko, Y.H., Lew, Y.M., Jung, S.W., Joe, S.H., Lee, C.H., Jung, H.G., Lee, M.S., 2008. Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. J. Clin. Psychopharmacol. 28, 375–383.

Konarzewska, B., Wolczynski, S., Szulc, A., Galinska, B., Poplawska, R., Waszkiewicz, N., 2009. Effect of risperidone and olanzapine on reproductive hormones, psychopathology and sexual functioning in male patients with schizophrenia. Psychoneuroendocrinology 34, 129–139.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435, 673–676.

Kulkarni, J., Riedel, A., de Castella, A.R., Fitzgerald, P.B., Rolfe, T.J., Taffe, J., Burger, H., 2002. A clinical trial of adjunctive oestrogen treatment in women with schizophrenia. Arch. Womens Ment. Health 5, 99–104.

Kulkarni, J., de Castella, A., Fitzgerald, P.B., Gurvich, C.T., Bailey, M., Bartholomeusz, C., Burger, H., 2008. Estrogen in severe mental illness: a potential new treatment approach. Arch. Gen. Psychiatry 65, 955–960.

Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocrinol. 25, 150–176.

Lee, P.R., Brady, D.L., Shapiro, R.A., Dorsa, D.M., Koenig, J.I., 2005. Social interaction deficits caused by chronic phencyclidine administration are reversed by oxytocin. Neuropsychopharmacology 30, 1883–1894.

Legros, J.J., Gazzotti, C., Carvelli, T., Franchimont, P., Timsit-Berthier, M., von Frenckell, R., Ansseau, M., 1992. Apomorphine stimulation of vasopressin- and oxytocin-neurophysins. Evidence for increased oxytocinergic and decreased vasopressinergic function in schizophrenics. Psychoneuroendocrinology 17, 611–617.

Lehman, A.F., Kreyenbuhl, J., Buchanan, R.W., Dickerson, F.B., Dixon, L.B., Goldberg, R., Green-Paden, L.D., Tenhula, W.N., Boerescu, D., Tek, C., Sandson, N., Steinwachs, D.M., 2004. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr. Bull. 30, 193–217.

Liedman, R., Hansson, S.R., Howe, D., Igidbashian, S., McLeod, A., Russell, R.J., Akerlund, M., 2008. Reproductive hormones in plasma over the menstrual cycle in primary dysmenorrhea compared with healthy subjects. Gynecol. Endocrinol. 24, 508–513.

Linkowski, P., Geenen, V., Kerkhofs, M., Mendlewicz, J., Legros, J.J., 1984. Cerebrospinal fluid neurophysins in affective illness and in schizophrenia. Eur. Arch. Psychiatry Neurol. Sci. 234, 162–165.

Loebel, A., Siu, C., Romano, S., 2004. Improvement in prosocial functioning after a switch to ziprasidone treatment. CNS Spectr. 9, 357–364.

Louza, M.R., Marques, A.P., Elkis, H., Bassitt, D., Diegoli, M., Gattaz, W.F., 2004. Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study. Schizophr. Res. 66, 97–100.

Mai, J.K., Berger, K., Sofroniew, M.V., 1993. Morphometric evaluation of neurophysin-immunoreactivity in the human brain: pronounced inter-

individual variability and evidence for altered staining patterns in schizophrenia. J. Hirnforsch. 34, 133–154.

Marx, C.E., Keefe, R.S., Buchanan, R.W., Hamer, R.M., Kilts, J.D., Bradford, D.W., Strauss, J.L., Naylor, J.C., Payne, V.M., Lieberman, J.A., Savitz, A.J., Leimone, L.A., Dunn, L., Porcu, P., Morrow, A.L., Shampine, L.J., 2009. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. Neuropsychopharmacology 34, 1885–1903.

Oades, R.D., Schepker, R., 1994. Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology 19, 373–385.

Parker, K.J., Kenna, H.A., Zeitzer, J.M., Keller, J., Blasey, C.M., Amico, J.A., Schatzberg, A.F., 2010. Preliminary evidence that plasma oxytocin levels are elevated in major depression. Psychiatry Res. 178, 359–362.

Patisaul, H.B., Scordalakes, E.M., Young, L.J., Rissman, E.F., 2003. Oxytocin, but not oxytocin receptor, is rRegulated by oestrogen receptor beta in the female mouse hypothalamus. J. Neuroendocrinol. 15, 787–793.

Purnine, D.M., Carey, K.B., Maisto, S.A., Carey, M.P., 2000. Assessing positive and negative symptoms in outpatients with schizophrenia and mood disorders. J. Nerv. Ment. Dis. 188, 653–661.

Rao, M.L., Kolsch, H., 2003. Effects of estrogen on brain development and neuroprotection–implications for negative symptoms in schizophrenia. Psychoneuroendocrinology 28 (Suppl 2), 83–96.

Riecher-Rossler, A., Hafner, H., 2000. Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. Acta Psychiatr. Scand. Suppl. 58–62.

Riecher-Rossler, A., Hafner, H., Stumbaum, M., Maurer, K., Schmidt, R., 1994. Can estradiol modulate schizophrenic symptomatology? Schizophr. Bull. 20, 203–214.

Ritsner, M.S., Gibel, A., Shleifer, T., Boguslavsky, I., Zayed, A., Maayan, R., Weizman, A., Lerner, V., Clin Psychiatry, J., 2010. Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial. J. Clin. Psychiatry.

Rosenfeld, A.J., Lieberman, J.A., Jarskog, L.F., 2010. Oxytocin, dopamine, and the amygdala: a neurofunctional model of social cognitive deficits in schizophrenia. Schizophr. Bull.

Salonia, A., Nappi, R.E., Pontillo, M., Daverio, R., Smeraldi, A., Briganti, A., Fabbri, F., Zanni, G., Rigatti, P., Montorsi, F., 2005. Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. Horm. Behav. 47, 164–169.

Sarnyai, Z., Kovacs, G.L., 1994. Role of oxytocin in the neuroadaptation to drugs of abuse. Psychoneuroendocrinology 19, 85–117.

Scantamburlo, G., Hansenne, M., Fuchs, S., Pitchot, W., Marechal, P., Pequeux, C., Ansseau, M., Legros, J.J., 2007. Plasma oxytocin levels and anxiety in patients with major depression. Psychoneuroendocrinology.

Shahrokh, D. K., Zhang, T. Y., Diorio, J., Gratton, A.Meaney, M. J., Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology. 151, 2276-2286.

Theodoridou, A., Rowe, A.C., Penton-Voak, I.S., Rogers, P.J., 2009. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm. Behav. 56, 128–132.

Thompson, K., Sergejew, A., Kulkarni, J., 2000. Estrogen affects cognition in women with psychosis. Psychiatry Res. 94, 201–209.

Uvnas-Moberg, K., Alster, P., Svensson, T.H., 1992. Amperozide and clozapine but not haloperidol or raclopride increase the secretion of oxytocin in rats. Psychopharmacology (Berl) 109, 473–476.

Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry 64, 663–667.

Young, L.J., Wang, Z., Donaldson, R., Rissman, E.F., 1998. Estrogen receptor alpha is essential for induction of oxytocin receptor by estrogen. NeuroReport 9, 933–936.

Zak, P.J., Kurzban, R., Matzner, W.T., 2005. Oxytocin is associated with human trustworthiness. Horm. Behav. 48, 522–527.

Zumoff, B., Strain, G.W., Miller, L.K., Rosner, W., Senie, R., Seres, D.S., Rosenfeld, R.S., 1990. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. J. Clin. Endocrinol. Metab. 71, 929–931.