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Preliminary evidence that oxytocin does not improve mentalizing in women with schizophrenia

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Abstract

Introduction: Mentalizing, the ability to infer other people's intentions and emotions, is commonly impaired in schizophrenia and may represent an endophenotype. The hypothalamic neuropeptide oxytocin has been shown to improve mentalizing in men with schizophrenia, but its effects in women remain unclear. Given sex differences in the clinical manifestations of schizophrenia and oxytocin system function, this is an important gap to address.

Methods: We tested the effects of a single-dose oxytocin challenge (40 IU) on mentalizing task performance among 26 women with schizophrenia and 38 healthy control women using a randomized, placebo-controlled, double-blind, crossover design. We aimed to replicate our prior study of oxytocin effects on mentalizing in men with schizophrenia, using the same oxytocin administration procedures and performance-based assessments. We used mixed-effects models and equivalence testing as well as Bayesian hierarchical models to examine oxytocin effects.

Results: In contrast to our previous finding in a male sample, oxytocin did not improve mentalizing in this sample of women with schizophrenia. Exploratory analyses showed that higher anti-dopaminergic medication dosage was associated with a decreased response to oxytocin, consistent with previous findings in men.

Conclusion: These findings provide preliminary evidence that exogenous oxytocin administration may have sex-specific effects on mentalizing in schizophrenia. Inclusion of women

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CRediT authorship contribution statement

Ellen R. Bradley: Methodology, Investigation, Analysis, Visualization, Writing- original draft preparation, review, and editing. Marlene Tai: Investigation, Analysis, Writing- original draft preparation. Michael Hankin: Analysis, Visualization. Josh D. Woolley: Conceptualization, Supervision, Resources, Writing- review and editing.

Declarations of interest

The authors declare that they have no financial disclosures.

in future clinical studies with larger samples is critical, as oxytocin effects observed in men may not extend to women with the disorder.

Keywords

schizophrenia; oxytocin; social cognition; sex differences

1. Introduction

Mentalizing, the ability to infer other people's intentions and emotions, is a core element of social cognition commonly impaired in schizophrenia (Green et al., 2015). Work in animal models and humans suggests that dysregulation of the hypothalamic neuropeptide oxytocin, a potent modulator of social behavior, contributes to social cognitive deficits associated with schizophrenia (Feifel et al., 2016). Multiple studies have shown that exogenous oxytocin administration can improve mentalizing among people with the disorder (Bradley and Woolley, 2017), however, samples have been comprised mostly or entirely of men. Indeed, in a meta-analysis (Burkner et al., 2017) of oxytocin effects on social cognitive deficits in schizophrenia, women comprised only 12 percent of the total sample.

This is an important issue to address for at least two reasons. First, oxytocin exerts sexually dimorphic effects on behavior (Gao et al., 2016) and brain responses to social stimuli (Lieberz et al., 2020). In schizophrenia, plasma oxytocin levels have sex-dependent associations with resting brain physiology (Rubin et al., 2018a) and symptom severity (Rubin et al., 2018b). Further, epigenetic alterations in the oxytocin receptor gene predict anhedonia and asociality specifically in women with the disorder (Bang et al., 2019). Second, the incidence of schizophrenia is only slightly lower in women (Abel et al., 2010) and there are substantial sex differences in the disorder's clinical manifestations. Women tend to experience a later onset, more severe depression and fewer negative symptoms, and may respond differently to anti-dopaminergic medications (Abel et al., 2010). Thus, it is unclear whether certain findings in men can be extended to the substantial population of women with schizophrenia. Despite the importance of considering sex differences in oxytocin research, to our knowledge no studies have investigated the effects of exogenous oxytocin on social cognition in women with schizophrenia.

To address this gap, we examined whether the most consistently-observed effect of exogenous oxytocin in men with schizophrenia—improved mentalizing—replicated in women with the disorder. In a randomized, placebo-controlled, double-blind, crossover study, we administered a single-dose oxytocin challenge to women with schizophrenia and healthy controls and assessed mentalizing performance. We also explored the relationship between anti-dopaminergic medication use and oxytocin response. In men, we have previously found that lower dosages of medication predict greater response to exogenous oxytocin (Bradley and Woolley, 2017), in line with evidence that modulation of both oxytocin and dopamine signaling underlie aspects of social behavior (Matthews and Tye, 2019).

2. Material and Methods

2.1 Participants

We recruited 26 women with schizophrenia and 38 healthy control women from outpatient clinics and via online advertisements in the San Francisco Bay Area. Patients were clinically stable, with no medication changes or hospitalizations within the last month. Controls had no Axis I disorder within the last year, no lifetime history of a psychotic disorder, and no history of a psychotic disorder in first degree relatives. All participants had no history of a neurological or substance use disorder within the last six months and negative urine toxicology screens on both testing days. Participants provided written informed consent and study protocols were approved by the Committee on Human Research at the University of California, San Francisco.

2.2 Procedures

We administered the Positive And Negative Syndrome Scale (PANSS) at baseline to quantify schizophrenia symptoms (Kay et al., 1987). Participants were randomized to drug order. On each testing day, 40 IU oxytocin or saline placebo (Wellspring Pharmacy, Berkeley, CA) was administered intranasally as in our previous study (Woolley et al., 2014). Participants completed the assessment beginning ~45 minutes and concluding ~75 minutes following drug administration. We selected this dosage and timing based on previous findings of behavioral and neural effects in men with schizophrenia at this dosage (Bradley and Woolley, 2017). Testing days were separated by at least one week.

2.3 Measures

2.3.1 Mentalizing—As in our previous study, we used the performance-based Social Inference–Enriched (SI-E) sub-section of The Awareness of Social Inference Test (TASIT) to assess mentalizing ability (McDonald et al., 2006). In the SI-E, participants view a series of videos in which actors engage in social interactions that require mentalizing to understand. We used validated alternate forms on each testing day, with the order of forms randomized between participants. We also used the same control task as in our previous study, which consists of items selected from the Social Inference–Minimal (SI-M) sub-section. In the SI-M, video content does not require mentalizing to understand. The control task ensures that participants can follow instructions and attend to video content. SI-M was implemented partway through the study, and thus has a smaller sample size (N=23 patients; N=25 controls).

2.3.2 Medication—We calculated chlorpromazine (CPZ) equivalents for patients' anti-dopaminergic medications using a standardized conversion table (Andreasen et al., 2010).

2.4 Statistical Analyses

We assessed normality using the Shapiro-Wilk test and evaluated group differences using Mann-Whitney tests. Next, we used mixed-effects models to test whether oxytocin improved mentalizing, regressing SI-E scores on a drug x group interaction with participant included as a random effect. Our sample size provided 80% power to detect a medium-sized effect of oxytocin on SI-E scores among patients (Cohen's d=0.57), which is significantly smaller

than the effect size that we previously observed in men with schizophrenia (Cohen's d=0.93; Woolley et al., 2014). We also used a Bayesian hierarchical model to complement the frequentist analyses and enhance interpretability of the strength of our findings. Finally, among patients, we explored whether response to oxytocin was associated with anti-dopaminergic medication use, computing mentalizing performance change scores and correlating these with CPZ equivalents.

3. Results

3.1 Sample characteristics

We found no statistically significant difference between the groups in years of education (patients: mean=15.2, SD=2.4; controls: mean=15.9, SD=2.3; p=0.10) or in age, though notably patients tended to be older (patients: mean=42.7, SD=14.8; controls: mean=36.2, SD=15.1; p=0.19; Cohen's d=0.43). For patients, the mean PANSS score was 57.7 (SD=12.1).

3.2 Mentalizing

We found a main effect of group, indicating that patients performed worse than controls on the SI-E overall (b=0.10; CI=0.05, 0.15; p<0.001). We found no drug x group interaction (b=−0.004; CI=−0.05, 0.04; p=0.85) or main effect of drug (b=0.01; CI=−0.03, 0.05; p=0.55), suggesting that oxytocin administration did not improve mentalizing in either patients or controls. We found no main effect of group (b=−0.01; CI=−0.15, 0.12; p=0.84) and no drug x group interaction on control task performance (b=0.01; CI=−0.14, 0.17; p=0.87; Table 1).

To improve the inference of our non-significant null hypothesis significance test p-values, we applied equivalence testing using the two one-sided test (TOST) procedure, which allows us to reject the presence of the smallest effect size considered worthwhile (Lakens et al., 2018). We selected equivalence bounds corresponding to an effect size half as large as that observed in the men in our prior study (Cohen's d=±0.465), reasoning that the absence of an effect of at least this magnitude suggests a meaningfully different response to oxytocin in women compared to men with schizophrenia. The equivalence test was significant, t(25)= −1.79, p=0.03, allowing us to reject the null hypothesis that oxytocin is associated with a medium or larger effect on SI-E scores among patients in this sample (Figure 1A). Bayesian modeling showed that the posterior mean of the effect size among patients in this sample was 0.16 with a 90th percentile of 0.52. The posterior probability of the effect in women meeting or exceeding the effect previously observed in men is 0.003, and the probability of it meeting or exceeding an effect half as large is 0.14, indicating a significantly smaller effect in women compared to men (Figure 1B).

Finally, we checked for potential confounds that could explain our null finding. Adding drug order (whether participants were randomized to oxytocin or placebo first) to the mixed-effects model, we found no drug x group x order interaction (b=0.06; CI=−0.04, 0.16; p=0.24) or main effect of order (b=0.03; CI=−0.05, 0.11; p=0.48) on SI-E scores. Comparing the current patient sample of women to the patient sample of men in our previous study, we found no statistically significant difference in terms of age (p=0.78),

education (p=0.07), PANSS scores (p=0.21), or control task scores (p=0.96). Though not significant, it is important to note that women tended to have higher placebo day SI-E scores (Cohen's d=0.44, p=0.11).

3.3 Medication

We found that higher anti-dopaminergic medication dosage (mean CPZ=264.5, SD=223.5) was associated with lower mentalizing performance change scores (ρ(−0.43), p=0.03; Figure 1C).

4. Discussion

We found preliminary evidence that a single dose of oxytocin does not improve mentalizing in women with schizophrenia, in contrast to our findings in men with the disorder. This suggests that exogenous oxytocin may have sexually dimorphic effects in schizophrenia, as has been observed in healthy people (Gao et al., 2016). Consistent with previous studies in men, we found that anti-dopaminergic medication dosage was negatively associated with response to oxytocin. Together, these findings add to evidence that oxytocin effects in schizophrenia depend on individual level factors (Bradley and Woolley, 2017) and highlight the importance of testing potential interventions for schizophrenia in women, as findings in men may not extend to women with the disorder.

Multiple factors that require further study may underlie our null findings. First, hormones including estrogen and cortisol may modulate the endogenous oxytocin system and consequently impact the response to exogenous oxytocin (Rubin et al., 2015). We were unable to examine menstrual cycle dynamics, hormonal contraceptive use, or endogenous hormone levels in this study. Other studies have found an association between cognitive performance and estrogen levels (e.g. Ko et al., 2006) as well as serum oxytocin levels (Rubin et al., 2015) among women with schizophrenia. Thus, the impact of endogenous-exogenous oxytocin interactions in women clearly requires further investigation. A second, related issue is that the 40 IU dosage may not be optimized for women. Dose-response curves for intranasal oxytocin are not well-established, but there is some evidence for a sex-dependent inverted U-shaped curve (Borland et al., 2018). Though we have previously found behavioral and neural effects of oxytocin following a 40 IU challenge in men, women may respond to a lower dosage. Third, the trend towards better placebo day mentalizing among women could be relevant—previous studies have found that men with more severe schizophrenia (Bradley et al., 2019) and men with stronger autistic-like traits (Spengler et al., 2017) show greater responsiveness to an exogenous oxytocin challenge. Fourth, we may have failed to capture differences between participants in this study and our previous study unrelated to sex that account for the divergent findings. Finally, we were not powered to detect smaller than medium-sized effects in this study. These limitations highlight the need for additional investigations in large samples of women with schizophrenia.

There is evidence that oxytocin exerts some of its behavioral effects via modulation of dopaminergic signaling (Matthews and Tye, 2019), but mechanisms underlying the inverse relationship between anti-dopaminergic medications and the response to exogenous oxytocin are unclear. Lower dosages of anti-dopaminergic medication are associated with higher

cerebrospinal oxytocin levels in schizophrenia (Sasayama et al., 2012), however, it is unknown whether this relationship reflects a direct anti-dopaminergic effect on the endogenous oxytocin system (possibly through increased prolactin secretion that in turn suppresses oxytocin release) or whether greater oxytocin system dysregulation is found in patients with more severe symptoms who take higher dosages of medication. Further work is needed to clarify interactions between the oxytocin and dopamine systems in schizophrenia.

A bias towards enrolling men in clinical research (Longenecker et al., 2010) has limited our understanding of the effects of oxytocin and other potential treatments in women with schizophrenia. Though this study had a modest sample size, our preliminary findings underscore the risk of extrapolating information from investigations focused on men to the total population of people with the disorder. Including women in future studies is essential both to gain insight about the pathophysiology of impaired social cognition in schizophrenia as well as to determine whether oxytocin has clinical utility, and for whom.

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Highlights

- Mentalizing deficits are a hallmark of schizophrenia.
- In previous studies, oxytocin improved mentalizing in men with schizophrenia.
- We tested whether oxytocin improved mentalizing in women with schizophrenia.
- Oxytocin administration was not associated with improved mentalizing in women.
- Oxytocin may have sex-specific effects that warrant further study in larger samples.

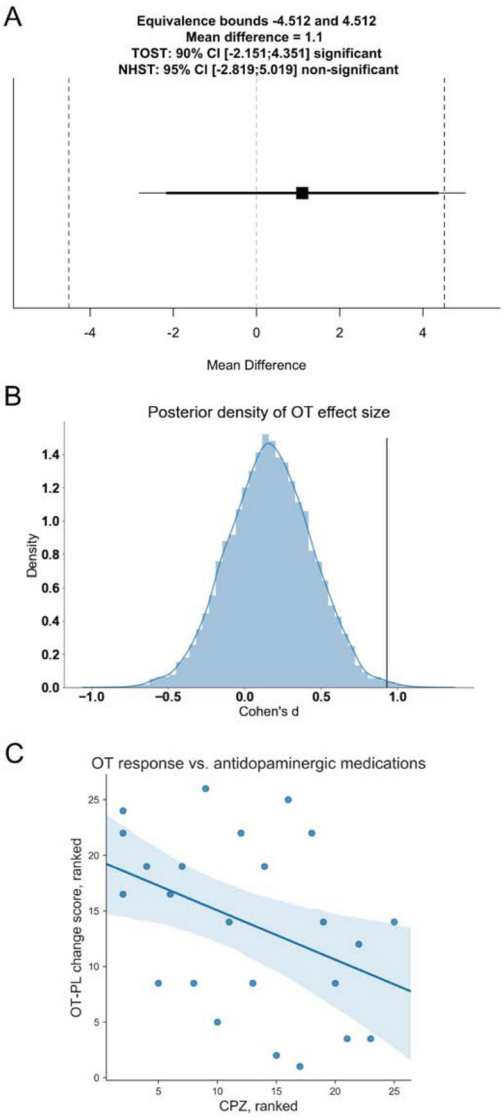

Figure 1A.

Equivalence test between oxytocin day versus placebo day mentalizing performance (SI-E scores) within the patient sample. The thick horizontal line indicates the 90% confidence interval from the two one-sided tests (TOST) procedure, the thin horizontal line shows the 95% confidence interval from the null-hypothesis significance test, and the dashed vertical lines show the equivalence bounds (Cohen's d=±0.465) in raw scores. **1B.** The posterior distribution for Cohen's d in the Bayesian hierarchical model reveals a low probability of an effect size in this sample of women with schizophrenia that is close to one as large as that observed our previous study in men with schizophrenia (vertical line), instead concentrating around a trivial or small positive effect size. **1C.** Oxytocin-induced change in mentalizing performance versus anti-dopaminergic medication use. Change scores were calculated by subtracting placebo day from oxytocin day SI-E scores. OT=oxytocin, PL=placebo, CPZ=chlorpromazine equivalents, SI-E=Social Inference–Enriched.

Table 1.

Mentalizing and control task scores by group and by drug. SI-E=Social Inference—Enriched, SI-M=Social Inference–Minimal, OT=oxytocin, PL=placebo.

	Patients			Controls			
	PL	OT	Cohen's *d*	PL	OT	Cohen's *d*	*p*-value (drug x group)
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		
Mentalizing task (SI-E)	72.9 (12.1)	74.0 (10.9)	0.10	82.8 (8.2)	83.4 (8.7)	0.08	0.90
Control task (SI-M)	79.1 (23.7)	78.5 (22.3)	0.03	77.8 (21.0)	78.4 (25.0)	0.03	0.87