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Oxytocin does not improve working memory in schizophrenia

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Dear Editors,

Impairment in working memory, the short-term encoding and maintenance of information, is a core deficit in schizophrenia that may represent an endophenotype. Though an important treatment target, no current pharmacologic interventions significantly improve working memory (Kahn and Keefe, 2013). Animal studies suggest that the hypothalamic neuropeptide oxytocin modulates memory processes (Chini et al., 2014), but oxytocin's ability to ameliorate working memory deficits in schizophrenia has been tested in only two small studies (Feifel et al., 2012; Michalopoulou et al., 2015) that yielded divergent findings.

To clarify whether oxytocin administration can acutely improve working memory in schizophrenia, we conducted a randomized, placebo-controlled, crossover study enrolling 70 clinically stable outpatients with schizophrenia and 80 age-matched neurotypical controls (Table 1). Participants had no major medical illnesses, no history of a substance use disorder within the past 6 months, and negative urine toxicology screens on testing days. We did not match groups on education, as decreased educational attainment is a consequence of schizophrenia (Resnick, 1992). All participants provided written consent and the study protocol was approved by the University of California, San Francisco Institutional Review Board. We administered 40 IU of intranasal oxytocin (Syntocinon, Novartis) or matched placebo on two testing days separated by at least two weeks. Approximately 90 minutes following drug administration on each day, participants completed the Letter Number Sequence (LNS) task, a measure of working memory from the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) that requires no specific academic skills.

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Contributors

J.D.W. designed the study and supervised data collection. E.R.B. and A.V. managed the literature searches and plan of analysis. S.A., A.V., and E.R.B. conducted the statistical analyses with support from A.N.N. E.R.B. wrote the manuscript. All authors assisted in revising the manuscript and approved the final version for submission.

Conflict of interest

All authors declare no conflicts of interest in relation to the subject of this study.

We used mixed-effects models to test whether oxytocin improved LNS performance, regressing LNS scores on a drug x group interaction with participant included as a random effect. We found a main effect of group, indicating that—as expected—patients performed worse overall ($b = -1.91$; CI = −3.02, −0.81; $p = 0.001$). However, neither the drug x group interaction ($b = -0.09$; CI = −0.81, 0.64; $p = 0.81$) nor the main effect of drug ($b = -0.15$; CI = −0.21, 0.52; $p = 0.41$) were significant. Given this null result, we conducted two follow-up analyses to clarify our findings: (1) There is evidence of differential effects of oxytocin in males and females (for a review see Bradley and Woolley, 2017); thus, we examined whether sex moderated oxytocin's effects on working memory. We regressed LNS scores on a group x sex interaction and a drug x sex interaction with participant included as a random effect. We did not include a 3-way interaction given the null interaction previously obtained. Neither the group x sex nor drug x sex interaction were significant (both $p > 0.25$). (2) 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 (Lakens et al., 2018). The TOST procedure allows for detection of the absence of a meaningful oxytocin effect using equivalence bounds, which we set based on calculations that our study had 80% power to detect an effect size of at least $d = 0.34$. The equivalence test was significant, $t(69) = -2.140$, $p = 0.018$, given bounds of $d = -0.34$ to $d = 0.34$ and an alpha of 0.05. Thus, we can reject the null hypothesis that oxytocin is associated with a meaningful difference in LNS performance in our patient sample.

Our finding that oxytocin did not modulate working memory performance among patients is in line with one previous study (Feifel et al., 2012) that failed to find an effect of a two-week course of oxytocin on working memory, but inconsistent with another study (Michalopoulou et al., 2015) that reported positive effects after a single dose. There are at least two possible explanations for these divergent findings. First, capturing oxytocin effects on working memory may be task-dependent. The LNS used here and by Feifel et al. (2012) tests visual spatial working memory and processing speed (Crowe, 2016), while the Digit Span task used by Michalopoulou et al. (2015) involves a significant immediate memory component (Hill et al., 2010). Second, different dosages of oxytocin and different administration protocols may lead to divergent results. Michalopoulou et al. (2015) administered a lower single dose (24 IU) than us, while Feifel et al. (2012) administered 20 IU twice daily for one week and then 40 IU twice daily for two weeks. While dose-response curves for intranasal oxytocin are not well-established, behavioral effects are known to vary with dosage, timing, and chronicity of administration (Bradley and Woolley, 2017).

Given the lack of clarity regarding oxytocin's therapeutic benefit in schizophrenia, we believe that it is critical to disseminate negative findings that might guide future investigations. To our knowledge, this is the largest study to examine the acute effect of intranasal oxytocin on working memory in people with schizophrenia. Our results suggest that oxytocin is unlikely to improve the working memory deficits associated with schizophrenia.

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Table 1.

Demographics, clinical information, and raw Letter Number Sequence (LNS) scores for placebo (PL) and oxytocin (OT) conditions.

	Patients (n=70)	**Controls (n=80)**	**Patients vs. Controls**
Sex	**19 female (37%)**	**25 female (31%)**	
	Mean (SD)		
Age	43.4 (14.5)	40.8 (14.2)	$p = 0.27$
Education years	14.4 (3.0)	15.9 (2.2)	$p < 0.001$
PANSS score			
Positive	13.5 (5.1)	-	-
Negative	13.9 (4.7)	-	-
General	26.2 (6.7)	-	-
LNS raw score	PL: 14.06 (4.21)	PL: 16.01 (3.07)	
	OT: 14.26 (4.29)	OT: 16.13 (2.89)	