Oxytocin does not improve emotional prosody recognition in schizophrenia-spectrum disorders

Brandon J. Chuang [a],[*], Timothy R. Campellone [b], Joshua D. Woolley [b],[c]

[a] University of California, Berkeley Department of Psychology, Berkeley, CA, USA
[b] San Francisco VA Medical Center, San Francisco, CA, USA
[c] University of California, San Francisco Department of Psychiatry, San Francisco, CA, USA

ARTICLE INFO

ABSTRACT

Schizophrenia-spectrum disorders (SSD) are associated with deficits in emotional prosody recognition. Whether administration of oxytocin can improve emotional prosody recognition accuracy in SSD is unknown. Sixty individuals with SSD and ninety-seven controls completed a placebo-controlled, double-blind, cross-over trial examining the effects of oxytocin on emotional prosody recognition accuracy. Compared to controls, SSD was associated with poorer emotional prosody recognition accuracy, regardless of stimulus valence or intensity, suggesting a generalized deficit. Oxytocin had no effect on emotional prosody recognition in either group, which is consistent with previous work suggesting that oxytocin only improves high-level social cognition in SSD.

1. Introduction

Schizophrenia-spectrum disorders (SSD) are associated with deficits in the ability to identify affect in the voice based on non-semantic acoustical cues, an ability known as emotional prosody recognition. These deficits are present across the course of the illness [1], and contribute to both poorer social skills [2], and worse functional outcomes in SSD [3]. Despite their clinical importance, there are no effective treatments for emotional prosody recognition deficits in SSD.

Oxytocin, a neuropeptide with prosocial effects in humans, has been shown to improve some aspects of social cognition in SSD [4]. However, a recent meta-analysis [5] suggests that oxytocin's positive effects may be specific for higher-level social cognitive processes, such as theory of mind, but not lower-level processes such as social cue perception. This suggests that oxytocin may not improve emotional prosody recognition, which is a lower-level social cognitive process in schizophrenia [6], but may still have effects in healthy populations [7]. The current study sought to clarify whether acute oxytocin administration improves emotional prosody recognition accuracy in individuals with and without SSD.

2. Methods

2.1. Participants

Sixty individuals with SSD (fifteen female) and ninety-seven healthy control (twenty-six female) participants were recruited from the San Francisco Bay Area (see Table 1). Participants were interviewed by a trained clinician and had no history of neurological disorders, did not meet DSM-IV-TR criteria for substance abuse in the past month or substance dependence within the last six months, and had a negative urine toxicology test at each visit. Control participants had no Axis I DSM-IV-TR disorder within the last year or any lifetime history of a psychotic disorder. All individuals with SSD had no psychiatric hospitalization or change in antipsychotic medication dosages for at least one month prior to starting the study and throughout the study. Participants were matched on age and sex but not on education level. PANSS and medication information can be found in Table 1. Informed consent was obtained from each participant, and all study procedures were approved by the University of California, San Francisco Committee on Human Research. This clinical study was registered on clinicaltrials.gov (identifier: NCT02577575).

2.2. Procedures

We conducted a randomized, double-blind, placebo-controlled, cross-over study with the two testing days separated by at least one week. On each test day, 40 IU of oxytocin or placebo was self-administered by a nasal spray with insufflations every 15 s, alternating between nostrils, over a 5-min period supervised by study staff. This process follows established guidelines for optimizing consistent CNS delivery [8]. We chose 40 IU because of evidence that shows that this is the optimal dosage for therapeutic effects in SSD [9]. Previous work has shown that intranasal oxytocin

Table 1
Demographic information.

	Schizophrenia-spectrum Disorders (N = 60)		Healthy Controls (N = 97)			
	Mean/N	SD/%	Mean/N	SD/%	P-value	Effect Size (d)
Demographics						
Age (years)	43.3	13.9	42.4	14.3	0.71	0.06
Range	18–65	–	18–63	–		
Education Level (N = 57; 96)**	14.5	3.3	15.5	2.2	0.001	0.36
Gender	–	–	–	–	0.80	
Male	45	75.0%	71	73.2%		
Female	15	25.0%	26	26.8%		
Diagnosis	–	–	–	–		
Schizophrenia	35	58.3%	–	–		
Schizoaffective	22	36.7%	–	–		
Schizophreniform	3	5.0%	–	–		
Mood Stabilizers	9	15.0%	–	–		
Race	–	–	–	–	0.99	
Caucasian	28	46.7%	45	46.4%		
African American	9	15.0%	16	16.5%		
Latino/Hispanic	5	8.3%	9	9.3%		
Asian American	17	28.3%	25	25.8%		
Other	1	1.7%	2	2.1%		
Experience in Close Relationships (N = 48; 56)						
Anxiety**	2.8	1.3	2.0	1.0	0.002	0.69
Avoidance	3.1	1.2	2.8	1.0	0.34	0.27
Clinical Symptoms (N = 58)						
Positive	14.2	5.1	–	–		
Negative	14.1	5.0	–	–		
General	27.6	7.1	–	–		
Medications (N = 47; 9 missing; 4 none)						
Chlorpromazine Equivalents (mg)	268.1	193.5	–	–		
Range	0–836.4	–	–	–		

*p < 0.05, **p < 0.01.

administration begins to have physiological effects within 30 min [10], cerebrospinal fluid (CSF) oxytocin levels peak at 75 min [11], and blood oxytocin levels rise at 30 min and remain high for at least 90 min after intranasal oxytocin administration [12]. Therefore, in the current study, behavioral testing began 60 min post-administration and continued for no longer than 120 min.

2.3. Emotional prosody task

The emotional prosody task [13], consists of two versions, each containing 27 auditory stimuli (e.g. Version A: "that's exactly what happened"; Version B: "let me tell you something"). Before testing began, we did a volume check to make sure participants could comfortably hear the test stimuli. Each stimulus consists of a man or woman uttering a phrase with emotional prosody (anger, fear, sadness, happiness, affection) or no emotion. Stimuli were not balanced across emotion in each version (i.e., there was a different number of stimuli for each emotion). To account for this imbalance, each emotion contributed equally to each respective valence composite score. In line with previous studies [14], we constructed composite positive (happiness, affection) and negative (anger, fear, sadness) emotional prosody recognition composite accuracy scores. Stimuli in this task also had a specific intended intensity (low, medium, high), which reflected the intensity conveyed by the actor [13]. As with the valence composite score, we computed intensity level composite scores weighted equally by intensity level within each valence. Participants indicated on a computer a number corresponding to the emotion (1–6) and then subsequently a number corresponding to the intensity (1–9) that they thought was portrayed in the phrase.

2.4. Data analysis

To examine the effect of oxytocin on emotional prosody recognition accuracy, we conducted a 2 Group (controls, SSD) X 2 Valence (negative, positive) X 3 Intensity (low, medium, high) X 2 Drug (placebo, oxytocin) Generalized Estimating Equation model with an unstructured correlation matrix. We included age as a covariate in the model given previous work showing lower emotional prosody recognition accuracy in older individuals [15]. GEE models are robust against violations of distributional assumptions and allow for the investigation of the nesting structure of our repeated measures design. We report standardized regression estimates and p values and followed up significant effects with nonparametric Mann-Whitney U and Wilcoxon Signed Rank tests. In order to explore null findings of oxytocin's effects, we conducted Two One-Sided T-Tests (TOST) equivalence testing. TOST can be used to statistically reject the presence of effects large enough to be considered worthwhile, i.e. to provide support for the absence of a meaningful effect. Based on our sample size and statistical power, we set the effect size threshold for TOST equivalence testing at $d = 0.40$.

3. Results

There were no group differences in age, sex, or race. Individuals with SSD had lower levels of education than controls and female controls had greater levels of education than male controls, but education was not related to performance. In addition, there were no effects of sex, task versions, or drug administration order (see Supplemental Materials).

There was no main effect of drug on overall emotional prosody recognition accuracy and no Drug interactions. Exploratory analyses of recognition accuracy for individual emotions also did not reveal any significant drug effects (see Supplemental Materials). Follow-up TOST equivalence tests were significant for individuals with SSD ($t(117.92) = -2.055, p = 0.02$) and controls $t(191.74) = -2.60, p = 0.005$) suggesting that the effects of oxytocin and placebo on emotional prosody recognition accuracy were equivalent in both groups. We found a significant main effect of group, with individuals with SSD having lower emotional prosody recognition accuracy than controls ($Z = -2.30, p = 0.02, d = 0.36$; see Fig. 1). We also found significant main effects of valence and intensity, which were qualified by a significant Valence × Intensity interaction (see Supplemental Materials). We also found a main effect of Age, with older participants having poorer overall emotional prosody recognition accuracy ($r = -0.45, p < 0.001$). There were no interactions with Age or Group.
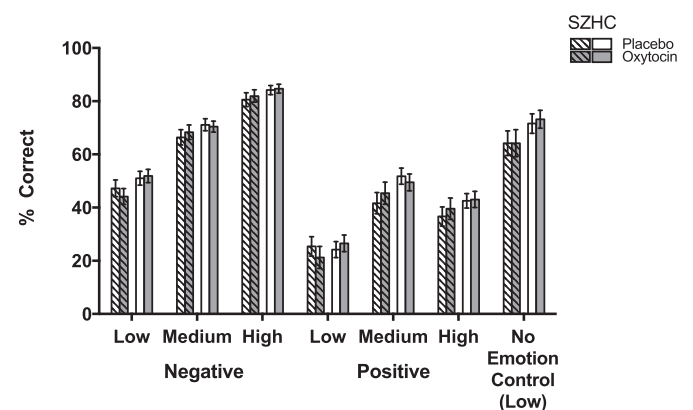

Fig. 1. Oxytocin's effects on overall emotional prosody recognition accuracy. Compared to controls, individuals with SSD had poorer emotional prosody recognition accuracy. There was no effect of oxytocin on emotional prosody recognition accuracy in either group.

4. Discussion

We did not find any benefit of oxytocin administration on emotional prosody recognition accuracy deficits in individuals with SSD, which is line with a recent meta-analysis [5]. Our study adds to the literature by showing that deficits in overall emotional prosody recognition in SSD are not specific to stimulus valence or intensity. Why individuals with SSD have emotional prosody recognition deficits remains unclear. Individuals with SSD have significant impairments in auditory processing, including tone-matching, rhythm discrimination, and pitch cues, each of which could contribute to emotional prosody recognition deficits [16]. Our findings also support previous studies indicating poorer overall emotional prosody recognition accuracy in older individuals [15], regardless of group. In addition to typical hearing loss, perception of auditory cues, such as pitch discrimination (Mitchell and Kingston, 2014), can worsen with age and may help explain poorer overall emotional prosody recognition accuracy in older individuals with and without SSD.

The present study is the first to examine the impact of oxytocin on emotional prosody recognition accuracy in SSD. Strengths of our study include the relatively large sample size, the within-subject design, and the inclusion of a neurotypical control group. Limitations of our study include that we did not establish whether each participant had standard hearing capability by testing hearing sensitivity and that may have been a confound in the results. Additionally, we did not collect response latencies and this could have been even more informative in combination with response accuracy. Another limitation is that we collapsed negative emotions by valence and that may have contributed to why we did not find effects of oxytocin. Negative emotions may differ with regards to other variables than valence such as approach-avoidance, threat, or pitch which we did not explore or collect and may have affected the negative valence findings. However, we did not find any oxytocin effects within groups with respect to individual emotions (see Supplemental Materials, Table S1). In addition, with regards to the null effects of oxytocin, it may be the specific type of task (i.e., auditory vs. visual stimuli) that was used that resulted in the null effects (e.g., oxytocin has effects on a theory of mind task when presented with minimal context rather than when presented with enriched contextual information [17]). Furthermore, task characteristics such as type of stimuli used have recently been found to impact the nature of social cognitive deficits associated with age in healthy populations [18]. Another limitation is the use of only one dosage of oxytocin (40 IU), which may be critical because previous studies suggest that oxytocin may have an optimal therapeutic benefit on emotional recognition at a lower concentration (e.g., 24 IU) in healthy individuals [19]. In addition, we did not collect genetic information, which may be critical because different combinations of oxytocin alleles may lead to diverse effects of oxytocin [7]. Other limitations include only using a single dose of oxytocin, allowing for the possibility that repeated administration may improve prosody recognition, and that we did not measure plasma oxytocin levels prior to intranasal application. Finally, while we administered pregnancy tests to rule out pregnancy, we did not assess menstrual cycle or phase of contraception use, both of which may have impacted oxytocin levels.

In conclusion, our study suggests that oxytocin administration does not improve prosody recognition deficits in SSD. Given that oxytocin effects in facial emotion recognition are mixed and moderate at best [20], it may be that oxytocin does not affect emotion recognition in either group regardless of modality. In light of recent studies highlighting issues related to the reliability and reproducibility of psychological research [21], dissemination of null findings is critical in reducing the "file drawer effect", wherein the failure to publish negative results skews the extant literature towards positive findings. Our null findings further elucidate the nuanced relationship between oxytocin and social cognition in SSD and provides important directions for future research.

Author contributions

JDW developed the study concept and design. BJC collected all study data and performed the data analysis and interpretation under the supervision of TRC and JDW. BJC and TRC drafted the paper and JDW provided critical revisions. All authors approved the final version of the paper for submission.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2020.100011.

References

[1] J. Edwards, P.E. Pattison, H.J. Jackson, R.J. Wales, Facial affect and affective prosody recognition in first-episode schizophrenia, Schizophr. Res. 48 (2001) 235–253.

[2] A.E. Pinkham, D.L. Penn, Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia, Psych Res 143 (2) (2006) 167–178.

[3] S. Martínez-Domínguez, R. Penadés, B. Segura, A. González-Rodríguez, R. Catalán, Influence of social cognition on daily functioning in schizophrenia: study of incremental validity and mediational effects, Psych Res 225 (3) (2015) 374–380.

[4] E.R. Bradley, J.D. Woolley, Oxytocin effects in schizophrenia: reconciling mixed findings and moving forward, Neurosci. Biobehav. Rev. 80 (2017) 36–56.

[5] P.C. Bürkner, D.R. Williams, T.C. Simmons, J.D. Woolley, Intranasal oxytocin may improve high-level social cognition in schizophrenia, but not social cognition or neurocognition in general: a multilevel Bayesian meta-analysis, Schizophr. Bull. 43 (6) (2017) 1291–1303.

[6] L.D. Oliver, J.D. Haltigan, J.M. Gold, G. Foussias, P. DeRosse, R.W. Buchanan, A.K. Malhotra, A.N. Voineskos, SPINS Group, Lower-and higher-level social cognitive factors across individuals with schizophrenia spectrum disorders and healthy controls: relationship with neurocognition and functional outcome, Schizophr. Bull. 45 (2019) 629–638.

[7] C.F. Bartholomeusz, E.P. Ganella, I. Labuschagne, C. Bousman, C. Pantelis, Effects of oxytocin and genetic variants on brain and behaviour: implications for treatment in schizophrenia, Schizophr. Res. 168 (3) (2015) 614–627.

[8] A.J. Guastella, I.B. Hickie, M.M. McGuinness, M. Otis, E.A. Woods, H.M. Disinger, H.K. Chan, T.F. Chen, R.B. Banati, Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research, Psychoneuroendocrinology 38 (5) (2013) 612–625.

[9] J.K. Wynn, M.F. Green, G. Hellemann, E.A. Reavis, S.R. Marder, A dose- finding study of oxytocin using neurophysiological measures of social processing, Neuropsychopharmacology 44 (2) (2019) 289–294.

[10] G.J. Norman, J.T. Cacioppo, J.S. Morris, K. Karelina, W.B. Malarkey, A.C. DeVries, G.G. Berntson, Selective influences of oxytocin on the evaluative processing of social stimuli, J. Psychopharmacol. 25 (2011) 1313–1319.

[11] N. Striepens, N. Striepens, K.M. Kendrick, V. Hanking, R. Landgraf, U. Wüllner, W. Maier, R. Hurlemann, Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans, Sci. Rep. 3 (2013) 3440.

[12] A. Gossen, A. Hahn, L. Westphal, S. Prinz, R.T. Schultz, G. Gründer, K.N. Spreckelmeyer, Oxytocin plasma concentrations after single intranasal oxytocin administration—a study in healthy men, Neuropeptides 46 (5) (2012) 211–215.

[13] P.N. Juslin, P. Laukka, Impact of intended emotion intensity on cue utilization and decoding accuracy in vocal expression of emotion, Emotion 1 (4) (2001) 381–412.

[14] V.P. Bozikas, M.H. Kosmidis, D. Anezoulaki, M. Giannakou, C. Andreou, A. Karavatos, Impaired perception of affective prosody in schizophrenia, J. Neuropsychiatry Clin. Neurosci. 18 (1) (2006) 81–85.

[15] L. Lambrecht, B. Kreifelts, D. Wildgruber, Age-related decrease in recognition of emotional facial and prosodic expressions, Emotion 12 (3) (2012) 529–539.

[16] D.I. Leitman, D.H. Wolf, P. Laukka, J.D. Ragland, J.N. Valdez, B.I. Turetsky, R.E. Gur, R.C. Gur, Not pitch perfect: sensory contributions to affective communication impairment in schizophrenia, Biol Psych 70 (7) (2011) 611–618.

[17] S.A. Grainger, J.D. Henry, H.R. Steinvik, E.J. Vanman, P.G. Rendell, I. Labuschagne, Intranasal oxytocin does not reduce age-related difficulties in social cognition, Horm. Behav. 99 (2018) 25–34.

[18] G.S. Hayes, S.N. McLennan, J.D. Henry, L.H. Phillips, G. Terrett, P.G. Rendell, I. Labuschagne, Task characteristics influence facial emotion recognition age-effects: a meta-analytic review, Psychol. Aging 35 (2) (2020) 295.

[19] F.B. Spengler, J. Schultz, D. Scheele, M. Essel, W. Maier, M. Heinrichs, R. Hurlemann, Kinetics and dose dependency of intranasal oxytocin effects on amygdala reactivity, Biol Psychiatry 82 (12) (2017) 885–894.

[20] M.J. Bakermans-Kranenburg, M.H. Van Ijzendoorn, Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy, Transl. Psychiatry 3 (5) (2013) e258-e258.

[21] J.P. Simmons, L.D. Nelson, U. Simonsohn, False-positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant, Psychol. Sci. 22 (11) (2011) 1359–1366.