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Endogenous oxytocin levels are associated with facial emotion recognition accuracy but not gaze behavior in individuals with schizophrenia

Michael J. Spilka^a, William R. Keller^b, Robert W. Buchanan^c, James M. Gold^c, James I. Koenig^d,
Gregory P. Strauss^a

^aDepartment of Psychology, University of Georgia, Athens, GA, USA

^bDartmouth College, Geisel School of Medicine, Department of Psychiatry, USA

^cMaryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, USA

^dNational Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

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Correspondence concerning this article should be addressed to Gregory P. Strauss (gstrauss@uga.edu) or Michael J. Spilka (michael.spilka@uga.edu), Department of Psychology, University of Georgia, Athens, GA, 30602, USA.

Abstract

Objective: Difficulties in social cognition are common in individuals with schizophrenia (SZ) and are not ameliorated by antipsychotic treatment. Intranasal oxytocin (OT) administration has been explored as a potential intervention to improve social cognition; however, results are inconsistent, suggesting potential individual difference variables that may influence treatment response. Less is known about the relationship between endogenous OT and social cognition in SZ, knowledge of which may improve the development of OT-focused therapies. We examined plasma OT in relationship to facial emotion recognition and visual attention to salient facial features in SZ and controls. **Methods:** Forty-two individuals with SZ and 23 healthy controls viewed photographs of facial expressions of varying emotional intensity and identified the emotional expression displayed. Participants' gaze behavior during the task was recorded via eye tracking. Plasma oxytocin concentrations were determined by radioimmunoassay. **Results:** SZ were less accurate than controls at identifying high intensity fearful facial expressions and low intensity sad expressions. Lower overall and high-intensity facial emotion recognition accuracy was associated with lower plasma OT levels in SZ but not controls. OT was not associated with visual attention to salient facial features; however, SZ had reduced visual attention to the nose region compared to controls. **Conclusion:** Individual differences in endogenous OT predict facial emotion recognition ability in SZ but are not associated with visual attention to salient facial features. Increased understanding of the association between endogenous OT and social cognitive abilities in SZ may help improve the design and interpretation of OT-focused clinical trials in SZ.

Keywords: eye tracking, facial emotion, oxytocin, schizophrenia, social cognition

Significant Outcomes

- Lower plasma oxytocin was associated with lower facial emotion recognition accuracy in schizophrenia.
- Plasma oxytocin was not related to eye gaze behavior during facial emotion recognition.
- Individuals with schizophrenia had higher plasma oxytocin than healthy controls despite reduced facial emotion recognition accuracy.

Limitations

- Other potential factors contributing to lower plasma oxytocin were not assessed (e.g., sex, antipsychotic medication, smoking status).
- Only peripheral oxytocin and not central nervous system oxytocin was assessed.

Data Availability Statement

Study data and analysis code are available from the corresponding author upon reasonable request.

Introduction

Difficulties in social cognition are well documented in schizophrenia (SZ)¹. These difficulties are present across illness phases, persist in patients treated with antipsychotic medication, and are important predictors of functional outcome²⁻⁴. The neuropeptide oxytocin has been examined as a novel pharmacological treatment to improve social cognition in SZ, motivated by research documenting the role of oxytocin in social behavior in animals^{5,6}, the positive effects of exogenous oxytocin administration on social cognition in humans⁷, and potential links between the oxytocin system and the pathophysiology of SZ^{8,9}. Despite promising initial trials, subsequent findings have been inconsistent, both in individuals with SZ^{10,11} and healthy controls (HC)¹². These inconsistencies have highlighted the importance of examining potential contextual and individual difference variables that may moderate the impact of oxytocin on social cognition and account for mixed findings across tasks and individuals^{11,12}.

One individual difference variable relevant to SZ is endogenous oxytocin. To date, comparisons of endogenous oxytocin levels between individuals with SZ and HC have yielded mixed results, including lower levels in SZ¹³⁻¹⁸, higher levels in SZ¹⁹⁻²³, or no difference between individuals with SZ and HC²⁴⁻³⁰. However, despite these inconsistencies, lower oxytocin levels are associated with greater symptom severity, particularly negative symptoms^{22,25,26,29,31,32}; however, see^{23,27,33}.

Similarly, a growing number of studies report associations between lower endogenous oxytocin and worse performance on tasks of social cognition in SZ (e.g., social cue perception, emotional body gesture identification, facial emotion recognition, emotional problem-solving, approach-avoidance behavior)^{14,18,20,21,26,33}; however, see^{15,23,34}. However, of the three previously published studies of facial emotion recognition and endogenous oxytocin, one found a significant

association in the HC but not the SZ group²⁷, another found an association in female but not male participants²⁶, and the other reported significant associations in a SZ sample comprised of individuals with neuroendocrine dysfunction, which may not be generalizable to the broader SZ population¹⁴. Therefore, although endogenous oxytocin appears to be an important variable related to clinical and social functioning in SZ, its association with facial emotion recognition remains unclear.

A related question is how oxytocin exerts its effects on facial emotion recognition, and social cognition more broadly. A leading hypothesis is that oxytocin increases the salience of social cues^{12,35}. For example, intranasal oxytocin administration in HC participants has been found to increase visual attention to the eye region of the face³⁶⁻³⁸; however, see 39,40, enhance recognition of low intensity facial expressions^{39,41}, and increases the detection of implicitly presented emotional faces⁴². As with the exogenous oxytocin findings described above, endogenous oxytocin might similarly be associated with sensitivity to social cues. If so, endogenous oxytocin patterns in SZ might also contribute to the documented reductions in visual attention to salient facial features during facial emotion perception⁴³⁻⁴⁸ that have been associated with emotion recognition difficulties in SZ^{43,44 49}. Characterizing the associations between endogenous oxytocin, facial emotion recognition, and visual attention to social cues in SZ may therefore help to improve the design and interpretation of exogenous oxytocin clinical trials and their combination with social cognition training programs.

Aims of the Study

In the current study, we aimed to clarify the relationship between endogenous oxytocin and facial emotion recognition accuracy in SZ and HC participants. We varied the intensity of facial expressions and recorded eye gaze behavior to examine whether higher endogenous

oxytocin levels reflected greater visual attention to emotional facial features. The following hypotheses were made: 1) SZ participants would have lower facial emotion recognition accuracy than HC participants, consistent with previous findings⁵⁰; 2) SZ would have reduced percentage of gaze fixations and dwell time to salient facial features compared to HC, consistent with previous findings⁴⁷; 3) lower plasma oxytocin levels would be associated with reduced facial emotion recognition in both groups; and 4) lower plasma oxytocin levels would be associated with reduced gaze fixations and dwell time to salient facial features in both groups.

Material and Methods

Participants

Participants included 42 individuals who met criteria for a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR⁵¹) diagnosis of schizophrenia or schizoaffective disorder (hereafter referred to as SZ), and 23 healthy controls (HC). SZ participants were recruited through the outpatient research program at the Maryland Psychiatric Research Center (MPRC) and evaluated while clinically stable (no changes in medication type/dosage during the past four weeks). Consensus diagnosis followed a best-estimate approach based on medical records review, the Structured Clinical Interview for DSM-IV (SCID⁵²), and multiple interviews. All SZ participants were treated with antipsychotic medication at time of testing.

HC participants were recruited through random-digit dialing and word of mouth among enrolled participants. They were screened using the SCID-I and SCID-II. Exclusion criteria for HCs were the lifetime presence of a psychotic disorder, current presence of any Axis I disorder (including substance abuse or dependence), and family history of psychosis. Additional exclusion criteria for HC and SZ participants were lifetime history of neurological disorders or

injury and age below 18 or above 65. Participants were screened for recent substance use by urine toxicology at time of testing. All participants gave written informed consent before participating and the study protocol was approved by the University of Maryland Institutional Review Board.

Procedure

Participants completed a standard clinical interview administered by a clinical psychologist (GPS) trained to MPRC reliability standards (reliability > 0.80). SZ participants were rated on the Brief Negative Symptom Scale⁵³, Brief Psychiatric Rating Scale⁵⁴, and Level of Function Scale⁵⁵. Plasma oxytocin concentration were determined by radioimmunoassay in extracted samples using a magnetic bead kit from Phoenix Pharmaceuticals, Inc. Samples were assayed in duplicate and averaged to determine the final oxytocin concentration. Assay sensitivity was 5 pg/ml, with minimal cross reactivity with vasopressin. The coefficient of variation averaged 5–8% across the assay. Oxytocin data was missing for 2 HC and 4 SZ participants.

Facial Emotion Recognition Task

Participants viewed photographs of facial expressions and had to make a forced-choice response to identify the emotional expression displayed. Gaze behavior during face viewing was recorded with an eye tracker. The task was programmed with Experiment Builder (SR Research Ltd., Mississauga, ON, Canada). Stimuli were color photographs of male and female faces from Matsumoto and Ekman's Japanese and Caucasian Facial Expressions of Emotion (JACFEE⁵⁶) corresponding to five basic emotions: anger, fear, happiness, sadness and surprise. Emotional intensity was varied using the FantaMorph software package (Abrosoft Co.) Each expression was morphed with a neutral expression by the same face model in 20% increments resulting in a

range of emotional intensities from 20% (80% neutral) to 100% (0% neutral). There were four unique face sets per expression for a total of 100 faces (5 expression categories $\times$ 5 intensities $\times$ 4 unique sets). Stimuli were presented for 8000ms in randomized order. Following each stimulus, a response screen displayed the five forced-choice response options (anger, fear, happiness, sadness and surprise) and participants were asked to verbally indicate their response, which the examiner recorded by key-press to trigger the next trial. A black screen with a central fixation cue preceded each trial. Stimuli were presented on a 17-inch CRT monitor and subtended a visual angle of approximately 29.6° of width and 23.3° of height at a viewing distance of 70 cm.

Eye tracking during the task was performed with an EyeLink 1000 desk-mounted eye tracking system (SR Research Ltd., Mississauga, ON, Canada) using monocular recording at a sampling rate of 2000 Hz with an average recording error of less than 0.5° visual angle. Chin and forehead rests were used to minimize head movement. A 9-point calibration and validation procedure was employed requiring a maximum error less than 1° visual angle, and drift-correction was performed before each trial.

Data processing and analysis

Sample characteristics and plasma oxytocin

Group differences in sample characteristics and plasma oxytocin were analyzed using one-way analysis of variance (ANOVA) and Pearson's chi-squared tests.

Analysis of facial emotion recognition accuracy

Prior to data analysis, the facial emotion intensity levels were combined into "low" and "high" intensity levels based on whether the morphing with the neutral expression was below or above 50%: low = 20%, 40% intensity expressions; "high" = 60%, 80%, 100% intensity

expressions. Facial emotion recognition accuracy was analyzed using a $2 \times 2 \times 5$ ANOVA (group [HC, SZ] $\times$ intensity [low, high] $\times$ emotion [anger, fear, happiness, sadness, surprise]). For all reported analyses, statistically significant findings ($p < .05$, two-tailed) were followed-up by pairwise comparisons when relevant. Greenhouse-Geisser adjustments to degrees of freedom were made when the assumption of sphericity was violated. The Bonferroni correction was applied to all pairwise comparison significance values. Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY).

Eye tracking data processing and analysis

Data processing was performed with EyeLink Data Viewer (SR Research Ltd., Mississauga, ON, Canada). Consecutive fixations with a duration less than 100ms and within 1° were merged, and remaining fixations less than 100ms in duration were removed. Trials containing fixation data for less than 70% (<5600 ms) of the face presentation window were excluded (HC: $M=3.27$, $SD=6.02$; SZ: $M=6.95$, $SD=10.52$) to remove trials with recording issues or unusually long blinks, and participants with more than 50% excluded trials were excluded from the eye tracking analysis (3 SZ; 0 HC). Gaze data from an additional SZ participant was excluded due to nearly half of this participant's fixation durations exceeding 2.5 standard deviations of the sample average fixation duration. Eye tracking data was not available for one HC participant due to computer malfunction. The resulting sample size for eye tracking data analysis was 38 SZ and 21 HC.

Prior to analysis, the 8000ms face presentation window was divided into "early" (0–4000ms) and "late" (4000–8000ms) trial epochs. Eye gaze dependent variables were the percentage of dwell time (%DwellTime) and percentage of fixations (%Fixations) to interest areas (IAs) corresponding to salient facial features: the left and right eyes (combined), nose, and

mouth, as well as a composite IA combining the above regions. IAs were selected based on prior research on visual scanpaths during face viewing in HC and SZ and based on studies indicating that the eyes, nose, and mouth regions of the face contain information used to accurately recognize facial expressions⁵⁷. IAs were manually defined for each stimulus image. Separate $2 \times 2 \times 2 \times 5$ ANOVAs (group [HC, SZ] $\times$ epoch [early, late] $\times$ intensity [low, high] $\times$ emotion [anger, fear, happiness, sadness, surprise]) were performed for %Fixations and %DwellTime within each IA.

Correlations

Associations between plasma oxytocin concentration and low intensity, high intensity, and overall facial emotion recognition accuracy were examined separately within each group using Spearman's rank correlation coefficient. Associations between plasma oxytocin and gaze variables within each group were also examined with Spearman correlations. These included %Fixations and %DwellTime to the eyes at early and late trial epochs (based on findings of increased attention to the eyes following intranasal oxytocin administration^{36,37,38}). We also examined the association between plasma oxytocin and %Fixations and %DwellTime to the composite salient facial features area at early and late trial epochs, since this composite IA might better capture overall visual attention to salient social information from the face. Correlations for the HC group were performed after removing a participant with an outlier value for plasma oxytocin; all correlation results were similar when retaining this outlier and these analyses are reported in the supplementary material. Further exploratory correlations were examined between plasma oxytocin and facial emotion recognition accuracy for each emotion category, as well as between plasma oxytocin and %Fixations and %DwellTime to the separate nose and mouth interest areas at each trial epoch, and between plasma oxytocin and %Fixations and %DwellTime

at each IA according to expression intensity level. Associations between plasma oxytocin and clinical functioning in SZ were previously reported elsewhere²². Finally, correlations were also examined between facial emotion recognition accuracy of low and high intensity expressions and gaze variables (%Fixations and %DwellTime to each interest area across trial epochs).

Results

Sample characteristics and plasma oxytocin

Participant characteristics and statistical comparisons are reported in Table 1. Groups did not significantly differ in age, sex, ethnicity, or parental education; however, the SZ group had lower years of education than the HC group, as expected. There were no group differences in oxytocin levels ($p=.107$). However, inspection of the data revealed a single outlier in the control group (z -score of 2.97 above the group mean). After removing this outlier, the group difference was significant ($p=.028$; $\eta_p^2=.08$), with higher oxytocin levels in SZ ($M=20.05\text{pg/ml}$, $SD=7.94$) than HC ($M=15.59\text{pg/ml}$, $SD=5.32$), consistent with our previously published reports using overlapping participant samples^{20,21,22}.

Facial emotion recognition accuracy

There were significant main effects of group (HC > SZ), $F(1,63)=8.08$, $p=.006$, $\eta_p^2=0.11$; intensity, $F(1,63)=1257.83$, $p<.001$, $\eta_p^2=0.95$; and emotion, $F(4,252)=72.55$, $p<.001$, $\eta_p^2=0.54$. There were also significant interactions between group and emotion (HC > SZ for fear and sadness), $F(4,252)=3.90$, $p=.007$, $\eta_p^2=0.06$; group and intensity (HC > SZ for high intensity expressions), $F(1,63)=4.82$, $p=.032$, $\eta_p^2=0.07$; emotion by intensity, $F(3.17,252)=23.24$, $p<.001$, $\eta_p^2=0.27$, and a three-way interaction between group, intensity and emotion, $F(3.17,252)=3.22$, $p=.022$, $\eta_p^2=0.05$. Follow-up pairwise comparisons for the three-way interaction indicated that the SZ group had reduced recognition accuracy compared to the HC group for high-intensity fearful

facial expressions (SZ: $M=59.72\%$, $SD=27.85$; HC: $M=83.57\%$, $SD=16.45$; $p<.001$) and low-intensity sad expressions (SZ: $M=50.00\%$, $SD=24.54$; HC: $M=65.22\%$, $SD=25.83$; $p=.022$) (Figure 1).

Correlations with plasma oxytocin

Correlations examining the association between plasma oxytocin concentration and facial emotion recognition accuracy are presented in Table 2. In the SZ group, plasma oxytocin was positively correlated with overall facial affect recognition accuracy (Figure 3), and separate correlations according to intensity level were significant for high but not low intensity expressions. In contrast, oxytocin in the HC group was not correlated with facial emotion recognition accuracy overall or at either intensity level. Exploratory correlations for each emotion category indicated a significant correlation between oxytocin and accuracy for sad expressions in the SZ group, $\rho(36)=0.37$, $p=.021$ (see supplementary material).

Eye tracking results

Significant eye tracking results involving group differences between HC and SZ are reported in detail below, while eye tracking results involving other factors (emotion, intensity, trial epoch) are reported in the supplementary material. Figures for the full set of eye tracking results are presented in the supplementary material.

Combined salient facial features

For %Fixations, there was a significant group by intensity interaction, $F(1,58)=4.61$, $p=.036$, $\eta_p^2=0.07$, such that the HC group increased their percentage of fixations to salient facial features when viewing low intensity ($M=75.88\%$, $SD=8.33$) compared to high intensity expressions ($M=73.42\%$, $SD=8.26$, $p=.007$), whereas the SZ group did not (low: $M=71.97\%$, $SD=14.05$; high: $M=71.80\%$, $SD=13.59$; $p=.884$). There were also significant main effects of

trial epoch, emotion, and intensity, and an interaction between trial epoch, emotion, and intensity (see supplementary material). There were no significant group-related effects for %DwellTime to salient features; however, there were main effects of trial epoch and emotion (see supplementary material).

Eyes

There were no significant group differences in %Fixations or %DwellTime to the eyes. There were main effects of trial epoch and emotion, and an emotion by intensity interaction for both %Fixations and %DwellTime, as well as a trial epoch by emotion interaction for %Fixations (see supplementary material).

Nose

For %Fixations, there was a significant main effect of group, $F(1,58)=4.67$, $p=.035$, $\eta_p^2=0.07$ (Figure 2). Individuals in the SZ group ($M=32.65\%$, $SD=14.53$) on average had a lower percentage of fixations to the nose region than CNs ($M=40.21\%$, $SD=10.24$). There were also significant main effects of trial epoch and emotion, and a significant interaction between intensity and emotion (see supplementary material).

For %DwellTime, there was a significant main effect of group, $F(1,58)=4.87$, $p=.031$, $\eta_p^2=0.08$; and a significant group by emotion interaction, $F(4,232)=2.63$, $p=.035$, $\eta_p^2=0.04$ (Figure 2). Follow-up analyses indicated that the SZ group had lower dwell time percentages to the nose region than the HC group when viewing angry (HC: $M=42.11\%$, $SD=13.31$; SZ: $M=31.72\%$, $SD=15.66$; $p=.011$), happy (HC: $M=39.60\%$, $SD=12.26$; SZ: $M=30.80\%$, $SD=15.08$; $p=.023$), and sad (HC: $M=41.04\%$, $SD=11.59$; SZ: $M=32.06\%$, $SD=16.21$; $p=.026$) facial expressions. There were additional main effects of trial epoch and emotion, and an intensity by emotion interaction (see supplementary material).

Mouth

For %Fixations, there was a significant group by intensity interaction, $F(1,58)=5.14$, $p=.027$, $\eta_p^2=0.08$. The HC group increased their percentage of fixations to the mouth when viewing low intensity ($M=15.51\%$, $SD=10.15$, $p=.019$) compared to high intensity ($M=14.21\%$, $SD=8.78$) expressions, whereas the SZ group did not (low: $M=15.88\%$, $SD=11.94$; $p=.884$; high: $M=16.08\%$, $SD=11.70$). There was also a significant group by trial epoch interaction, $F(1,58)=6.85$, $p=.011$, $\eta_p^2=0.11$. The HC group made a greater percentage of fixations to the mouth during the early ($M=16.61\%$, $SD=10.48$) compared to the late trial epoch ($M=12.85\%$, $SD=8.39$, $p<.001$), whereas this difference was nonsignificant in the SZ group (early: $M=16.53\%$, $SD=12.05$; late: $M=15.48\%$, $SD=11.74$). Additional main effects of trial epoch, emotion, and the emotion by intensity interaction are reported in the supplementary material.

For %DwellTime to the mouth, there was a significant group by trial epoch interaction, $F(1,58)=4.50$, $p=.038$, $\eta_p^2=0.07$. This was due to the HC group having slightly higher %DwellTime than the SZ group during early face viewing (HC: $M=18.36\%$, $SD=11.75$; SZ: $M=18.14\%$, $SD=13.85$) but lower %DwellTime than the SZ group during late face viewing (HC: $M=14.23\%$, $SD=9.42$; SZ: $M=16.38\%$, $SD=12.99$); however, follow-up pairwise comparisons were not significant and both groups decreased their dwell time to the mouth from the early to late trial epochs. There were also main effects of trial epoch, emotion, intensity, and an emotion by intensity interaction (see supplementary material).

Correlations with plasma oxytocin There were no significant correlations between plasma oxytocin and overall %DwellTime and %Fixations to the eyes or to the composite salient features interest area in the SZ and HC groups (Table 2). Exploratory analyses also did not find any significant associations between oxytocin and gaze variables when examining the other

interest areas of the face (nose, mouth) or when examining associations between oxytocin and gaze to each interest area for low and high intensity facial expressions (see supplementary materials).

Correlations with facial emotion recognition

In the SZ group, facial emotion recognition accuracy was not significantly associated with %Fixations and %DwellTime to any salient facial features (see supplementary materials). However, in the HC group, greater recognition accuracy of low-intensity expressions was associated with increased attention to the mouth at early (%Fixations: $\rho(20)=0.56$, $p=.006$; %DwellTime: $\rho(20)=0.60$, $p=.004$) and late (%Fixations: $\rho(20)=0.50$, $p=.017$; %DwellTime: $\rho(20)=0.57$, $p=.006$) trial epochs, but reduced early %DwellTime to the nose ($\rho(20)=-0.58$, $p=.005$). Gaze behavior was not associated with recognition accuracy of high-intensity expressions (see supplementary materials).

Discussion

The current study examined endogenous oxytocin levels in relationship to facial emotion recognition accuracy and gaze behavior in participants with SZ and HCs. The SZ group had reduced facial emotion recognition accuracy compared to the HC group for high intensity fearful expressions and low intensity sad expressions, and accuracy was qualitatively lower for SZ than HC for most emotional expressions at each intensity level. These findings are consistent with the previously documented difficulties in facial emotion recognition in SZ⁵⁰, and evidence of more pronounced difficulties identifying negative emotional expressions, particularly fear^{58,59}.

In the SZ group, lower overall facial emotion recognition accuracy for high intensity but not low intensity expressions was associated with lower levels of endogenous oxytocin. Both groups generally had low recognition accuracy for the low intensity emotions, potentially

contributing to the lack of association between oxytocin and recognition accuracy for low intensity expressions. The significant association between endogenous oxytocin and facial emotion recognition accuracy in SZ replicates similar findings in women with SZ²⁶ and in SZ patients with neuroendocrine dysfunction¹⁴, and is consistent with studies documenting the association between lower endogenous oxytocin and worse performance on other tasks of social cognition^{18,20,21}. Together, these findings suggest that individual differences in endogenous oxytocin are relevant biological predictors of social cognition in SZ.

The comparison of visual gaze behavior during facial emotion recognition indicated reduced visual attention to the nose region of the face in SZ compared to HC. This is consistent with previous findings of reduced visual attention to salient facial features during facial emotion perception in SZ⁴⁷; however, there were no group visual attention differences to the eyes and mouth regions or for the composite of all the salient facial features. Nonetheless, directing visual attention to the nose region just below the eyes has been found to be the most optimal strategy for face discrimination, including emotional discrimination⁶⁰, potentially suggesting that the SZ group employed a less efficient viewing strategy.

Reduced gaze to salient facial features was not significantly associated with lower endogenous oxytocin in either group. These findings suggest that visual attention to salient features does not mediate the relationship between endogenous oxytocin and facial emotion recognition accuracy in SZ. However, although oxytocin is hypothesized to increase salience to social cues¹², including increasing gaze to the eye region of the face³⁸, this enhanced social salience might also occur without observable changes in gaze behavior; for example, through an increased neural response to the social information under visual focus³⁵. Another possibility is that endogenous oxytocin does not reflect individual differences in social salience sensitivity

despite the enhancing effects of exogenous oxytocin on social salience. Additionally, our findings suggest that lower endogenous oxytocin is not associated with the gaze behavior abnormalities during face viewing that are frequently reported in SZ, and which are believed to contribute to facial emotion recognition difficulties in the disorder. However, the SZ group in our sample did not exhibit prominent abnormalities in visual attention to salient facial features. We would also note that the pattern of correlations between gaze behavior and facial emotion recognition accuracy in the HC group was not observed in the SZ group. Since such associations are not consistently reported in the literature, the precise nature of the relationship between gaze behavior and facial emotion recognition in SZ remains to be determined. To our knowledge, no other study has examined endogenous oxytocin in relation to gaze behavior, and additional studies using other paradigms are needed to further clarify whether endogenous oxytocin is associated with visual attention in SZ.

The SZ group had higher plasma oxytocin than the HC group (after outlier removal), consistent with our previously published findings using an overlapping sample²⁰⁻²². However, prior studies have reported higher, lower, or no difference in oxytocin levels when comparing SZ and HC. This variability across studies suggests that endogenous oxytocin might be a true source of variability across individuals with SZ. Given the positive association between oxytocin and facial emotion recognition, identifying the underlying processes contributing to individual differences in endogenous oxytocin may in turn help to further clarify the nature of facial emotion and other social cognitive difficulties in SZ. This information may also be beneficial to clinical trials of exogenous oxytocin in SZ; for example, in determining responsiveness to oxytocin administration in SZ.

Several limitations must be considered in interpreting the current results. All SZ individuals were taking antipsychotic medications, and we were unable to examine whether antipsychotic dosage influenced plasma oxytocin concentrations. However, the relationship between plasma oxytocin concentration and chlorpromazine equivalent dosage was nonsignificant in overlapping samples of SZ participants²⁰⁻²², suggesting that the observed group differences in plasma oxytocin levels were not due to the effects of antipsychotic medication use. Similarly, the sample size was insufficient to explore the potential influence of other variables on plasma oxytocin levels, including cigarette smoking, biological sex, and diagnosis (e.g., schizophrenia vs. schizoaffective disorder). In addition, we assessed baseline plasma oxytocin, rather than acute changes in oxytocin release during facial emotion perception, and future research is needed to examine whether acute changes in oxytocin release have different associations with gaze behavior and facial emotion recognition. Finally, plasma oxytocin is measure of peripheral oxytocin, which is not consistently correlated with central nervous system (CNS) oxytocin levels⁶¹; therefore, implications of the current results for CNS oxytocin functioning are unclear.

In summary, plasma oxytocin appears to be a marker of facial emotion recognition performance in SZ but is not associated with visual attention during facial emotion perception. Future research is needed to understand the presence of higher levels of plasma oxytocin in SZ despite reduced facial emotion recognition accuracy, and whether endogenous oxytocin levels predict the effect of exogenous oxytocin administration on social cognition, which may inform future clinical trials.

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Tables

Table 1

Participant Characteristics

	Schizophrenia Participants	Healthy Controls	Statistic, <i>p</i> -value
<i>N</i>	42	23	
Age	44.62 (11.05)	43.86 (8.99)	$F(1,62) = 0.08, p = .783$
Gender (Male/Female)	28/14	15/7	$\chi^2(1, N = 65) = 1.87, p = .393$
Ethnicity/Race (%)			$\chi^2(1, N = 65) = 2.93, p = .570$
White	90.47%	91.30%	
Black	4.76%	4.35%	
American Indian or Alaska Native	2.38%	0%	
Mixed Race	2.38%	0%	
Participant Education (years)	12.88 (2.10)	15.14 (1.86)	$F(1,62) = 18.00, p < .001$
Parental Education (years)	13.35 (2.53)	14.11 (2.50)	$F(1,62) = 1.34, p = .251$
Plasma oxytocin (pg/ml)	20.05 (7.94)	16.64 [†] (7.08)	$F(1,56) = 5.08^{\dagger}, p = .028$
Symptoms			
BNSS Total	23.82 (16.55)	—	
BPRS Total	38.03 (9.72)	—	
BPRS Positive	2.37 (1.13)	—	
BPRS Negative	2.13 (1.09)	—	
BPRS Disorganized	1.48 (0.46)	—	
Functional outcome			
LOF Total	19.41 (7.50)	—	
LOF Social	4.82 (2.58)	—	
LOF Work	2.10 (2.81)	—	

Note. Means and standard deviations (in parentheses) presented where appropriate. BNSS = Brief Negative Symptom Scale; BPRS = Brief Psychiatric Rating Scale; LOF = Level of Function Scale.

[†]After outlier removal.

Table 2

Correlations between plasma oxytocin and facial affect recognition, eye tracking variables, and clinical symptoms

	Schizophrenia Participants		Healthy Controls [†]	
	ρ	p	ρ	p
Facial affect recognition accuracy				
Overall	0.44	.006	0.02	.920
High intensity expressions	0.56	<.001	−0.08	.748
Low intensity expressions	0.189	.259	0.11	.637
% Fixations				
Eyes, early epoch	−0.03	.849	0.17	.482
Eyes, late epoch	−0.01	.962	−0.12	.622
Combined salient features, early epoch	−0.18	.310	0.11	.586
Combined salient features, late epoch	−0.26	.139	−0.08	.759
% Dwell Time				
Eyes, early epoch	−0.00	.986	−0.05	.847
Eyes, late epoch	−0.00	.996	−0.03	.892
Combined salient features, early epoch	−0.24	.167	0.00	.994
Combined salient features, late epoch	−0.31	.073	−0.16	.509

Note. [†] After outlier removal.

Figures

Figure 1. Facial emotion recognition accuracy in the SZ and HC groups according to emotion and intensity. Diamonds denote means. Boxplots indicate the median, interquartile range, and outlier points (outside 1.5 times the interquartile range above the upper quartile and below the lower quartile). $*p < .05$. $***p < .001$.

Figure 2. Spearman's rank correlations between facial emotion recognition accuracy and plasma oxytocin (OT) concentration for the schizophrenia group (SZ; $p = .006$) and healthy control group (HC; $p = .920$). Linear fit lines are included for illustration purposes. The outlier in the HC group is denoted in pink.

Figure 3. Dwell time percentage and fixation percentage to the nose region in the SZ and HC groups according to emotional expression. Diamonds denote means. Boxplots indicate the median, interquartile range, and outlier points (outside 1.5 times the interquartile range above the upper quartile and below the lower quartile). Asterisks indicate significant differences at $p < .05$.