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Oxytocin increases eye gaze in schizophrenia

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Abstract

Abnormal eye gaze is common in schizophrenia and linked to functional impairment. The hypothalamic neuropeptide oxytocin modulates visual attention to social stimuli, but its effects on eye gaze in schizophrenia are unknown. We examined visual scanning of faces in men with schizophrenia and neurotypical controls to quantify oxytocin effects on eye gaze.

In a randomized, double-blind, crossover study, 33 men with schizophrenia and 39 matched controls received one dose of intranasal oxytocin (40 IU) and placebo on separate testing days. Participants viewed 20 color photographs of faces while their gaze patterns were recorded. We tested for differences in fixation time on the eyes between patients and controls as well as oxytocin effects using linear mixed-effects models. We also tested whether attachment style, symptom severity, and anti-dopaminergic medication dosage moderated oxytocin effects.

In the placebo condition, patients showed reduced fixation time on the eyes compared to controls. Oxytocin was associated with an increase in fixation time among patients, but a decrease among controls. Higher attachment anxiety and greater symptom severity predicted increased fixation time on the eyes on oxytocin versus placebo. Anti-dopaminergic medication dosage and attachment avoidance did not impact response to oxytocin.

Consistent with findings that oxytocin optimizes processing of social stimuli, intranasal oxytocin enhanced eye gaze in men with schizophrenia. Further work is needed to determine whether changes in eye gaze impact social cognition and functional outcomes. Both attachment anxiety and symptom severity predicted oxytocin response, highlighting the importance of examining potential moderators of oxytocin effects in future studies.

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Contributors

J.D.W. designed the study and supervised data collection. E.R.B. and A.S. managed the literature searches and plan of analysis. AS conducted the statistical analyses with contributions from A.N.N. E.R.B. wrote the manuscript with contributions from A.S. 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.

Keywords

schizophrenia; oxytocin; eye-tracking; social behavior; attachment

1. Introduction

The eyes are central to social communication, allowing us to encode and convey information about attention, emotions, and meaning (Gobel et al., 2015; Itier and Batty, 2009). Humans are sensitive to eye contact from an early age (Symons et al., 1998), and the eyes capture more attention than do other facial features (Farroni et al., 2002; Janik et al., 1978). People with schizophrenia, however, focus less on the eyes when viewing faces and engaging in social interactions (E. Gordon et al., 1992; Loughland et al., 2002; Phillips and David, 1997). They also tend to misjudge where other people are looking (Hooker and Park, 2005) and misinterpret emotional cues from the eyes (Kington et al., 2000; Streit et al., 1997). These impairments have been associated with the negative symptoms (Tso et al., 2012) and social cognitive deficits (Choi et al., 2010; Roux et al., 2014) that negatively impact real-world functioning (Couture et al., 2006; Penn et al., 2000). In addition, others often perceive abnormal eye gaze from people with schizophrenia (Lavelle et al., 2014), leading to negative judgements (Kleinke, 1986; Sasson et al., 2017) that contribute to social exclusion and may ultimately exacerbate psychotic symptoms (Selten et al., 2017). Though eye gaze is a clinically relevant measure of effective social interaction (Conner, 2004) and potentially a high-yield treatment target (Combs et al., 2011; Dadds et al., 2008), we lack interventions that address abnormal eye gaze in schizophrenia.

Oxytocin, an evolutionarily conserved neuropeptide that influences a wide range of social behaviors (Bethlehem et al., 2013), plays a central role in fine-tuning sensory systems (Marlin et al., 2015; Oettl et al., 2016) and may have effects on eye gaze specifically. In non-human primates, oxytocin receptors are found in regions that modulate visual attention (Freeman et al., 2014), and in multiple animal species, oxytocin influences visual signal processing and attention shifts during social interactions (Nagasawa et al., 2015; Rault et al., 2017). Administration of oxytocin enhances eye gaze in non-human primates (Kotani et al., 2017; Putnam et al., 2016), neurotypical humans (Domes et al., 2013b; Guastella et al., 2008a; Hubble et al., 2017a), and those with autism spectrum disorder (ASD; Andari et al., 2010b; Auyeung et al., 2015). Furthermore, oxytocin has been shown to heighten perception of information concentrated in the eye region: administration in neurotypical humans improves the ability to recognize emotions (Marsh et al., 2010; Schulze et al., 2011) and interpret mental states from the eyes (Domes et al., 2007b). Thus, modulation of eye gaze may be a potential mechanism by which oxytocin impacts social behavior (Guastella et al., 2008b).

Abnormal eye gaze in schizophrenia may be related to oxytocin system dysregulation, which has been implicated in the pathophysiology of the disorder. In animal models, oxytocin influences correlates of both positive (Caldwell et al., 2009; Feifel and Reza, 1999) and negative symptoms (Meziane et al., 2015; Peñagarikano et al., 2015). In humans, oxytocinergic gene variants (Montag et al., 2013) as well as abnormal levels of plasma (Kéri

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et al., 2009) and cerebrospinal fluid (CSF; Sasayama et al., 2012) oxytocin have been observed in schizophrenia. These findings have motivated clinical studies examining the effects of intranasal oxytocin in schizophrenia, several of which highlight the possibility that oxytocin may improve social cognitive deficits in schizophrenia by influencing visual exploration of faces. For example, oxytocin administration has been shown to improve mentalizing, the ability to infer the beliefs and intentions of other people (Burkner et al., 2017a; Woolley et al., 2014a). Mentalizing depends on processing multiple social cues, including information concentrated in the eye region (Baron-Cohen et al., 2001; Schyns et al., 2016). To our knowledge, however, no studies have investigated whether oxytocin specifically impacts the abnormal eye gaze associated with schizophrenia.

To address this gap, we examined the effects of oxytocin administration on spontaneous eye movements during viewing of faces among patients with schizophrenia and healthy controls using a randomized, placebo-controlled, double-blind, crossover design. We used eye-tracking to provide a high temporal resolution psychophysiological measure of visual attention (Manor and E. Gordon, 2003), and specifically quantified fixation time on the eyes. We hypothesized that patients would spend less time looking at the eyes compared to controls in the placebo condition, and that oxytocin would increase time spent looking at the eyes in both patients and controls. Because response to oxytocin administration depends on multiple factors that may reflect endogenous oxytocin system functioning (Bartz et al., 2015; Bradley and Woolley, 2017), we also examined whether attachment style, symptom severity, and anti-dopaminergic medication use predicted the effect of oxytocin on time spent looking at the eyes.

2. Methods and Materials

2.1 Participants

We recruited 33 men with schizophrenia confirmed by the Structured Clinical Interview for DSM-IV and 39 age-matched healthy controls from outpatient clinics in the San Francisco Bay Area. Patients were clinically stable, with no medication changes 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 no reported visual impairments that could not be corrected by glasses or contact lenses. All participants gave informed consent in accordance with the University of California, San Francisco Institutional Review Board.

2.2 Procedures

On each study day, which were separated by at least one week, a technician administered 40 IU oxytocin or saline placebo (Wellspring Pharmacy, Berkeley, CA) intranasally according to a standardized procedure (Guastella et al., 2013). We selected 40 IU based on prior work by our group (Bradley et al., 2019; Woolley et al., 2017a; 2014b; 2015) as well as findings from a recent study that identified 36-48 IU as optimal in schizophrenia (Wynn et al., 2018). Participants completed a passive viewing task beginning ~50 minutes and concluding ~60 minutes following drug administration.

For the passive viewing task, participants were seated approximately 70 cm in front of a monitor and instructed to look freely at a series of 20 color photographs of faces displaying direct gaze (Figure 1). On each study day, participants were randomly assigned to view one of two matched sets of photographs. Each set contained faces with different emotional expressions: six fearful faces, seven happy faces, and seven neutral faces. The order of faces was randomized for each participant. For each each trial, participants had to maintain visual fixation on a cross to trigger display of the face. The face then appeared for 5 seconds. We recorded eye gaze patterns throughout the task with the Eyelink II tracker (SR Research, Ontario, Canada) using a sampling rate of 500 per second. The Eyelink II outputs actual gaze position on the display screen, using a head-position compensation system combined with an initial calibration using a 3 × 3 target display. Per-participant per-day average calibration error was 0.88 (1.30) degrees, which is within acceptable limits (SR Research Ltd, 2009).

2.3 Measures

2.3.1 Eye-tracking—We quantified total fixation time on the eyes, considered to be sum of the right and left eyes of each face, for each trial.

2.3.2 Positive and Negative Symptom Scale—We administered the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987) at baseline to assess symptoms of schizophrenia in patients.

2.3.3 Chlorpromazine equivalents—Given that anti-dopaminergic medication may influence oxytocin effects (Woolley et al., 2014a; 2017b) and changes in dopamine levels may disrupt oculomotor control (Egaña et al., 2013), we quantified anti-dopaminergic medication use using chlorpromazine (CPZ) equivalents (Andreasen et al., 2010). For two patients, dosage could not be confirmed; they were excluded from this analysis.

2.3.4 Experiences in Close Relationships—Given that attachment style has been shown to moderate the effect of oxytocin administration (Bartz et al., 2015; Mitchell et al., 2016), we assessed attachment using the Experiences in Close Relationships-Relationships Structures (ECR-RS) scale, (Fraley et al., 2011) which quantifies attachment avoidance (internal reliability within our sample: Cronbach's alpha = 0.93), and attachment anxiety (Cronbach's alpha = 0.89).

2.4 Statistical analyses

We analyzed fixation time on the eyes with linear mixed-effects models (Bates et al., 2015) in R (R Core Team). Fixation time was a continuous outcome variable; group (patients and controls), emotion (fearful, happy, and neutral), and drug (oxytocin and placebo) were fixed effect factors. Attachment anxiety, attachment avoidance, CPZ equivalents, and symptom severity were continuous fixed effect predictors. Participant was a random effect factor in all models. We included a random slope for drug effects where drug was included in the model. *P*-values were obtained by Satterthwaite approximations to degrees of freedom, which minimizes type I error and is not overly sensitive to sample size (Kuznetsova et al., 2017; Luke, 2017).

3. Results

3.1 Preliminary analyses

3.1.1 Demographic data—We found no differences in age, attachment anxiety, or attachment avoidance between patients and controls (Table 1). We did not match groups on education given that decreased educational attainment is a consequence of schizophrenia, and matching may therefore obscure group differences and generate misleading results (Resnick, 1992).

3.1.2 Emotion—Prior studies suggest that emotion may modulate gaze patterns (Hunnius et al., 2011) and oxytocin effects on gaze (Domes et al., 2013b; Hubble et al., 2017a). To avoid potential confounds, we tested the effect of stimulus emotion on fixation time on the eyes. The drug x group x emotion interaction was not significant ($p = .52$). We then examined whether emotion moderated oxytocin effects on fixation time regardless of group. The drug x emotion interaction was not significant ($p = .586$). We then examined whether emotion affected fixation time regardless of drug or group. Participants showed reduced fixation time on the eyes of happy ($b = -124.14$ milliseconds, $t = -3.15$, $p = .002$) and fearful ($b = -106.61$ milliseconds, $t = -2.60$, $p = .009$) faces compared to neutral faces. Given that emotion did not interact with group or drug, we collapsed across emotion for subsequent analyses.

3.2 Group differences in fixation time on placebo

As expected, patients showed reduced fixation time to the eyes compared to controls in the placebo condition ($b = -406.99$ milliseconds, $t = -2.36$, $p = .021$).

3.3 Effects of oxytocin

Next, we tested our main hypothesis that oxytocin would increase fixation time on the eyes in both patients and controls. The drug x group interaction was significant ($b = 425.25$ milliseconds, $t = 3.49$, $p < .001$) such that patients showed increased fixation time on oxytocin compared to placebo ($b = 226.37$ milliseconds, $t = 2.52$, $p = .014$), but controls showed decreased fixation time on oxytocin compared to placebo ($b = -198.88$ milliseconds, $t = -2.41$, $p = .019$; Figure 2).

3.4 Moderation of oxytocin effects

Finally, we tested factors that potentially moderate oxytocin effects on fixation time on the eyes.

3.4.1 Attachment—The drug x group x ECR attachment anxiety score interaction was not significant ($p = .776$). We then examined whether attachment anxiety moderated oxytocin effects regardless of group. The interaction between drug and attachment anxiety was significant ($b = 157.39$ milliseconds, $t = 2.94$, $p = .004$; Figure 3A). Fixation time on the eyes decreased with increasing attachment anxiety at a trend level on placebo ($b = -134.35$ milliseconds, $t = -1.79$, $p = .078$), but not on oxytocin ($b = 23.04$ milliseconds, $t = 0.31$, $p = .759$). At one standard deviation below our sample's mean attachment anxiety score, participants showed decreased fixation time on oxytocin compared to placebo ($b = -187.76$

milliseconds, $t = -2.13$, $p = .037$). At one standard deviation above the mean, participants showed increased fixation time on oxytocin compared to placebo ($b = 179.81$ milliseconds, $t = 2.04$, $p = .045$). The simple effect of drug was not significant at mean attachment anxiety ($p = .949$).

We then examined whether differences in attachment anxiety explained the group difference in oxytocin response, testing a model including both drug x group and drug x attachment anxiety interactions. The drug x group ($b = 371.83$ milliseconds, $t = 3.11$, $p = .003$) and drug x attachment anxiety ($b = 128.94$ milliseconds, $t = 2.51$, $p = .014$) interactions both independently predicted fixation time on the eyes.

There was no significant drug x group x attachment avoidance interaction ($p = .411$), or drug x attachment avoidance interaction ($p = .167$).

3.4.2 Symptom severity—

The drug x PANSS score interaction was significant ($b = 18.90$ milliseconds, $t = 3.27$, $p = .003$). Fixation time on the eyes increased with increasing PANSS score in the oxytocin condition ($b = 22.52$ milliseconds, $t = 2.72$, $p = .011$), but not in the placebo condition ($b = 3.62$ milliseconds, $t = 0.38$, $p = .703$). Participants showed increased fixation time on the eyes on oxytocin compared to placebo at both our sample mean PANSS score ($b = 226.37$ milliseconds, $t = 2.96$, $p = .006$) and one standard deviation above the mean ($b = 480.36$ milliseconds, $t = 4.41$, $p < .001$), but not at one standard deviation below the mean ($b = -27.62$ milliseconds, $t = -0.25$, $p = .802$; Figure 3B). Results were similar for each subscale of the PANSS.

3.4.3 Anti-dopaminergic medication dosage—

There was no significant drug x CPZ equivalents interaction ($p = .382$).

See Supplemental Material for details and additional analyses.

4. Discussion

We found that men with schizophrenia looked at the eyes less than neurotypical controls, consistent with evidence of diminished attention to salient facial features in schizophrenia (Manor et al., 1999; Williams et al., 1999). A single dose of intranasal oxytocin enhanced eye gaze among patients, suggesting that oxytocin increased visual attention to the part of the face richest in social information. In contrast, oxytocin decreased eye gaze in controls. We also found that higher attachment anxiety predicted response to oxytocin in both patients and controls, with participants with higher attachment anxiety showing enhanced eye gaze on oxytocin compared to placebo. However, attachment anxiety did not explain the group difference in response to oxytocin; both having schizophrenia and higher attachment anxiety independently predicted oxytocin response. Finally, more severe symptoms, but not higher dosage of anti-dopaminergic medication, predicted greater response to oxytocin. Together, these results suggest that oxytocin administration may increase visual attention to socially relevant information in men with schizophrenia and provide further evidence that multiple factors moderate the response to exogenous oxytocin.

The mechanisms underlying diminished eye gaze in schizophrenia are not fully understood, but may stem from aberrant salience processing that drives visual attentional biases. People with schizophrenia demonstrate hypersensitivity to threat (Bentall and Kaney, 2011; Blackwood et al., 2001), experiencing elevated arousal (Llerena et al., 2012) and aversion (Cohen and Minor, 2010) in response to neutral stimuli. These biases may reflect dysregulation of the amygdala, a key component of neural circuits modulating salience processing (Love, 2014): schizophrenia is associated with aberrancies in baseline amygdala activity (Anticevic et al., 2012; Pinkham et al., 2015), amygdala activation (Hall et al., 2008; Taylor et al., 2012), and amygdala-frontal functional connectivity (Bjorkquist et al., 2016) in response to social stimuli. During visual scanning, the amygdala plays a critical role in conveying feedback to the visual cortex (Adolphs et al., 1998) and recruiting attention to relevant stimuli (M. J. Green and Phillips, 2004). Patients' diminished eye gaze may reflect aberrant processing of faces due to amygdala dysfunction that results in automatic, unconscious biases to perceive threat in the eyes (M. J. Green and Phillips, 2004). This initial perceived threat may activate a stress response, subsequently driving visual avoidance of the eyes to reduce anxiety (Alvares et al., 2012). Evidence of unconscious amygdala hyperactivation in response to faces (Lindner et al., 2016; Rauch et al., 2010) and avoidance of faces specifically during later stages of visual processing (Jang et al., 2016) in schizophrenia support this hypothesis. Notably, the fact that we used photographs of unfamiliar faces (Gobbini and Haxby, 2006) with direct gaze (Emery, 2000) may have exacerbated threat perception among patients.

Enhanced eye gaze on oxytocin could then reflect decreased threat perception from the eyes, leading to reduced visual avoidance among patients. This may result from dampened amygdala reactivity, as animal (Huber, 2005; N. Liu et al., 2015) and human studies (Kanat et al., 2015; Petrovic et al., 2008) suggest that oxytocin impacts salience processing via modulation of amygdala activity. Oxytocin knockout mice have social recognition impairments that are reversed by oxytocin infusion into the amygdala (Ferguson et al., 2001; 2000), and oxytocin administration modulates amygdala activation in response to emotional faces in healthy humans (Domes et al., 2007a; Kirsch et al., 2005; Quintana et al., 2016) and in those with schizophrenia (Shin et al., 2015). Importantly, oxytocin-induced changes in amygdala activation have been linked to changes in visual attention to faces (Gamer et al., 2010). There is also evidence that oxytocin modulates functional connectivity of the amygdala to frontal regions (Dodhia et al., 2014; Koch et al., 2016; Labuschagne et al., 2010), as well as to the insula and middle/dorsal anterior cingulate cortex—regions implicated in processing emotional stimuli (Gorka et al., 2015). Furthermore, oxytocin has anxiolytic properties (Alvares et al., 2012; Ebitz et al., 2013), attenuating hypothalamic–pituitary–adrenal axis activity (Cardoso et al., 2014; Neumann, 2002) and facilitating release of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the amygdala to disrupt signaling necessary for fear responding (Viviani and Stoop, 2008). Together, these findings suggest that oxytocin may have increased eye gaze among patients by reducing the tendency to perceive threat from and avoid the eyes.

The amygdala is a central target of the dopamine system (Ross and Young, 2009) and is thought to mediate oxytocin-dopamine interactions (Skuse and Gallagher, 2009) that play a central role in motivation (Love, 2014) and may also underlie our findings. The mesolimbic pathway is responsive to oxytocin (Kohli et al., 2018; Shahrokh et al., 2010), and regions receiving dopamine projections are hubs for oxytocin effects on functional connectivity (I. Gordon et al., 2016; Rilling et al., 2018). Through modulation of dopamine signaling, oxytocin may have shifted the salience of facial stimuli (Aragona and Wang, 2009; Groppe et al., 2013), boosting motivation to pursue social information (Caldwell and Albers, 2016) and thereby enhancing eye gaze among patients. Though we did not find an association between anti-dopaminergic medication dosage and oxytocin effects here, we have previously observed that higher dosages of anti-dopaminergic medication correlate with decreased oxytocin effects in schizophrenia (Woolley et al., 2015; 2017c) and higher dosages of anti-dopaminergic medication have been associated with lower endogenous oxytocin levels (Goldman et al., 2008; Sasayama et al., 2012). However, the neurobiological underpinnings of these relationships are unclear. Given the complexity of oxytocin-dopamine interactions, this is an area requiring significant further study. In sum, multiple mechanisms may underlie our finding that oxytocin enhanced eye gaze in patients, as oxytocin likely modulates activity across neural networks that regulate social behavior.

Though the oxytocin effect we observed in patients is similar to effects in people with ASD (Andari et al., 2010a; Auyeung et al., 2015; Kanat et al., 2017), our findings in healthy controls are inconsistent with prior studies (Gamer et al., 2010; Guastella et al., 2008b; Hubble et al., 2017b). The 40 IU dosage that we administered may account for this, as prior studies used 24 IU and oxytocin effects vary with dosage (Cardoso et al., 2013; Quintana et al., 2015). Although it has the highest affinity for the oxytocin receptor (Busnelli et al., 2012), oxytocin also binds to arginine vasopressin receptors (Chini and Manning, 2007) at high dosages, which can precipitate a heightened stress response (Neumann and Landgraf, 2012). Thus, 40 IU may have been excessive in controls, generating increased vigilance that led to avoidance of the eyes. As dose-response curves for intranasal oxytocin are not yet well-established, further work using multiple dosages is needed to test this hypothesis. Previous studies in people with schizophrenia (Shin et al., 2015; Woolley et al., 2014a) and ASD (Domes et al., 2013a; Kanat et al., 2017) have also found different oxytocin effects in patients versus controls, possibly reflecting endogenous oxytocin system dysfunction in disorders characterized by abnormal social behavior (Bartz et al., 2011; Spengler et al., 2017). This may also explain our finding that patients with more severe symptoms showed greater eye gaze enhancement on oxytocin. The fact that attachment anxiety predicted oxytocin response further supports the endogenous oxytocin system's role in moderating the effect of exogenous oxytocin (Bartz et al., 2010; Mitchell et al., 2016). Early life adversity leads to decreased oxytocin receptor density and CSF oxytocin concentration in animals (Champagne, 2010; Winslow et al., 2003), and is linked with altered amygdala-prefrontal functional connectivity (Fan et al., 2014) and abnormal oxytocin system function (Toepfer et al., 2017) in humans. Thus, in participants with high attachment anxiety, endogenous oxytocin system dysfunction may account for the diminished eye gaze on placebo and greater response to oxytocin that we observed. Though we excluded participants with recent substance abuse, lifetime history of a substance use disorder may be important for future studies to examine as another potential moderator given the links between endogenous oxytocin system function and vulnerability to addition (Baracz et al., 2018). Overall, the

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variability in oxytocin response suggests that the relationship between the oxytocin system and the pathophysiology of abnormal social behavior warrants further investigation.

It will also be important to determine whether enhanced eye gaze is one of the mechanisms that drives oxytocin-induced improvements in social cognition in schizophrenia. Deficits in visual attention to social stimuli (Y. Liu et al., 2016; Matsumoto et al., 2015) and the ability to detect eye contact (Tso et al., 2012) are associated with negative symptoms, and may impact functioning in schizophrenia via effects on social cognition (M. F. Green et al., 2012). For example, in people with schizophrenia, impaired performance on a mentalizing task that required reading cues from faces was entirely attributable to a lack of visual attention to the eyes (Roux et al., 2014). Interestingly, meta-analytic findings suggests that oxytocin selectively improves mentalizing ability in schizophrenia (Burkner et al., 2017b). Thus, oxytocin may affect social cognition in schizophrenia by enhancing visual attention to social stimuli that ultimately facilitates higher-level social cognitive processes such as mentalizing. Impaired mentalizing is a core deficit in schizophrenia (Fett et al., 2011) that predicts diminished social skills and poor social functioning (Bora et al., 2009). Thus, oxytocin-enhanced eye gaze that improves mentalizing may contribute to improved functional outcomes. This is speculative, however; as we did not link oxytocin-induced enhancement of eye gaze to social cognition or behavior, its functional consequences are unclear and must be explored in future work.

This study has other important limitations. First, we included only men to reduce heterogeneity given oxytocin's sexually dimorphic effects (Dumais et al., 2013; Gao et al., 2016). The few studies conducted with women have found varying oxytocin effects on eye gaze (Bertsch et al., 2013; Domes et al., 2010; Lischke et al., 2012a) and oxytocin may have different effects on amygdala reactivity to emotional stimuli in men and women (Lischke et al., 2012b). Second, we screened participants for impaired vision using a questionnaire and verified that they used appropriate corrective lenses or glasses during the passive viewing task, but cannot rule out the possibility of undiagnosed visual impairments that could have impacted gaze duration. Third, passively viewing faces does not reflect the dynamics of interaction with another person. Further study is needed to assess eye gaze using ecologically valid paradigms that capture real-world social interactions. Fourth, given our small sample size, findings must be replicated and extended by others.

Our findings suggest that intranasal oxytocin optimizes processing of social stimuli in men with schizophrenia by directing visual attention to the eyes, possibly due to decreased threat perception and heightened social motivation. Oxytocin may have utility as a treatment for abnormal eye gaze in schizophrenia, but further work is needed to link enhanced eye gaze to relevant clinical outcomes. Given that abnormal eye gaze is found in multiple neuropsychiatric disorders (Leppanen et al., 2017), future work using eye-tracking may help to elucidate common mechanisms and identify new treatment targets across diagnoses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of stimuli used in the passive viewing task. Photographs were drawn from the NimStim set (Tottenham et al., 2009). Photographs were cropped so that only the face was visible.

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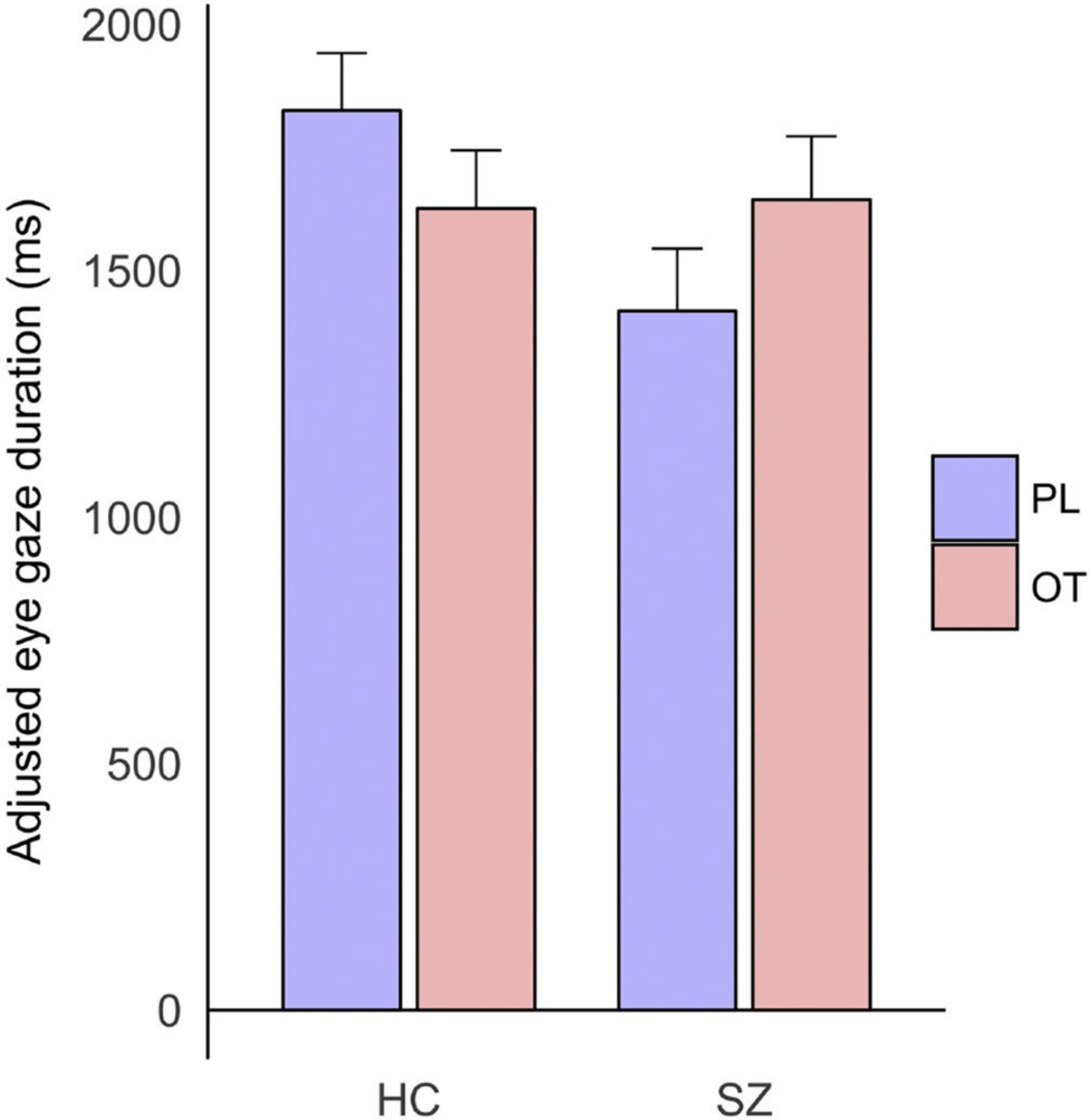

Figure 2.

Oxytocin effects on fixation time on the eyes. Modeled data are shown, with standard error bars. HC = healthy controls; SZ = participants with schizophrenia. PL = placebo; OT = oxytocin.

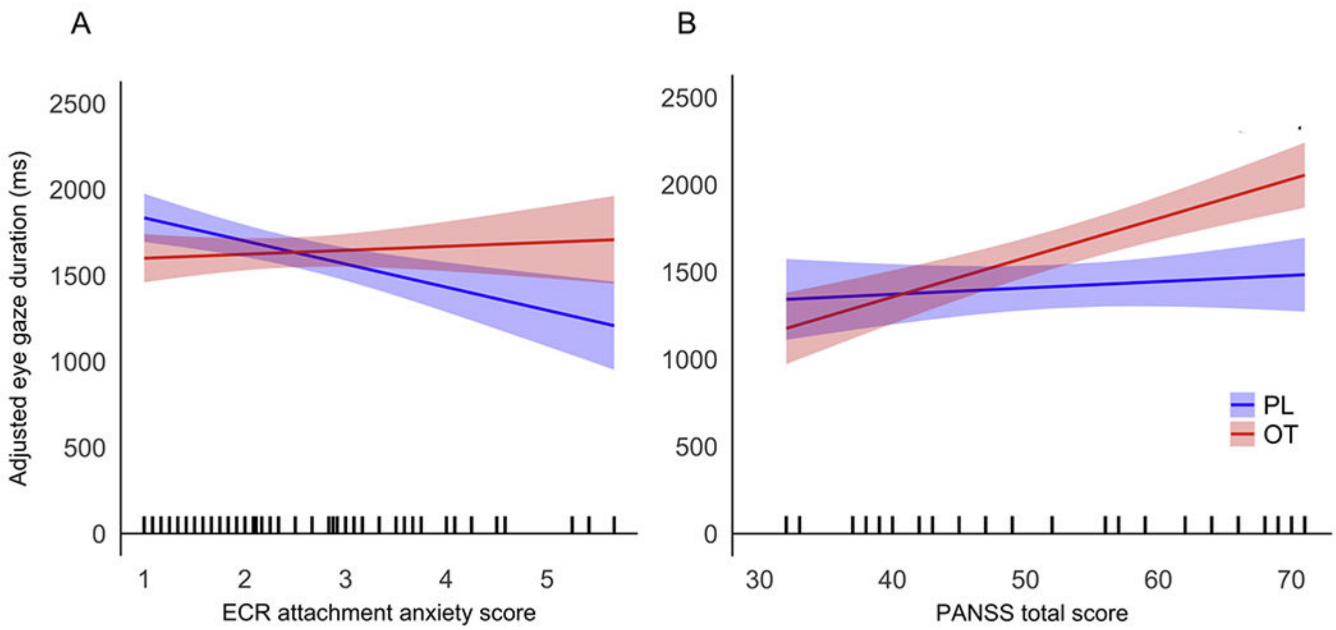

Figure 3.

Moderation of oxytocin effects by attachment anxiety and symptom severity. Modeled data are shown, with standard error bands. Tick marks on the x axis indicate individual participants' scores. A) Effect of the Experiences in Close Relationships (ECR) scale attachment anxiety score on fixation time on the eyes. B) Effect of total Positive and Negative Symptom Scale (PANSS) score on fixation time on the eyes.

Table 1.

Demographics and clinical information.

	Schizophrenia (n=33)	Controls (n=39)	Controls vs. Schizophrenia
	Mean (SD)	**Mean (SD)**	
Age	40.3 (15.5)	39.8 (13.7)	$p = 0.88$
Education years	13.9 (2.2)	16.1 (2.1)	$p < 0.001$
ECR score			
Attachment anxiety	2.7 (1.2)	2.3 (1.1)	$p = 0.14$
Attachment avoidance	3 (1.1)	3.1 (1)	$p = 0.86$
PANSS score			
Positive subscale	12.8 (5)	-	-
Negative subscale	14 (5.2)	-	-
General subscale	26 (6.9)	-	-
CPZ equivalents	239.8 (245.7)	-	-