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Research Paper

The importance of pro-social processing, and ameliorating dysfunction in schizophrenia. An FMRI study of oxytocin

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ABSTRACT

Schizophrenia is often a severe and debilitating mental illness, frequently associated with impairments in social cognition that hinder individuals' abilities to relate to others and integrate effectively in society. Oxytocin has emerged as a putative therapeutic agent for treating social deficits in schizophrenia, but the mode of action remains unclear. This placebo-controlled crossover study aimed to elucidate the neural underpinnings of oxytocin administration in patients with schizophrenia. 20 patients with schizophrenia were examined using functional magnetic resonance imaging under oxytocin (40 IU) or placebo nasal spray. Participants performed a stochastically rewarded decision-making task that incorporated elements of social valence provided by different facial expressions, i.e. happy, angry and neutral. Oxytocin attenuated the normal bias in selecting the happy face accompanied by reduced activation in a network of brain regions that support mentalising, processing of facial emotion, salience, aversion, uncertainty and ambiguity in social stimuli, including amygdala, temporo-parietal junction, posterior cingulate cortex, precuneus and insula. These pro-social effects may contribute to the facilitation of social engagement and social interactions in patients with schizophrenia and warrant further investigation in future clinical trials for social cognitive impairments in schizophrenia.

1. Introduction

Schizophrenia is often a severe and debilitating mental illness, frequently associated with impairments in social cognition, such as emotion perception, theory of mind, empathy, attributional style and social decision-making, which hinder individuals' abilities to relate to others and integrate effectively in society (Fett et al., 2011; Penn et al., 2000). There are significant associations between social cognitive abilities and the functional outcomes of schizophrenia, suggesting that therapeutic interventions that remediate social cognition may in turn improve the long-term prognosis of the disorder (Fett et al., 2011). However, such therapeutic interventions are not currently available, as social cognitive impairments are not effectively treated by antipsychotic medications (Penn et al., 2009; Sergi et al., 2007) and existing psychosocial interventions show limited gains (Kurtz and Richardson, 2012).

Oxytocin (OXT), a hormone involved in parturition, lactation, and parental bonding (Insel and Young, 2001), has shown pro-social effects in healthy individuals. For example, OXT increases the amount of time spent gazing at socially relevant regions of the face (Guastella et al., 2008), it increases cooperation between in-group members (De Dreu et al., 2011), it attenuates the aversive aspects of negative social interactions and increases trust and generosity without influencing risk-taking (Baumgartner et al., 2008; Kosfeld et al., 2005). These effects are hypothesised to be mediated through the interactions of OXT with mesolimbic dopamine (DA) (Shamay-Tsoory and Abu-Akel, 2016).

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Recently oxytocin has gained momentum as a potential treatment for psychiatric conditions such as PTSD and substance disorder treatments. Several studies have examined the effects of OXT on social cognitive abilities in schizophrenia with promising results (Feifel et al., 2016). For example, intranasal OXT improved the ability of patients with schizophrenia to recognise facial emotions (Averbeck et al., 2012), make social judgements (Pedersen et al., 2011), recognise humour and sarcasm (Davis et al., 2013) and kinship (Fischer-Shofty et al., 2013). OXT also increased empathic accuracy (Davis et al., 2014) and improved the ability of individuals with schizophrenia to empathise with peers (Abu-Akel et al., 2014).

However, not all data have replicated such findings, and there remains a lack of consensus on how reliable and robust the effects of exogenous administration are upon both healthy and clinical populations. Bradley and Woolley (2017) reviewed the extant literature on the topic, and noted two critical challenges for the field. The first is the complexity of neuroendocrine functioning, wherein downstream effects post-OXT administration may be varied and difficult to fully elucidate; this is amplified by study variation in the key issue of single or multiple OXT dosing, and how this might differentially affect functioning. The second has been the variability in the choice of outcome markers used in schizophrenia, itself a notably heterogeneous condition – and trials vary in inclusion/exclusion criteria on key factors including age, gender, medications and so forth - limiting cross-comparison of trials and potentially challenging study validity. This latter difficulty has been further highlighted in a multilevel Bayesian meta-analysis by Burkner et al. (2017) that found an overall improvement in social cognition, but highlighted that this was significantly larger in 'high level' social cognition tasks (for example, theory of mind and mentalising) than in 'lower level' ones (such as social cue perception). Fundamentally, the pharmacokinetics and pharmacodynamics of exogenous OXT remain incompletely understood (Leng and Ludwig, 2016). The US National Institute of Mental Health (NIMH) has called for better 'target engagement', showing a measurable physiological effect, correlating with improved clinical outcomes in the field (Insel, 2016).

Most tasks used researching OXT have focused on how social feedback influences responses. Our study differs in that it is a cognitive task introducing a social variable which, to a rational observer, should have no bearing on performance. However, we have demonstrated over multiple studies that this social variable exacerbates decision making in a very specific domain (happy vs angry faces) (Averbeck and Duchaine, 2009; Evans et al., 2011) and that this deviation can be mitigated in healthy controls using intranasal OXT (Evans et al., 2010). These studies employed a forced-choice, stochastically rewarded decision-making task that incorporated elements of social valence provided by different facial expressions to show that the emotional information contained in the face influenced task performance. Healthy individuals and participants with schizophrenia demonstrated a stronger preference for happy relative to angry faces, even when the angry face was more financially rewarding (Averbeck and Duchaine, 2009; Evans et al., 2011). However, patients with schizophrenia were even more averse toward choosing the angry faces than the healthy controls (Evans et al., 2011). Interestingly, intranasal OXT mitigated this bias in healthy individuals by increasing the probability of choosing an angry face when it was associated with reward, thereby decreasing their aversion to angry faces (Evans et al., 2010).

Functional neuroimaging studies in healthy participants and individuals with schizophrenia during the processing of social stimuli following administration of a single dose of intranasal OXT have shown alterations in activation of social brain regions, including temporal lobe structures, such as the middle and superior temporal gyri, the fusiform gyrus, limbic and associated regions such as the amygdala, the prefrontal and anterior cingulate cortices and the insula (Wigton et al., 2015). However, there has been variation between studies, and the neural effects of OXT on social brain regions in schizophrenia are yet to be fully elucidated in both health and patient cohorts and results have been mixed (Williams and Burkner, 2017). For example, Shin et al. (2015) showed attenuation of neural activity in the amygdala in response to perception of happy and fearful faces, whilst conversely (Abram et al., 2020) demonstrated enhanced amygdalar activation, returning toward normalised functional connectivity, in a patient cohort. In a theory of mind task, (De Coster et al., 2019) showed OXT increased behavioural accuracy, correlated with enhanced right temporo-parietal junction activity, in patients compared with health controls, the former also showing greater medial prefrontal cortical activation than those administered placebo. In terms of facial emotion recognition, (Dey and Rao, 2017) found that, compared with placebo, single-dose OXT altered brain regions involved in emotion processing in a cohort of 12 patients with schizophrenia, though no differences were determined in terms of the accuracy of emotion recognition.

In the present study, we sought to investigate the neural and behavioural effects of a single dose of intranasal OXT during decisions incorporating facial affect in individuals with schizophrenia. Based on the evidence above, we hypothesised that patients with schizophrenia would show a bias toward selecting the happy face, even when financial feedback supported the angry face as the optimal choice and that OXT would attenuate this bias; this will be accompanied by attenuation of neural activity in regions implicated in facial emotion recognition, mentalising and social decision-making, such as the amygdala and associated brain regions.

2. Methods

2.1. Participants

20 right-handed male patients with an ICD-10 (WHO, 1992) diagnosis of schizophrenia or schizoaffective disorder were recruited from local mental health teams. Female participants were not included as it was considered that this could have potentially confounded the results given previous findings of sex effects of OXT in neuroimaging studies (Wigton et al., 2015). Inclusion of a control group of healthy individuals was not absolutely necessary given the double-blind placebo-controlled within-subject crossover design, where every patient was their own 'control'. Additionally we sought to study the effects of OXT in schizophrenia, having already researched the effects in a healthy sample (Evans et al., 2010, 2011). Demographic information is presented in Table 1. Intelligence quotient (IQ) was measured using the two-item Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Diagnosis of the patients with schizophrenia was confirmed by assessment of case notes and by correspondence with each individual's consultant psychiatrist. Symptom severity in these patients was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Table 1
Demographic and clinical characteristics.

	Patients with schizophrenia (N = 20) (mean (SD))
Age (years)	37.90 (7.43)
WASI IQ	98.85 (13.24)
NS-SeC	2.80 (1.70)
Gender	20M
Age at onset (years)	24.50 (6.48)
Duration of illness (years)	13.40 (6.53)
CPZ equivalents	430.05 (236.27)
PANSS	
Positive symptoms	14.95 (4.97)
Negative symptoms	18.30 (4.99)
General symptoms	30.70 (7.10)
Total	63.95(14.65)

IQ = Intelligence quotient; M = Male; F = Female; SD = Standard deviation.
WASI = Wechsler Abbreviated Scale of Intelligence.
NS-SeC = National Statistics Socio-economic Classification 1) (1).
CPZ = Chlorpromazine equivalent 2).

Participants were excluded if they: exhibited any significant visual or hearing impairments; suffered from any neurological disorders; reported any drug dependencies over the last 6 months. Patients with schizophrenia were all stable on their current medication with no changes over the last 6 months. Written informed consent was obtained from all subjects after complete description of the study. Participants were compensated for their participation in the study on completion of the testing. The study was approved by the Camberwell and St. Giles Research Ethics Committee, London. All experiments were performed in accordance with the relevant guidelines and regulations.

2.2. Task

Subjects undertook a stochastically rewarded decision-making task incorporating faces of varying social valence as used in our earlier studies (Averbeck and Duchaine, 2009; Evans et al., 2010; Evans et al., 2011; Furl et al., 2012). Participants were assessed twice, one week apart; each visit consisted of a neuroimaging scan, comprising two sessions each with four stimuli blocks of 30 trials. Blocks consisted of either happy-angry (emotionally valenced block) or neutral-neutral (neutral block) face trials. In each trial, two faces were presented on a screen: in the emotionally valenced block, happy and angry faces were of the same identity, in the neutral face block they were of different identities. Identities were kept consistent in the emotionally valent block to avoid any confounding preferences toward any one identity, and emotionally valenced identities were balanced across blocks. The same identities used for the emotionally valenced blocks were also used in the neutral block. Probabilities were assigned to the faces at the beginning of each block such that one face would "win" 60% of the time, the other face 40%. This was designed so that the angry face won more in half of the blocks, and the happy face won more in the other half; with analogous distribution between the two neutral faces with each identity winning at the same 60/40 split in half the blocks. Stimulus block presentation, face order (left or right of screen), and the probability of a face winning, were counterbalanced across participants and visits. At the start of each block, participants were instructed that one face was more likely to win, and that they were to pick the face which, at that time, they believed this to be. After making a decision, they were told whether or not they had won – a win earning 10 pence, a loss making no change – and were then shown their current winnings (Fig. 1). A longer task description can be found in our first paper (Averbeck and Duchaine, 2009).

2.3. Pharmacological manipulation

The study was a double-blind crossover study of self-administered oxytocin (40 IU Syntocinon, Novartis) and matched saline placebo nasal sprays, so that each participant received both treatments, one at each visit. Participants were trained on the correct technique for such administration according to the guidelines from Guastella et al. (2013), and each spray was acquired approximately 1 h before being administered to ensure an adequate storage temperature.

fMRI testing began 45 min after drug/placebo administration, which is line with previous fMRI studies showing significant changes in neural activity after OXT administration within this time frame (Domes et al., 2007; Kirsch et al., 2005; Kosfeld et al., 2005; Wittfoth-Schardt et al., 2012). Participants were monitored closely after spray delivery and no adverse events occurred. The first task administered in the scanner was a trust-related decision-making task which does not form part of this study. As intranasal OXT-induced changes have been demonstrated up to 2 h post-administration (Martins et al., 2020); herein, the task relevant to the present study was performed approximately 90 min post-oxytocin/placebo administration.

2.4. fMRI data acquisition

Functional magnetic resonance imaging (fMRI) data were acquired on a Discovery MR750 3 T scanner at the Centre for Neuroimaging Sciences, London (T2* weighted gradient-echo echo-planar images (GE-EPIs), repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 75°, 64 × 64 matrix, 21.1 cm field of view). A 12-phase head coil array was used over the whole head for RF transmission and reception. Each whole-brain image contained 39 3-mm axial slices separated by a distance of 0.3 mm with in-plane isotropic voxel resolution of 3.3 × 3.3 mm. Two runs of 430 scans were acquired for each participant per visit.

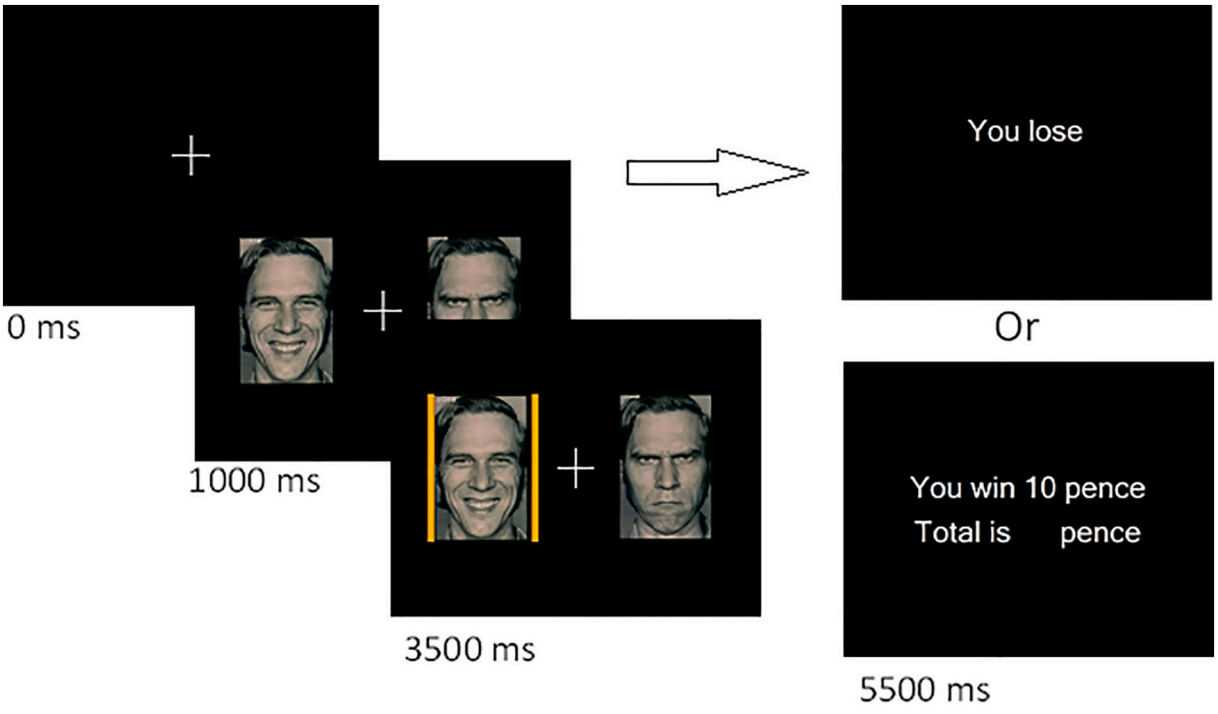


Fig. 1. Task presentation in the fMRI scanner for an example trial.

The first four volumes were discarded to allow for transient effects. A T1-weighted structural scan using a fast-spoiled gradient-echo pulse sequence (TR = 7.312 ms, TE = 3.016 ms, flip angle = 11°, time to inversion = 400 ms) was acquired for registration purposes at the beginning of the session.

Participants made their responses with their index and middle fingers of their right hand. Head movement was minimised using headphones and additional padding around the head and ears as well as around the arms and legs.

2.5. Analysis

2.5.1. fMRI data

All data were preprocessed and analysed using Statistical Parametric Mapping 12 (SPM12) (www.fil.ion.ucl.ac.uk/spm) in MATLAB R2014a (MathWorks Inc. Sherbon, MA, USA). All volumes were realigned to match the first volume of each session and each session was coregistered to the mean image of each session and the T1-weighted structural image, forward deformations from the segmentation process were used to normalise the images to a standard template of the Montreal Neurological Institute (MNI) brain, finally all the images were smoothed using an 8-mm full-width at half-maximum Gaussian kernel.

First-level event-related general linear models (GLMs) were constructed in SPM to analyse the images with each event modelled as a delta (stick) function. Each block was split to represent whether the block had used emotional faces (i.e. happy and angry) or neutral faces (of differing identities). Events of interest within each block were modelled using regressors representing decision-making (via a regressor indicating the time point at which a face was chosen in each trial as indexed by a button press), the presentation of the faces, feedback (win or lose), whether the facial affect was emotional or neutral and the motion parameters. Additionally, parametric modulators representing the probability of the chosen face winning as calculated by an ideal observer on the decision-making regressor, and a parametric modulator for reward prediction error on the feedback regressor were also modelled. Each regressor, except for the motion parameters, was convolved with a canonical hemodynamic response function and its temporal derivative. Missed trials were not modelled as events. Blocks where subjects failed to respond for greater than 50% of the trials were excluded from analysis as they were deemed to not be appropriately attending to the task. Only one block was excluded for one subject after oxytocin administration during the emotionally valenced face condition.

Contrasts were created to look at the effects of neural activity during decision-making or time of choice (determined by the button press) for all valid blocks comparing neural activity after oxytocin administration versus placebo between the emotionally valenced faces, as well as the neutral faces. In addition to exploring the effect of drugs in just emotionally valenced and neutral triels, to assess interaction effects between drugs and emotion, an overall examination of blocks looking at the effects of drug (i.e. oxytocin versus placebo) and emotion (i.e. emotionally valenced versus neutral faces) were entered into 2 × 2 full factorial in SPM12 with drug and emotion as conditions.

Contrasts were whole brain cluster-level family wise error (FWE) corrected at $p < 0.05$ with a height threshold of $p < 0.001$, uncorrected, and voxels which survived peak level FWE correction at $p < 0.05$ are reported. Reported voxels coordinates were converted from Montreal Neurological Institute (mni) coordinates into Talairach coordinates using the function icbm_spm2tal and entered into Talairach Daemon to confirm their location in grey matter (Lancaster et al., 1997, 2000). Results are reported as their original mni coordinates as output by SPM12.

Given that the amygdala appears to be reliably influenced by oxytocin (Zink and Meyer-Lindenberg, 2012), region of interest (ROI) analyses using small volume correction (SVC) were carried out with volumes of interest defined using WFU PickAtlas Tool (Maldjian et al., 2003) for the left and right amygdala.

Effect sizes were calculated and adjusted for same size using Cohen's d (Cohen, 1992a, 1992b) according to Thalheimer and Cook's (2002) method and were corrected for the number of subjects used, for all two-sample and paired *t*-tests to assess the strength of each finding.

2.5.2. Behavioural data

As the probability of each face winning was liable to change across the course of each block, with one face potentially "winning" more often earlier in the block but "losing" overall; the probability that each face would win was calculated for each trial using an ideal observer model. This model assessed probability in terms of the number of times a face won (i.e. they picked that face and were told they won) or would-have-won (i.e. if they picked the other face and were told they lost) over the number of valid trials. Using these probabilities, performance estimates were calculated across all trials by comparing the face the subject picked to the face the ideal observer assigned the highest probability of winning. In the case that both faces had equal probability of winning (i.e. at 50% probability) either face picked was deemed optimal. Overall performance estimates were calculated across all trials as the number of times the participant picked the face deemed optimal over the number of valid trials (i.e. 30 minus any misses). These estimates were then averaged across all blocks which were not excluded to get an overall performance estimate for all blocks using emotionally valenced and neutral faces.

To assess how facial expression biased decision-making, all trials were separated into when participants agreed with the ideal observer and when they disagreed with the ideal observer for the happy and angry facial valence as well as for the two neutral face identities. A 2 × 2 contingency table was calculated for each block type (i.e. emotionally valenced and neutral) representing counts for choices by the ideal observer and choices by the participant. When the probability for each face winning was ambiguous (i.e. equal probabilities for both faces), the contingency count for each face was increased by 0.5. Using this table it was possible to calculate the conditional probability of each participant choosing the happy face when they should have chosen the angry face given the current evidence for the angry face $p(\text{happy}|\text{angry})$ as well as when they chose the angry face when they should have chosen the happy face given the current evidence for the happy face $p(\text{angry}|\text{happy})$. The difference between these two measures was calculated to represent the degree of bias toward picking the happy face ($p(\text{happy}|\text{angry}) - p(\text{angry}|\text{happy})$). This measure indicates how often participants ignore the evidence that has accumulated for the negatively valenced face and chose the positively valenced face compared to how often they ignored evidence that had accrued for the positively valenced face and chose the negatively valenced face. This bias distribution was examined across all participants and entered into a one sample *t*-test to see if it significantly differed from 0. It is important to note these conditional probabilities were calculated separately to the probability that each face would win. This process has been replicated in multiple studies to represent the degree of bias where the methods are described in further detail (Averbeck and Duchaine, 2009; Evans et al., 2010, 2011; Furl et al., 2012).

3. Results

3.1. Behavioural analyses

Participants performed above chance ($p < 0.01$) in detecting the "winning" face across all drug and emotionally/neutrally valenced conditions, and did not significantly differ in performance between the placebo and oxytocin conditions ($p > 0.1$) (Table 2). The bias toward selecting the happy face and avoiding the angry face was significant in patients with schizophrenia after placebo ($t(19) = 2.82$, $p = 0.011$): however, after oxytocin, this bias was completely attenuated ($t(19) = 1.25$, $p = 0.225$). There was no bias toward selecting either of the neutral identities in patients with schizophrenia after being administered

Table 2
Performance and bias estimates.

	Emotional faces	Neutral faces	Performance estimates	
	Mean (SD)	Mean (SD)	Emotional faces	Neutral faces
Placebo	58.7% (11.2%)	62.7% (13.6%)	$t(19) = 3.46$, $p = 0.003$*	$t(19) = 4.19$, $p < 0.001$*
Oxytocin	61.4% (12.0%)	62.8% (14.9%)	$t(19) = 4.22$, $p < 0.001$*	$t(19) = 3.85$, $p = 0.001$*

	Emotional faces	Neutral faces	Bias measure	
	Mean (SD)	Mean (SD)	Emotional faces	Neutral faces
Placebo	0.14 (0.22)	0.02 (0.12)	$t(19) = 2.82$, $p = 0.011$*	$t(19) = 0.88$, $p = 0.388$
Oxytocin	0.06 (0.20)	−0.02 (0.13)	$t(19) = 1.25$, $p = 0.225$	$t(19) = 0.85$, $p = 0.407$

* $p < 0.05$; SD = standard deviation.

placebo or oxytocin (Table 2).

3.2. fMRI analyses

3.2.1. All faces vs drug condition

When comparing neural activity during decision-making across both the emotional and neutral conditions, neither whole brain nor ROI analyses showed any differences in neural activity between oxytocin and placebo administration.

3.2.2. Emotionally valenced faces vs drug condition

However, when choosing between two emotionally valenced faces (i.e. happy and angry faces), whole brain analysis revealed significant clusters of increased activation within the right insula and bilateral temporal gyri including the temporoparietal junction (TPJ), the precuneus extending into the right cuneus, right posterior cingulate and left cingulate gyrus after placebo compared to oxytocin administration. Contrast estimates showed this effect was driven by an attenuation of neural activity after oxytocin administration and an increase in neural activity after being administered placebo (Fig. 2; Table 3).

3.2.3. ROI (emotionally valenced faces vs drug condition)

An amygdala-focused ROI analysis at the time of choice, performed using small volume correction (SVC), demonstrated increased activation in bilateral amygdalae–left ($x = -25$, $y = -4$, $z = -14$, $t(38) = 4.89$, $p = 0.002$, $k = 32$, FWE peak level corrected for SVC) and right ($x = 27$, $y = -8$, $z = -14$, $t(38) = 3.74$, $p = 0.020$, $k = 2$, FWE peak level corrected for SVC) after placebo compared to oxytocin administration. Contrast estimates showed that such differences were driven by a stronger attenuation of neural activity in the amygdala in the oxytocin condition and a slight increase in activity in the placebo condition (Fig. 3).

3.2.4. Neutral faces vs drug condition

There were no activation differences apparent when selecting between two neutral faces of differing identities, in either whole brain analysis nor ROI analysis of the amygdalae.

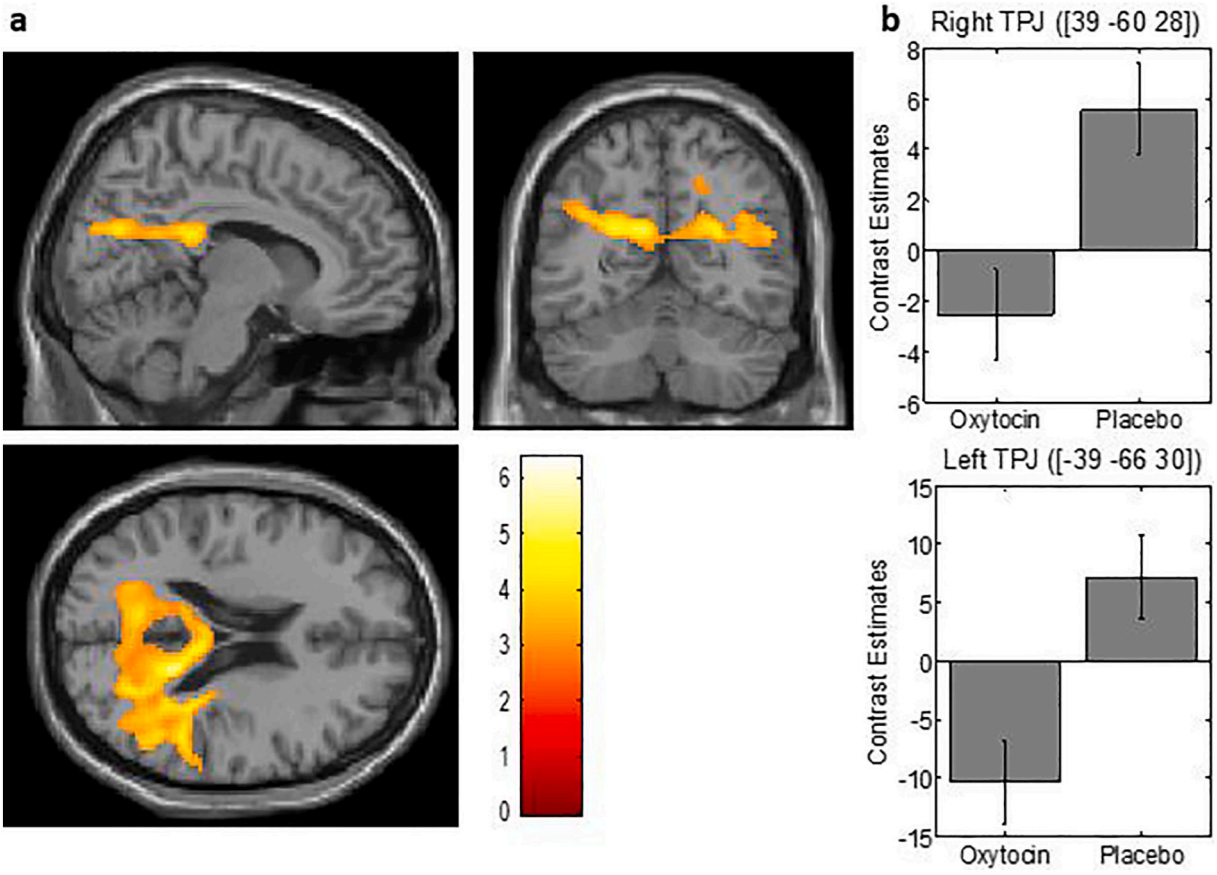


Fig. 2. Neural activity in the temporoparietal junction.
(a) Neural activity for decision-making between emotionally valenced faces for oxytocin administration versus placebo. After taking oxytocin, patients with schizophrenia demonstrated attenuated levels of neural activity from the bilateral precuneus along the bilateral TPJ than after taking placebo. This image is shown at an uncorrected height threshold of $p < 0.001$ for clusters surviving an FWE cluster-level correction of $p < 0.05$ (b) Contrast estimates and 90% confidence intervals for the left and right TPJ showing that neural activity is attenuated after being administered oxytocin versus placebo.

Table 3
Neural correlates for decision-making in patients with schizophrenia for oxytocin and placebo.

Side	Brain region	BA	x y z	t-Score	p (cluster FWE corrected)	k	Effect size
Placebo > oxtocin (emotionally valenced faces at time of choice)							
R	Posterior cingulate	29	17 -48 22	6.39	<0.001	1119	2.07
L	Posterior cingulate	31	-23 -60 24	4.73	<0.001	1119	1.53
R	Posterior cingulate	31	25 -66 22	4.67	<0.001	1119	1.52
R	Posterior cingulate	23	7 -34 20	4.62	<0.001	1119	1.50
R	Posterior cingulate	31	25 -60 24	4.41	<0.001	1119	1.43
L	Posterior cingulate	31	-29 -66 26	4.20	<0.001	1119	1.36
L	Precuneus	31	-11 -62 24	5.04	<0.001	1119	1.64
R	Precuneus	31	7 -70 24	4.25	<0.001	1119	1.38
R	Insula	13	49 -40 20	4.25	<0.001	1119	1.38
R	Insula	13	33 -36 20	4.25	<0.001	1119	1.38
R	Insula	13	31 -32 22	4.00	<0.001	1119	1.30
L	MTG	39	-33 -66 28	4.24	<0.001	1119	1.38
R	STG	22	39 -56 20	3.73	<0.001	1119	1.21
R	MTG (TPJ)	39	39 -60 28	3.62	<0.001	1119	1.17
L	MTG (TPJ)	39	-39 -66 30	3.84	<0.001	1119	1.25
L	Amygdala[a]		-25 -4 -14	4.89	0.002[b]	32	1.59
R	Amygdala[a]		27 -8 -14	3.74	0.020[b]	2	1.21
Oxytocin > placebo (emotionally valenced faces at time of choice)							
No significant voxels							

Corresponding coordinates for each brain region listed represent the peak voxels for each corresponding region within each significant cluster. All areas reported were found to be significant at a family wise error cluster level corrected threshold of <0.05 after running a whole brain analysis at an uncorrected height threshold of $p < 0.001$ and a cluster size of k > 100; Effect size calculated as Cohen's d; k = cluster size; BA = Brodmann's Area; FWE = Family wise error; MTG = Medial temporal gyrus; STG = Superior temporal gyrus; TPJ = Temporoparietal junction.

[a] Regions which were found to be significant using small volume correction.

[b] Significance assessed at FWE peak level.

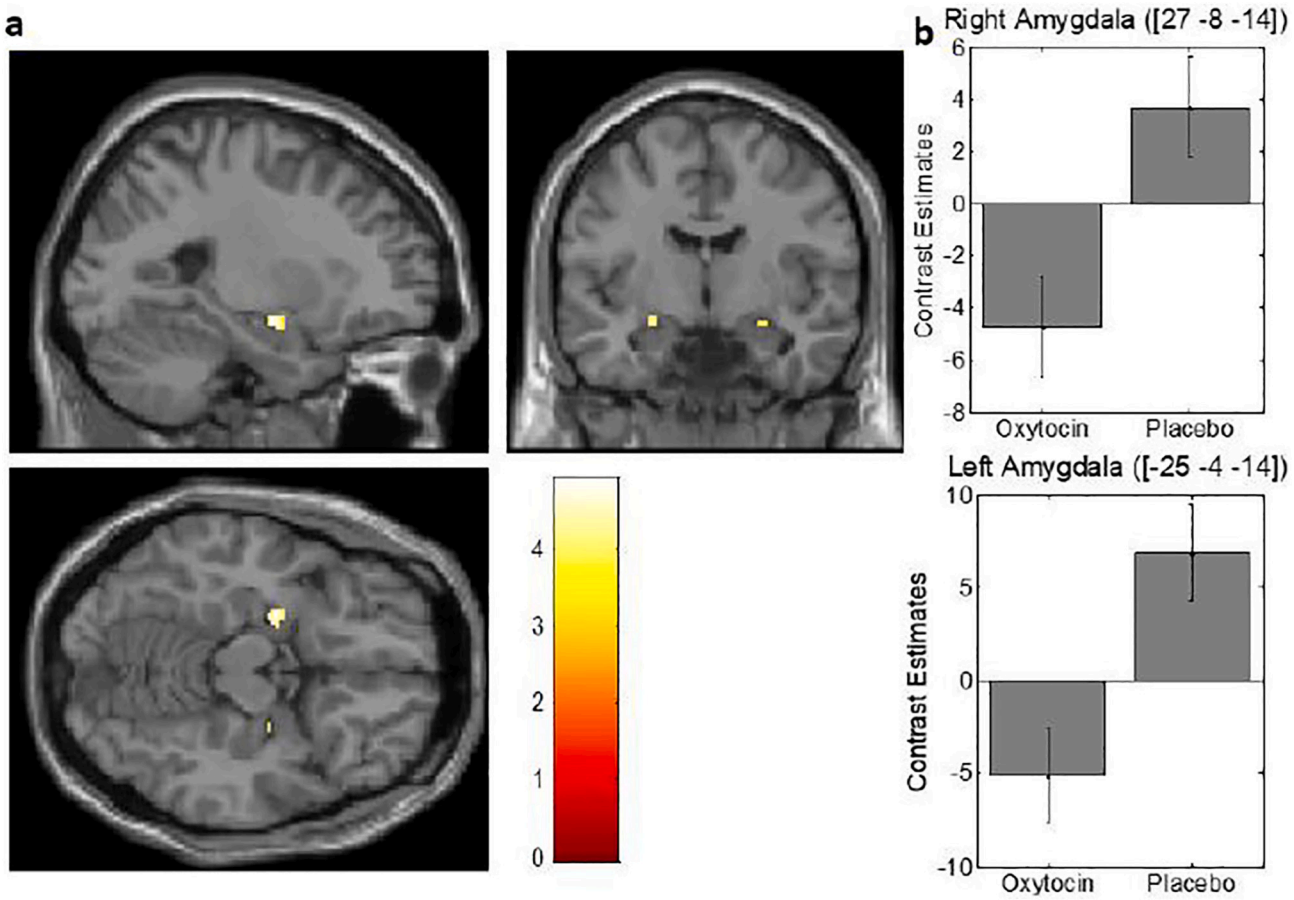


Fig. 3. Neural activity in the amygdala.
(a) Neural activity for decision-making between emotionally valenced faces for oxytocin administration versus placebo. After taking oxytocin, patients with schizophrenia demonstrated attenuated levels of neural activity within the bilateral amygdala than after taking placebo. This image is shown at an uncorrected height threshold of $p < 0.001$ with areas surviving an FWE peak-level correction of $p < 0.05$ (b) Contrast estimates and 90% confidence intervals for the left and right amygdala showing that neural activity is attenuated after being administered oxytocin versus placebo.

3.2.5. Interaction effects between neutral and emotionally valenced faces vs drug condition

Further, no significant interaction effects were observed between emotionally valenced faces versus neutral faces and drug in any analysis.

4. Discussion

Behavioural evidence suggests that OXT may improve social cognitive abilities in schizophrenia. However, the neural effects of OXT on social brain regions are underexplored in schizophrenia. Our fMRI study addressed this gap by examining the neural effects of OXT in schizophrenia using a stochastically reward decision-making task that incorporated emotionally valenced stimuli, i.e. happy and angry and also neutral faces, as social variables. At the behavioural level, OXT attenuated the bias in selecting the happy face, which remained significantly different from zero in the placebo condition. At the neural level, during the emotionally valenced condition, OXT reduced neural activity in a network of brain regions that support mentalising and the processing of facial emotion, salience, aversion, uncertainty, and ambiguity in social stimuli, including the amygdala, TPJ, posterior cingulate cortex (PCC), precuneus and insula (Arioli et al., 2021, Adolphs, 2010, Domes et al., 2007). OXT did not exert any effects during the emotionally neutral condition. Our findings are in accordance with previous fMRI studies in healthy individuals, where OXT induced significant neural changes in the amygdala, TPJ and insula during the emotional but not the neutral condition (Domes et al., 2007; Labuschagne et al., 2010) and support the notion that OXT acts specifically on emotionally valenced/salient stimuli (Evans et al., 2010), not only in healthy individuals but also in patients with schizophrenia.

Several lesion and functional neuroimaging studies in animals and humans indicate that amygdala has major contributions to social cognitive abilities; it processes emotion from faces, it codes and assigns salience to environmental stimuli and processes ambiguity and uncertainty in the environment (Adolphs, 2010).

OXT modulates amygdala activation during salience processing in social decision-making in healthy individuals. For example, during a monetary trust game, participants on OXT increased their investment despite feedback that their trust had been breached by their partners. This effect was associated with reduced amygdala activation (Baumgartner et al., 2008), suggesting that the aversive outcomes associated with the lack of reciprocation had a decreased effect on the OXT group and that OXT may attenuate the salience of the negative aspects of social interactions (Evans et al., 2010). Additionally, attenuated neural activity in healthy controls has often been found during the implicit processing of emotional faces (Wigton et al., 2015). It has been proposed that OXT modulates the salience of social stimuli by regulating dopamine's salience coding and attention reorienting signal and that amygdala is the most likely site where the interaction between DA and OXT takes place (Shamay-Tsoory and Abu-Akel, 2016).

OXT induces reduction of amygdala activation in response to emotional faces in healthy individuals (Domes et al., 2007), which has been suggested to reflect reduced uncertainty associated with the predictive value of a social stimulus (Whalen, 2007). Furthermore, OXT reduces amygdala activation during fear-inducing visual stimuli in healthy individuals and it also reduces amygdala's coupling to brainstem regions associated with autonomic and behavioural manifestation of fear (Kirsch et al., 2005).

A recent fMRI study in schizophrenia showed that OXT attenuates amygdala activity during processing of emotional faces (Shin et al., 2015). In line with the above, our finding that OXT attenuated the activation of amygdala during the emotionally valenced condition in schizophrenia may reflect a reduction in the salience assigned to emotionally valenced stimuli.

OXT also attenuated the activation within bilateral TPJ in our study. fMRI studies have systematically associated TPJ with social cognitive operations, such as mentalising (Saxe and Wexler, 2005), empathy (Jackson et al., 2006), perspective taking (Ruby and Decety, 2003), prosocial tendencies like altruism (Morishima et al., 2012), and with recent fMRI evidence supports specific TPJ contributions to social decision-making (Carter and Huettel, 2013). In an fMRI study of healthy biological fathers, OXT reduced TPJ neural responses to social stimuli, which comprised of own child, unfamiliar child/novel and other familiar child conditions as a function of their salience i.e. in the own child and unfamiliar/novel child conditions, which are considered more salient compared to the other familiar child condition (Wittfoth-Schardt et al., 2012). Suppressed TPJ activation under OXT during the emotionally valenced condition in our study may imply a similar effect on processing of social salient stimuli in schizophrenia. Similarly, the attenuated activation of precuneus and PCC in our study, may also suggest that OXT attenuates the salience of emotionally valenced stimuli in schizophrenia, as PCC and precuneus are associated in addition to mentalising (Atique et al., 2011) and emotion understanding (Leitman et al., 2010) with emotionally salient stimuli processing (Maddock et al., 2003).

In our study, OXT also induced attenuation of right insula activation during the emotionally valenced condition. Insula activation is associated with the representation of negative social interactions (e.g. social exclusion, unfair treatment, unreciprocated cooperation) (Eisenberger et al., 2003; Rilling et al., 2008; Sanfey et al., 2003) as risky and/or aversive so that individuals avoid such interactions in the future (Sanfey, 2007). In schizophrenia during an fMRI experiment of judging trustworthiness in faces, right insula activation increased as the trustworthiness of the faces decreased (Baas et al., 2008). Interestingly, OXT has been shown to attenuate insula activation during negative social interactions (e.g. breach of trust) in healthy individuals (Baumgartner et al., 2008). In line with the above, the OXT-induced attenuated activation in the insula in our study may suggest that OXT attenuates the perceived aversion and/or risk during emotionally valenced social decision-making in schizophrenia.

While our findings showed only attenuation of neural activity after the administration of OXT, it is important to note that many studies have found the opposite or have not found any changes in neural activity (Tabak et al., 2019). Recent studies exploring theory of mind, (De Coster et al., 2019), found that OXT increased behavioural accuracy alongside increasing neural activity in the right temporo-parietal junction and medial prefrontal cortex, in patients compared with health controls. A number of other meta-analyses have also explored the differing findings in neural activity following OXT administration (Tully et al., 2018; Wang et al., 2017). Given the variability of findings, it is important that further investigations be done exploring how task type, and how implicit versus explicit facial processing affects neural activity with OXT.

Among the limitations of our study, we should acknowledge the relatively small number of participants; nevertheless, in reviewing the extant literature on the topic, we believed this sample size to be reasonable to detect differences between OXT and placebo. OXT plasma levels were not available in our study. Several studies have found that plasma levels of OXT do not correlate with levels in the CSF (Kagerbauer et al., 2013; Striepens et al., 2013). Intranasal administration of OXT however results in increased CSF OXT levels. For example, in rodents, CSF OXT levels are almost immediately elevated following intranasal administration and can remain elevated for up to 90 min in the amygdala and hippocampus (Neumann et al., 2013). A recent study in healthy humans, used arterial spin labelling to measure intranasal OXT-induced changes in resting regional cerebral blood flow (rCBF), with a dose similar to ours (40 IU) and found that the OXT-induced changes in a brain network of regions implicated in social cognition and emotion, were sustained over the entire posttreatment observation interval (25–78 mi) (Paloyelis et al., 2016).

Overall, these findings show that oxytocin is capable of attenuating the salience, ambiguity and the aversion/risk associated with negatively emotionally valenced stimuli in patients with schizophrenia across areas which are associated with social processing. These changes are

accompanied by changes in bias attenuation indicative of increased prosocial behaviour as a function of decreasing the aversive aspects of negatively valenced social stimuli. These pro-social effects may contribute to the facilitation of social engagement and social interactions in patients with schizophrenia and warrant further investigation in future clinical trials for social cognitive impairments in schizophrenia.

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CRediT authorship contribution statement

Rebekah Wigton: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Derek K. Tracy:** Writing – original draft, Writing – review & editing, Supervision. **Tess M. Verneuil:** Data curation, Resources, Writing – original draft. **Michaela Johns:** Investigation, Writing – original draft. **Thomas White:** Methodology, Software, Validation. **Panayiota G. Michalopoulou:** Methodology, Formal analysis. **Bruno Averbeck:** Conceptualization, Methodology, Supervision. **Sukhwinder Shergill:** Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors all confirm that they have no conflict of interest in this current work.

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