Radboud Repository
sharing science

Social approach and avoidance behaviour for negative emotions is modulated by endogenous oxytocin and paranoia in schizophrenia

Brown, E.C.; Tas, C.; Kuzu, D.; Esen-Danaci, A.; Roelofs, K.; Brüne, M.

2014, Article / Letter to editor (Psychiatry Research, 219, 3, (2014), pp. 436-442)

Doi link to publisher: https://doi.org/10.1016/j.psychres.2014.06.038

Version of the following full text: Publisher's version

Published under the terms of article 25fa of the Dutch copyright act. Please follow this link for the

Terms of Use: https://repository.ubn.ru.nl/page/termsofuse

Downloaded from: https://hdl.handle.net/2066/131582

Download date: 2025-05-05

Note:

To cite this publication please use the final published version (if applicable).

Psychiatry Research 219 (2014) 436–442

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Social approach and avoidance behaviour for negative emotions is modulated by endogenous oxytocin and paranoia in schizophrenia

Elliot C. Brown [a,*], Cumhur Tas [b,c], Duygu Kuzu [d], Aysen Esen-Danaci [e], Karin Roelofs [f], Martin Brüne [c]

[a] Maryland Psychiatric Research Centre, University of Maryland School of Medicine, Baltimore, MD, USA
[b] Department of Psychology, Üsküdar University, Istanbul, Turkey
[c] Research Department of Cognitive Neuropsychiatry and Psychiatric Preventive Medicine, LWL University Hospital, Ruhr University Bochum, Germany
[d] Department of Psychology, Arel University, Istanbul, Turkey
[e] Department of Psychiatry, Celal Bayar University, Manisa, Turkey
[f] Behavioural Science Institute and Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 9 October 2013
Received in revised form
2 April 2014
Accepted 22 June 2014
Available online 8 July 2014

Keywords:
Oxytocin
Schizophrenia
Paranoia
Social behaviour
Threat avoidance

ABSTRACT

Patients with schizophrenia suffer from dysfunctional social behaviour. Social approach and avoidance (AA) has been associated with motor responses, as the affective valence and gaze direction of facial stimuli can bias push and pull motor tendencies. The aim of this study was to investigate the role of endogenous oxytocin in social AA behaviour in schizophrenia. Basal plasma oxytocin levels were collected from 28 patients who were then given a joystick-based Approach-Avoidance Task (AAT). Reaction times were recorded and AAT effect scores calculated for responses to happy and angry faces, which either had direct or averted gaze. Individual differences in basal oxytocin had a significant relationship with AAT responses, and patients with higher levels of oxytocin tended to avoid angry faces more. Furthermore, greater avoidance of angry faces was correlated with more severe psychotic (positive and general) symptoms and greater paranoia. This suggests that the endogenous effects of oxytocin may be specific to the interpretation of negative threatening emotions in schizophrenia patients, and also provides evidence that psychotic symptoms and paranoia can impact on social AA behaviour by heightening threat avoidance.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

The term "schizophrenia" refers to a group of mental disorders characterised primarily by negative and positive psychotic symptoms but are also marked with impairments in social behaviour. With regard to the motivational drives underlying social interaction, it has been hypothesised that many signs and symptoms associated with schizophrenia can be understood in the context of dysregulated social approach and avoidance (i.e. fight–flight) behaviour (Brüne, 2008), an interpretation that has received at least partial support through studies using ethological observation of patients' nonverbal behaviour (Annen et al., 2012; Geerts and Brune, 2009). Paranoia stemming from persecutory delusions is also a common feature in schizophrenia, which has been related to impairments in social perception, leading to misinterpretations of social stimuli and an increased sensitivity to social threat leading to greater social avoidance (Bentall et al., 1995; 2001). More recently, much work has focused on the underlying neurobiological factors related to dysfunctional social behaviour, with one popular chemical of interest being oxytocin. However, little work has been done to investigate social approach and avoidance behaviours in schizophrenia, nor how this may be affected by underlying neurobiological or psychopathological features of the illness.

Social approach and avoidance behaviour is directly related to the emotional valence of social stimuli (Roelofs et al., 2005). For example, approach and avoidance (AA) movements can create attitudinal biases, in which arm flexion induces more positive affective ratings of valenced stimuli, whereas arm extension induces more negative affective ratings (Cacioppo et al., 1993; Centerbar and Clore, 2006). A joystick-based task has been previously used to explore motor responses to social approach and avoidance behaviour (AAT; Rinck and Becker, 2007), whereby subjects either pull the joystick towards themselves, or push it away when presented positive or negative emotional faces. By comparing reaction times for different emotional faces, people tend to have faster congruent responses (i.e. pull (/approach) happy and push (/avoid) angry) than incongruent responses (i.e. pull-angry and push-happy). This low-level difference

* Corresponding author at: Maryland Psychiatric Research Centre (MPRC), Department of Psychiatry, University of Maryland School of Medicine, 55 Wade Avenue, P.O. Box 21247, Baltimore, MD 21228, USA.
E-mail address: elliot.c.brown@gmail.com (E.C. Brown).

http://dx.doi.org/10.1016/j.psychres.2014.06.038
0165-1781/© 2014 Elsevier Ireland Ltd. All rights reserved.

seen in motor responses is thought to reflect associations between social AA behaviour and the processing of emotional valence.

Different pathological conditions, particularly those with impairments in social behaviour, have been shown to exhibit abnormalities in approach and avoidance responses on the AAT. For example, socially anxious individuals have a greater tendency to avoid angry faces (Heuer et al., 2007) when compared to socially non-anxious participants. In contrast, individuals with high levels of psychopathy demonstrate a lack of avoidance to angry faces (Louise von Borries et al., 2012). Gaze direction is an important factor in regulating social interaction and has also been found to modulate responses on the AAT, with direct gaze inducing a greater tendency to avoid angry faces in socially anxious people as compared to averted gaze (Roelofs et al., 2010), as those faces more directly communicate threat towards the perceiver (Adams and Kleck., 2005). In the case of schizophrenia, there is evidence to suggest that paranoid patients misinterpret gaze direction, which may lead to the perpetuation of persecutory delusions and feelings of paranoia (Rosse et al., 1994). Paranoid patients have also been found to take longer to make judgements about gaze direction (Franck et al., 2002), make more errors in gaze discrimination (Russell et al., 2001) and also misinterpret averted gaze as being directed towards them (Hooker and Park, 2005).

The neuropeptide oxytocin has been extensively investigated in terms of its role in social behaviour (McCall and Singer, 2012), and as a potential therapeutic tool for enhancing prosocial behaviour (e.g. Yamasue et al., 2012). There have been some suggestions that oxytocin can enhance the salience of social cues, increasing the affective valence, and thus also the attention towards social stimuli (Averbeck, 2010; Tabak, 2013), which is also indicated by an increase in amygdala activity (Gamer et al., 2010). Studies have found that oxytocin also modulates tendencies for social AA with one example showing that the administration of intranasal oxytocin in healthy people can induce a decrease in aversion specifically to angry faces (Evans et al., 2010). Kemp and Guastella (2010) suggest that oxytocin can increase approach-related behaviour and decrease withdrawal. Indeed a recent study showed that oxytocin administration induces a shift from threat avoidance to threat approach on the AAT (Radke et al., 2013).

People with schizophrenia seem to have a general tendency for avoiding negative social situations (Liddle, 1987). In particular, pathological threat beliefs in schizophrenia have been suggested to play a central role in the initiation and conditioning of avoidant mechanisms (Moutoussis et al., 2007), which are likely to be inclusive of social avoidance behaviours. Evans et al. (2011) presented participants with happy and angry faces in an associative learning task and found that people with schizophrenia, when compared to healthy controls, had a greater aversion to angry faces, even when choosing an angry face led to positive feedback. However, the possible implications of the variation in psychotic paranoid thoughts on these findings were not taken into account in that study. Furthermore, some recent studies have explored endogenous levels of oxytocin in schizophrenia, demonstrating negative correlations between plasma/central oxytocin and negative symptoms such as social and emotional withdrawal (Rubin et al. 2010; Sasayama et al., 2012). Most research investigating the effects of oxytocin in schizophrenia have focused on social cognitive domains but have not addressed the effect on social AA behaviours.

The overall aim of this study was to investigate social AA responses in a group of patients with schizophrenia, and how gaze direction impacted on these responses. More specifically, we tested whether endogenous oxytocin levels would have a relationship with social AA responses for positive and negative emotions. We also explored the possible effects of symptom severity and paranoia on social AA. It was hypothesised that basal oxytocin, symptom severity and paranoia in schizophrenia would have an influence on the AA responses to negative and positive emotional social stimuli, and that differences in eye gaze may also play a role in this effect. Here we use schizophrenia as a model disorder to investigate the role of oxytocin and pathological threat beliefs (i.e. paranoia) in social behaviour, in terms of social AA. Due to the potential impairments in emotion recognition known in schizophrenia (Mandal et al., 1998), we also controlled for facial emotion recognition abilities.

2. Methods

2.1. Participants

Twenty-eight right-handed participants (15 male) diagnosed with schizophrenia were recruited from the Psychosis Unit of the Psychiatry Department at Celal Bayar Hospital University, with a mean age of 33.62 years (S.D.=8.61) and 11.56 years (S.D.=3.86) of education. Diagnosis was confirmed with the DSM-IV SCID and all participants were outpatients and considered as clinically stable (i.e., there was no psychiatric hospitalization in the past 6 months, and antipsychotic medication had been stable for the past 6 months) and had a mean number of 2.15 (S.D.=1.57) hospitalisations. Mean duration of illness of the group was 12.19 years (S.D.=6.43). Psychotic symptomatology of all participants was assessed with the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987)). The PANSS is a 30-item semi-structured interview designed to assess five symptom categories associated with schizophrenia: positive symptoms (i.e., hallucinations and delusions), negative symptoms (i.e., avolition and anhedonia), cognitive symptoms (i.e., thought disorder), hostility, and depression. A qualified and PANSS-trained psychiatrist assigned a score from 1 to 7 for each item, with higher scores indicating more severe psychopathology. For the whole group, the PANSS positive mean score was 12.56 (S.D.=3.58), PANSS negative mean was 16.63 (S.D.=5.50) and PANSS general was 27.26 (S.D.=7.98). All patients were taking atypical antipsychotic medication and therefore chlorpromazine equivalents were calculated for all patients to check for medication effects. The group mean chlorpromazine equivalent was 429.63 (S.D.=273.25). Importantly, none of the female participants were taking oral contraception, and no significant differences in basal oxytocin levels were found between male and female patients ($F(1,27)=2.69$, $p=0.114$). The study received ethical approval from the local ethics committee at Celal Bayar University, Manisa, Turkey.

2.2. Tasks

2.2.1. The Approach-Avoidance Task (AAT)

The stimuli used in the AAT task were based on a previous set of photographs of faces used in other AAT tasks (Roelofs et al., 2010), which had been selected from Ekman and Friesen (1976) and Karolinska Institute databases (Lundqvist et al., 1998). All photographs had been cropped to the hairline and were in black and white. Four different male and four female actors were used with half of the faces expressing anger and the other half expressing happiness. The eye gaze of the faces had been modified (Roelofs et al. 2010) resulting in half of the faces having a direct gaze and the other half having an averted gaze. This resulted in a total of 32 different stimuli (8 actors × 2 emotions × 2 gaze directions). The task was structured in four blocks: two experimental blocks, and two practice blocks preceding each experimental block. There were 24 trials in each practice block, making a total of 48 practice trials. Each stimulus was presented thrice in a pseudo-random order in the experimental block making a total of 192 experimental trials, with 96 in each block.

Participants were seated in front of the computer screen and a joystick was fixed to the table between the participant and the screen. The task was self-paced so participants triggered the onset of stimulus presentation by pressing the fire button on the joystick. A blank (black) screen was presented between each trial, and at stimulus onset, pictures appeared in the centre of the screen. In one practice/main block, participants were asked to push the joystick away from themselves when they saw an angry face and pull the joystick towards themselves when they saw a happy face ("congruent" condition). In the other practice/main block, participants were asked to do the opposite and pull the joystick towards themselves whenever an angry face was presented and to push the joystick away from themselves when a happy face was presented ("incongruent" condition). The order of the congruent and incongruent blocks was counterbalanced across participants. When the joystick was pushed during stimulus presentation, the face would shrink, getting smaller and smaller till it disappeared, and when the joystick was pulled, the face would zoom in until it disappeared after the maximum size was reached. Participants were asked to respond as quickly as possible, but also to be as accurate as possible. Initiation response times (RTs) (i.e. the first deviation

from the central resting position of the joystick) were recorded for all responses and taken as the RTs for all analyses. All incorrect trials (8.2%) were excluded from the analysis. The mean pooled reaction time on the AAT for the whole group for all included trials was 1023.62 s (S.D.=586.88).

2.2.2. AAT effect scores

AAT effect scores were calculated for mean RTs for each condition by subtracting pull RTs from push RTs (i.e. push–pull) (Roelofs et al., 2010). This resulted in 4 mean AAT effect scores for each participant for each of the different faces: happy direct-gaze, happy averted-gaze, angry direct-gaze and angry averted-gaze. A more positive AAT effect score reflects greater approach and a more negative score reflects greater avoidance (see details Roelofs et al., 2005). The AAT effect scores were used for the latter part of data analysis.

2.2.3. Facial Emotion Recognition and Discrimination Test

To control for deficits in emotion recognition, the Face Emotion Identification Task and the Face Emotion Discrimination Task (FEIT and FEDT (Kerr and Neale, 1993)) were given to participants. The FEIT consists of 19 photographs of emotional faces presented on screen, and participants are required to identify which emotion is expressed in each photograph. The FEDT presents 30 pairs of photographs of emotional faces and requires the participant to decide if the two faces in each pair display the same emotion.

2.2.4. The Paranoia Scale

The Paranoia Scale (Fenigstein and Vanable, 1992) is a self-report questionnaire originally designed to assess paranoid and persecutory thoughts in university students. It consists of 20 statements of which the participant is asked to rate each item on a 5-point scale, with 1 being not applicable to them at all, up to 5 being extremely applicable to them. All ratings are summed to give a total paranoia score, with a greater number reflecting greater paranoia.

2.3. Procedure

Self-report questionnaires and blood collection were completed before performance of the AAT. All tests were performed between 11:00 a.m. and 3:00 p.m., because of the peak pulsatile release of oxytocin (Amico et al., 1983). Patients were asked to refrain from eating or doing physical exercise 60 min before the start of the experiment. The whole testing session took approximately 30 min and all behavioural measures were taken by a qualified resident psychiatrist.

2.3.1. Blood sample collection and assessment

Blood samples were collected through a peripheral venous catheter inserted in the forearm by a medical doctor before the beginning of the experiment and basal oxytocin levels were measured from these samples. Each sample was drawn into EDTA tubes that contained the polypeptide aprotinin (EDTA-Aprotinin Tubes, Greiner Bio-One GmbH, Germany). Shortly after collection, the samples were centrifuged at 4 °C at 4000 g for 20 min after which plasma was separated into two tubes. Plasma was stored in a freezer at −80 °C until the assessment day and assayed in duplicates. For the analyses, in consideration of the debate on the plasma extraction procedure (Szeto et al., 2011), we preferred to use a novel commercially available extraction-free Elisa kit (Bachem S-1355 Oxytocin – EIA Kit, Extraction-free CE-marked) in which the samples are incubated for one night. For human serum or plasma samples, typical sensitivity (Av. IC50) was 0.15 ng/ml, with a range of 0–10 ng/ml. The sensitivity of the assay used is relatively lower than the extraction required products, but is still in the acceptable range of recent recommendations (McCullough et al., 2013). The limit of detection was 1.2 pg/well and intra- and inter-assay variability were 9% and 15% as reported by the manufacturers. It is important to note here that plasma oxytocin levels collected at a single time point are considered to reflect a reliable and stable measure of baseline levels which may be used as an index of central oxytocinergic activity (Amico et al., 1983; Bartz and Hollander, 2006; Pierrehumbert et al., 2010).

2.3.2. Data analysis

Firstly, inter-correlations were conducted with AAT scores to check for the consistency of the approach-avoidance effect across conditions. Following this, the relationship between basal oxytocin levels and approach and avoidance was explored. Notably, in this population, the RTs on the AAT were skewed towards higher values and also demonstrated a high variance between subjects, as compared to previous studies with nonclinical samples. Therefore, in consultation with a statistician, we treated a Repeated Generalised Linear Model (GLZ: GENMOD function in SPSS) analysis, a combination of repeated ANOVA and non-linear multiple regression (see details, Anderson et al., 2010), which permits analysis on longitudinal data without the assumption of normality. Here, a gamma with link function for RTs has been selected as suggested for the analysis of non-linear distributions (Madsen and Thyregod, 2011). As opposed to transforming data into linearity, the use of a non-linear model accounts for the flexibility on the range of allowable values for predictable functions, which direct modelling of the response variable cannot address, and also permits analysis of raw data instead of averaging the data by considering participants with higher RTs as outliers (Madsen and Thyregod, 2011). In the GLZ equation, we treated the raw RTs for each trial as the dependent variable; emotion (i.e. happy and angry), response (i.e. push and pull) and gaze (i.e. direct and averted) as categorical factors and basal oxytocin levels as a continuous factor. As a note of caution, as opposed to the traditional repeated ANOVA the GLZ function permits including continuous data as a predicting factor and thus we have investigated up to 4-way interaction in this study (emotion, response, gaze, basal oxytocin).In accordance with the longitudinal nature of this analysis, 4508 trials for 28 subjects were taken in this step.

A planned post-hoc analysis was then performed by dividing the sample into high and low basal oxytocin level groups using a median split to further investigate the interactions seen between AAT performance, oxytocin levels and other illness-related features. Group differences in the AAT effect scores were assessed using Mann–Whitney-*U* tests. We checked for group differences with respect to symptomatology, medication, face recognition/discrimination and paranoia with independent *t*-tests. Lastly, correlational analyses between oxytocin, symptomatology, paranoia and AAT effect scores were performed, and *p*-values less than 0.05 were considered significant. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Intercorrelations among AAT effect scores

We found significant inter-correlations between happy straight and happy averted AAT effect scores (r_s (28)=0.51; p=0.006). Although, it appears that the correlation between AAT effect scores for angry straight and angry averted was only approaching significance (r_s (28)=0.35; p=0.07). Furthermore we also found significant inverse correlations between AAT scores for angry-straight vs. happy-straight (r_s (28)= −0.479, p=0.01) and angry-straight vs. happy-averted (r_s (28)= −0.413, p=0.03). Such relationship was also seen in the same trend for angry averted although it was not reaching significance for happy-straight (r_s (28)= −0.256, p=0.18) or happy-averted (r_s (28)= −0.187, p=0.34).

3.2. Relationship between AAT and oxytocin

The results from the Repeated Generalised Linear Model (GLZ) analysis using the AAT raw RTs and oxytocin levels revealed significant main effects of gaze direction (Wald-χ^2=4.90, p=0.02), response (Wald-χ^2=15.13, p= ≤0.001) and basal oxytocin levels (Wald-χ^2=7.51, p=0.006). The model also revealed significant 2-way interaction effects between emotion and response (Wald-χ^2=18.33, p= ≤0.001) and response and oxytocin level (Wald-χ^2=5.96, p=0.015), and a 3-way interaction between gaze direction, emotion and oxytocin level (Wald-χ^2=22.94, p= ≤0.001). Most critically, the 4-way interaction between gaze direction, emotion, response and oxytocin level was significant (Wald-χ^2=8.19, p=0.004). The summary of the estimated mean scores for each condition when oxytocin levels are taken as a continuous factor (4-way) is summarised in Table 1. Mean AAT effect scores for high and low oxytocin groups are shown in Fig. 1.

3.3. Relationship between AAT and outcome variables

The group comparison on other measures showed that there were no significant differences between high and low oxytocin groups in terms of symptomatology and medication. Importantly, we found that the group differences in performance on the face discrimination and face recognition tasks were not significant. Group differences in paranoia also did not reach significance, although the group means did demonstrate that the high oxytocin group exhibited greater paranoia. The summary of results with statistics is given in Table 2.

A correlation analysis further confirmed the relationship between oxytocin and the AAT response, as levels of oxytocin were negatively correlated with AAT effect scores for angry faces

Table 1
Summary of the estimated mean reaction times (ms) for the AAT task.

Emotion	Response	Gaze	Mean	S.E.	95% Wald Confidence Interval	
					Lower	Upper
Angry	Pull	Avert	986.30	17.38	952.23	1020.36
		Direct	1039.87	18.08	1004.43	1075.30
	Push	Avert	1046.06	18.09	1010.59	1081.53
		Direct	1041.32	18.54	1004.97	1077.67
Happy	Pull	Avert	959.33	16.68	926.63	992.02
		Direct	975.48	16.91	942.33	1008.64
	Push	Avert	1066.07	18.46	1029.89	1102.26
		Direct	1014.68	17.82	979.74	1049.62

Notes: Oxytocin levels were entered into the equation as a factor for calculating estimates.

To further investigate the 4-way interaction between gaze, emotion, response and oxytocin, we compared the low and high basal oxytocin group on AAT effect scores in each condition (displayed in Fig. 1). Following the splitting of the sample, accordingly, the low oxytocin group exhibited a group mean of 161.1 pg/ml (S.D.=36.6) and the high oxytocin group had a mean of 381.1 pg/ml (S.D.=163.4). When high and low oxytocin groups were compared on AAT effect scores, significant differences for responses to angry faces with averted gaze ($z=-2.07$, $p=0.039$), and for angry faces with direct gaze ($z=-2.11$, $p=0.035$) were revealed. However, there were no significant differences between oxytocin groups in AAT effect scores for happy faces.

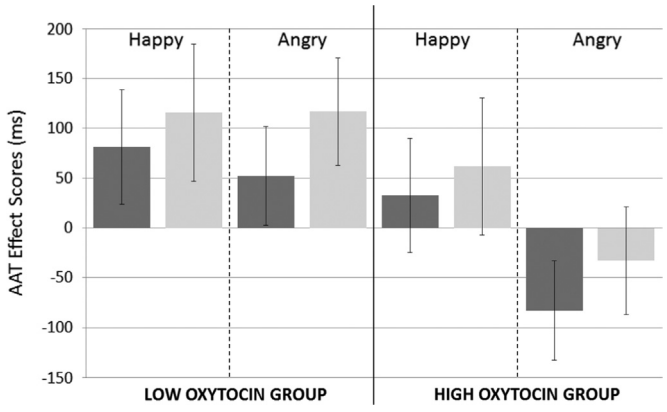

Fig. 1. AAT effect scores reflecting push minus pull mean RTs for each condition, comparing RTs for the low and high basal oxytocin groups. A more positive score reflects greater approach and a more negative score reflects more avoidance.

Table 2
Means and S.D. for symptom severity, behavioural measures and medication between low and high oxytocin groups. P-values show the result of separate ANOVAs comparing the two groups.

	Low oxytocin group		High oxytocin group			p
	Mean	S.D.	Mean	S.D.	t-value (d.f.)	
PANSS Positive	10.79	2.94	10.43	4.13	0.27(27)	0.80
PANSS Negative	16.57	4.86	16.21	6.33	0.17(27)	0.87
PANSS General	26.07	6.79	28.29	8.89	0.74(27)	0.47
CPZ	357.14	194.00	514.29	369.21	1.41(27)	0.17
FEIT	11.64	2.79	11.92	3.23	0.25(27)	0.81
FEDT	23.79	4.41	24.85	4.62	0.62(27)	0.55
Paranoia	34.65	9.72	40.92	13.87	1.39(27)	0.18

Notes for Table 1: PANSS=Positive and Negative Syndrome Scale, CPZ=Chlorpromazine equivalent, FEIT=Face Emotion Identification Task, FEDT=Face Emotion Discrimination Task.

with direct gaze ($r_s(28)=-0.396$, $p=0.04$), as shown in Fig. 2. However, the correlation between basal oxytocin and AAT effect scores for angry faces with an averted gaze did not reach significance (r_s (28)= −0.188, $p=0.35$) although the direction

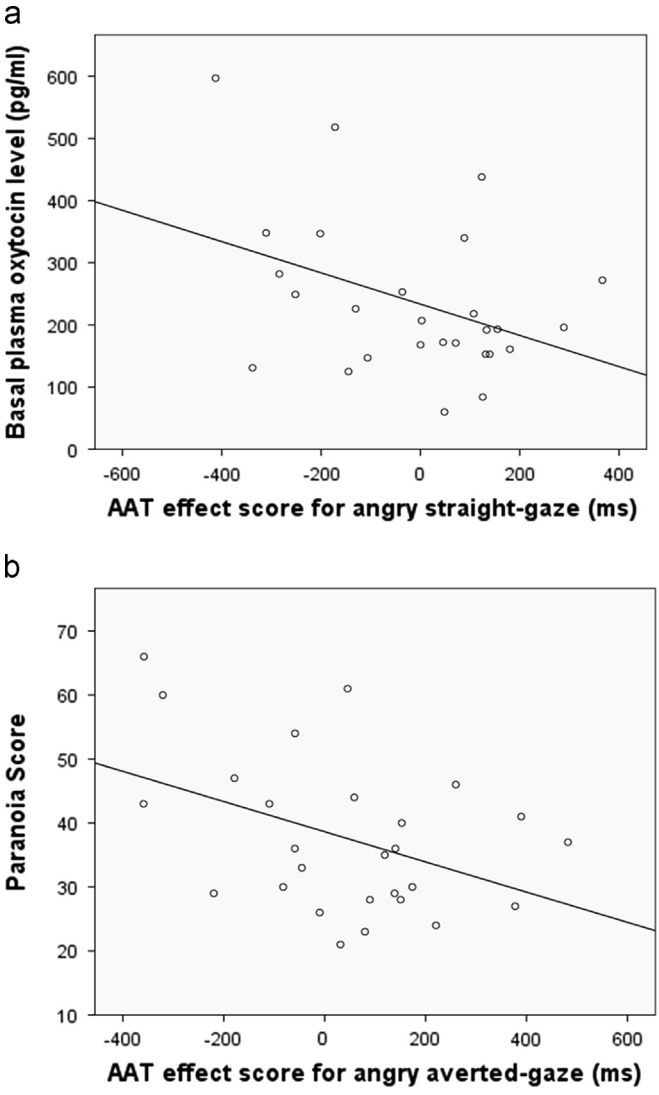

Fig. 2. Scatter plots showing line of best fit to demonstrate the relationship between a) basal plasma oxytocin levels and AAT effect scores (R^2 Linear=0.157), and, b) paranoia and AAT effect scores (R^2 Linear=0.178).

was still negative. Notably, there were no significant correlations between basal oxytocin levels and the subdomains of the PANSS scale. Though interestingly, the correlations between responses to angry faces with an averted gaze and PANSS positive (r_s (28)= −0.406, $p=0.07$) and PANSS general (r_s (28)= −0.393, $p=0.08$) factors were approaching significance, but not for the PANSS negative factor (r_s (28)= −0.282, $p=0.22$). In addition, we observed significant correlations between paranoia and AAT effect scores for angry averted-gaze (r_s (28)= −0.422, $p=0.03$) but not between angry straight-gaze (r_s (28)= −0.155, $p=0.44$), as shown in Fig. 2.

4. Discussion

The aim of our study was to investigate social approach and avoidance (AA) behaviour in patients with schizophrenia and its relationship with basal levels of oxytocin and psychotic symptomatology. We used a joystick based AA task that has been shown to demonstrate a relationship between arm flexion/extension and responses to positive/negative affective social stimuli, whereby healthy subjects are faster to push angry faces away/pull happy faces towards themselves (i.e. congruent condition) as compared

to pulling angry faces/pushing happy faces away (i.e. incongruent condition) (Rinck and Becker, 2007). Our results further validate this effect, found in healthy populations, which was exhibited by schizophrenia patients with a greater basal level of oxytocin. Our first hypothesis was that differences in endogenous oxytocin would exert differential effects on AA responses to angry and happy faces, which was evidently confirmed. We found that differences in basal oxytocin levels were only associated with responses to negative emotions but not positive ones. In addition, it was highlighted that this effect was correlated with angry faces with a straight gaze but not to those with an averted gaze in which patients with higher levels of oxytocin exhibited greater avoidance of negative emotions. Furthermore, there appeared to be a trend for patients with more severe positive and general psychotic symptoms to also exhibit greater avoidance to negative emotions, but only those with an averted gaze. More specifically, it was revealed that paranoia significantly correlated with social AA for negative emotions, whereby the more paranoid patients exhibited greater avoidance to angry faces with an averted gaze. As an additional point, previous reports found significant associations between positive and negative symptoms and oxytocin (Rubin et al., 2010; Sasayama et al., 2012), however, we did not find such a correlation. This important null finding may be due to the nature of our patient sample, considering all patients were clinically stable and had relatively less severe symptoms compared to previous studies. In brief, the data demonstrates that basal oxytocin levels were associated with social AA behaviour towards negative emotions in a schizophrenia population. Furthermore, we also showed that pathological paranoia in schizophrenia is also related to social AA.

The main finding that the patients with a relatively higher level of oxytocin exhibited a greater aversion to negative emotions compared to positive ones is an intriguing one. It is evident that the difference in AA responses in our data was not related to a deficit in emotion processing in general, but instead reflected a specific response that was determined by the valence of the emotion. These results seem to be in-line with previous studies looking at the effects of oxytocin on responses to emotional stimuli in healthy subjects. For example, Ellenbogen et al. (2012) showed an increased speed to disengage from angry faces after oxytocin administration. There is also evidence that oxytocin can enhance the impact of negative social stimuli (Grillon et al., 2013; Guzman et al., 2013), as Striepens et al. (2012) found increased defensive responses to negative stimuli after administration of oxytocin using emotional scenes. This main finding of our study is also consistent with the notion that oxytocin can increase the salience of emotional cues (Averbeck, 2010). More recently, the only known study looking at the effects of oxytocin administration specifically on AAT responses (Radke et al., 2013) also found effects only for angry faces with a direct gaze, and not for the angry averted gaze or happy faces. However, the effects of endogenous basal oxytocin levels on the AAT in this schizophrenia population did not fully correspond to the effects of the administration of oxytocin reported in the healthy subjects in the study from Radke and colleagues, which demonstrated more approach to angry faces with oxytocin. In contrast, higher basal oxytocin in this schizophrenia population seemed to be associated with greater avoidance of angry faces. Here we provide some possible explanations for these conflicting results. Burgdorf and Panksepp (2006) suggest that dopaminergic activity may be driving the approach of positive affective motivational states, and considering the known abnormalities in the dopaminergic system in schizophrenia (Seeman, 1987), this may be disrupting approach motivations, and subsequently disrupt the congruent approach response in the AAT, which is specific to positive emotions. Furthermore, some have suggested that the social context may interact with the effects of oxytocin on social behaviour (Bartz et al., 2011). For example, Scheele et al. (2012) have demonstrated that even the relationship status of the participants (which, notably, has been found to be associated with a heightened plasma oxytocin level) can influence the effects of oxytocin administration in an adapted version of the AAT. In fact, our data shows that other socially relevant trait variables can have an influence on AA behaviour, in that the patients who had more threat beliefs and thoughts of persecution responded differently to negative emotions as compared to those that had less intense beliefs that others were out to harm them. Such explanation is also in line with the previous literature discussing the implications of pathological threat beliefs on behaviour (Bentall et al., 1995, 2001; Moutoussis et al., 2007).Thus, our study also highlights the potential effects of psychopathological contexts, particularly those manifested in schizophrenia, which can have an influence on social AA behaviour. Though importantly, the effects of oxytocin on AA responses did not interact with the effects of paranoia and psychotic symptomatology, and therefore it is likely that basal endogenous oxytocin and persecutory beliefs are acting independent from each other in their influences on social AA.

The difference we found in AA responses relative to the eye gaze direction of the emotional faces provides further insight into the processing of social stimuli in schizophrenia, and how both basal oxytocin and the degree of paranoia can lead to differences in the interpretation of emotions. In relation to our finding that the oxytocin effect was more specific to angry faces with a direct gaze, previous studies have shown that oxytocin administration can increase gaze towards the eye region (Guastella et al., 2008). Therefore it may be the case that patients with a higher level of basal oxytocin may have paid considerable attention to the eyes of faces, and therefore would have been more sensitive to (the negative impact of) social cues. Consequently this would have made the emotion more salient and thus leading to greater avoidance of these negative emotions. This would be in-line with previous suggestions that direct gaze has a more threatening, and potentially avoidance inducing effect when people are presented with negative emotional stimuli and social threat cues (Adams and Kleck, 2005). The finding that more paranoid patients were more avoidant of angry faces with an averted gaze, but not those with a direct gaze, does seem somewhat counterintuitive, particularly in light of the findings from Adams and Kleck (2005). One possible explanation for this may be that the more paranoid patients made misinterpretations of the averted gaze and thus could have had a greater tendency to interpret an averted gaze as a direct gaze, as shown by some previous studies (Hooker and Park, 2005; Russell et al., 2001). A greater tendency to interpret averted gaze as being direct in patients that were more paranoid would have thus led them to be more avoidant of the social threat cue expressed by the angry face. It has been previously found that patients with schizophrenia tend to actively avoid attending to the eye regions of faces (Morris et al., 2009). However, taken together, our findings may further suggest that both neurobiological and psychopathological factors can play a role in influencing the degree to which schizophrenia patients attend to social cues such as eye regions, because if all patients were actively avoiding attending to the eye region, then we should not have seen an effect of gaze on AAT responses.

This study has several strengths and limitations. We used multidimensional data in order to explain behavioural expressions of schizophrenia patients in this study. We believe that such approaches give more insights into understanding social behaviour in schizophrenia patients. However, the design of this study cannot rule out the possibility that the effect we found between oxytocin and AAT may not be specific to schizophrenia. Another limitation is that our study has a cross-sectional design and therefore limits the proposal of causal relationships among independent variables. Importantly, the relationship between endogenous levels of plasma oxytocin and exogenous administration of

oxytocin is still not clear, and therefore caution should be taken when making direct comparisons between studies using the two measures. Despite these drawbacks, this study is relevant to the development of therapeutic strategies for improving social functioning in schizophrenia and may contribute to understanding previous findings suggesting an association between oxytocin and underlying pathophysiology psychotic symptoms associated with active social withdrawal and paranoid thoughts.

Deficits in social motivational drives have substantial relevance in functional recovery in schizophrenia (Barch and Dowd, 2010). To our knowledge this is the first study exploring the effects of basal oxytocin levels and paranoia on social AA behaviour in schizophrenia patients. This study demonstrates that the effects of basal plasma oxytocin levels on the motivational and affective systems of social AA may be heterogeneous, with some being affected more than others. Additionally it is evident that pathological traits specific to schizophrenia, namely paranoia caused by persecutory delusions and threat beliefs, may also play a crucial role in social AA behavioural outcomes. Our findings encourage replication with future studies using oxytocin administration in schizophrenia, while also considering these endogenous individual differences as confounders when assessing the effect of exogenous neuroendocrinological manipulation of social behaviours and motivations. This study also highlights the importance of taking socially relevant psychopathological traits, particularly paranoia, into consideration when investigating social behaviour in schizophrenia.

Conflicts of interest

All authors declare that they have no relevant financial disclosures or conflicts of interest.

Acknowledgements

The author ECB was supported in this study by a Research Fellowship for Foreign Citizens from the Scientific and Technological Research Council of Turkey (TUBITAK).

References

Adams Jr., R.B., Kleck, R.E., 2005. Effects of direct and averted gaze on the perception of facially communicated emotion. Emotion 5, 3–11.
Amico, J.A., Tenicela, R., Johnston, J., Robinson, A.G., 1983. A time-dependent peak of oxytocin exists in cerebrospinal fluid but not in plasma of humans. The Journal of Clinical Endocrinology & Metabolism 57, 947–951.
Anderson, C.J., Verkuilen, J., Timothy Johnson, T., 2010. Applied Generalized Linear Mixed Models: Continuous and Discrete Data. Springer, New York.
Annen, S., Roser, P., Brune, M., 2012. Nonverbal behaviour during clinical interviews: similarities and dissimilarities among schizophrenia, mania, and depression. The Journal of Nervous and Mental Disease 200, 26–32.
Averbeck, B.B., 2010. Oxytocin and the salience of social cues. Proceeding of the National Academy of Sciences of the USA 107, 9033–9034.
Barch, D.M., Dowd, E.C., 2010. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophrenia Bulletin 36, 919–934.
Bartz, J.A., Hollander, E., 2006. The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behaviour. Hormones and Behaviour 50, 518–528.
Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends in Cognitive Sciences 15, 301–309.
Bentall, R.P., Kaney, S., Bowen-Jones, K., 1995. Persecutory delusions and recall of threat-related, depression-related and neutral words. Cognitive Therapy and Research 19, 445–457.
Bentall, R.P., Corcoran, R., Howard, R., Blackwood, N., Kinderman, P., 2001. Persecutory delusions: a review and theoretical integration. Clinical Psychology Review 21, 1143–1192.
Brüne, M., 2008. Textbook of Evolutionary Psychiatry: The Origins of Psychopathology. Oxford University Press, Oxford, UK.
Burgdorf, J., Panksepp, J., 2006. The neurobiology of positive emotions. Neuroscience & Biobehavioural Reviews 30, 173–187.
Cacioppo, J.T., Priester, J.R., Berntson, G.G., 1993. Rudimentary determinants of attitudes. II: arm flexion and extension have differential effects on attitudes. Journal of Personality and Social Psychology 65, 5–17.
Centerbar, D.B., Clore, G.L., 2006. Do approach-avoidance actions create attitudes? Psychological Science 17, 22–29.
Ekman, P., Friesen, W.V., 1976. Pictures of Facial Affect. Consulting Psychologist Press, Palo Alto, CA.
Ellenbogen, M.A., Linnen, A.M., Grumet, R., Cardoso, C., Joober, R., 2012. The acute effects of intranasal oxytocin on automatic and effortful attentional shifting to emotional faces. Psychophysiology 49, 128–137.
Evans, S., Shergill, S.S., Averbeck, B.B., 2010. Oxytocin decreases aversion to angry faces in an associative learning task. Neuropsychopharmacology 35, 2502–2509.
Evans, S., Shergill, S.S., Chouhan, V., Bristow, E., Collier, T., Averbeck, B.B., 2011. Patients with schizophrenia show increased aversion to angry faces in an associative learning task. Psychological Medicine 41, 1471–1479.
Fenigstein, A., Vanable, P., 1992. Paranoia and self-comsciousness. Journal of Personality and Social Psychology 62, 129–138.
Franck, N., Montoute, T., Labruyère, N., Tiberghien, G., Marie-Cardine, M., Daléry, J., d'Amato, T., Georgieff, N., 2002. Gaze direction determination in schizophrenia. Schizophrenia Research 56, 225–234.
Gamer, M., Zurowski, B., Büchel, C., 2010. Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. Proceeding of the National Academy of Sciences of the USA 107, 9400–9405.
Geerts, E., Brune, M., 2009. Ethological approaches to psychiatric disorders: focus on depression and schizophrenia. Australian and New Zealand Journal of Psychiatry 43, 1007–1015.
Grillon, C., Krimsky, M., Charney, D.R., Vytal, K., Cornwell, B., 2013. Oxytocin increases anxity to unpredictable threat. Molecular Psychiatry 18, 958–960.
Guastella, A.J., Mitchell, P.B., Dadds, M.R., 2008. Oxytocin increases gaze to the eye region of human faces. Biological Psychiatry 63, 3–5.
Guzman, Y.F., Tronson, N.C., Jovasevic, V., Sato, K., Guedea, A.L., Mizukami, H., Nishimori, K., Radulovic, J., 2013. Fear-enhancing effects of septal oxytocin receptors. Nature Neuroscience 16, 1185–1187.
Heuer, K., Rinck, M., Becker, E.S., 2007. Avoidance of emotional facial expressions in social anxiety: The Approach-Avoidance Task. Behaviour Research and Therapy 45, 2990–3001.
Hooker, C., Park, S., 2005. You must be looking at me: the nature of gaze perception in schizophrenia patients. Cognitive Neuropsychiatry 10, 327–345.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale PANSS for schizophrenia. Schizophrenia Bulletin 13, 261–276.
Kemp, A.H., Guastella, A.J., 2010. Oxytocin: prosocial behaviour, social salience, or approach-related behaviour? Biological Psychiatry 67, e33–34 (author reply e35).
Kerr, S.L., Neale, J.M., 1993. Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? Journal of Abnormal Psychology 102, 312–318.
Liddle, P.F., 1987. Schizophrenic syndromes, cognitive performance and neurological dysfunction. Psychological Medicine 17, 49–57.
Louise von Borries, A.K., Volman, I., de Bruijn, E.R., Bulten, B.H., Verkes, R.J., Roelofs, K., 2012. Psychopaths lack the automatic avoidance of social threat: relation to instrumental aggression. Psychiatry Research 200, 761–766.
Lundqvist, D., Flykt, A., Öhman, A., 1998. The Karolinska Directed Emotional Faces – KDEF, CD ROM. Department of Clinical Neuroscience, Psychology Section, Karolinska Institute, Sweden.
Madsen, H., Thyregod, P., 2011. Introduction to General and Generalized Linear Models. Chapman and Hall, Boca Raton, FL, USA.
Mandal, M.K., Pandey, R., Prasad, A.B., 1998. Facial expressions of emotions and schizophrenia: a review. Schizophrenia Bulletin 24, 399–412.
McCall, C., Singer, T., 2012. The animal and human neuroendocrinology of social cognition, motivation and behaviour. Nature Neuroscience 15, 681–688.
McCullough, M.E., Churchland, P.S., Mendez, A.J., 2013. Problems with measuring peripheral oxytocin: can the data on oxytocin and human behavior be trusted? Neuroscience & Biobehavioral Reviews 37, 1485–1492.
Morris, R.W., Weickert, C.S., Loughland, C.M., 2009. Emotional face processing in schizophrenia. Current Opinion in Psychiatry 22, 140–146.
Moutoussis, M., Williams, J., Dayan, P., Bentall, R.P., 2007. Persecutory delusions and the conditioned avoidance paradigm: towards and integration of the psychology and biology of paranoia. Cognitive Neuropsychiatry 12, 495–510.
Pierrehumbert, B., Torrisi, R., Laufer, D., Halfon, O., Ansermet, F., Beck Popovic, M., 2010. Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. Neuroscience 166, 168–177.
Radke, S., Roelofs, K., de Bruijn, E.R.A., 2013. Acting on anger: oxytocin-induced modulations of social approach-avoidance tendencies. Psychological Science 24, 1573–1578, http://dx.doi.org/10.1177/0956797612472682.
Rinck, M., Becker, E.S., 2007. Approach and avoidance in fear of spiders. Journal of Behaviour Therapy and Experimental Psychiatry 38, 105–120.
Roelofs, K., Elzinga, B.M., Rotteveel, M., 2005. The effects of stress-induced cortisol responses on approach-avoidance behaviour. Psychoneuroendocrinology 30, 665–677.
Roelofs, K., Putman, P., Schouten, S., Lange, W.G., Volman, I., Rinck, M., 2010. Gaze direction differentially affects avoidance tendencies to happy and angry faces in socially anxious individuals. Behaviour Research and Therapy 48, 290–294.

Rosse, R.B., Kendrick, K., Wyatt, R.J., Isaac, A., Deutsch, S.I., 1994. Gaze discrimination in patients with schizophrenia: a preliminary report. American Journal of Psychiatry 151, 919–921.

Rubin, L.H., Carter, C.S., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J.A., Maki, P.M., 2010. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophrenia Research 124, 13–21.

Russell, T.A., Corcoran, R., Morris, R.G., 2001. Are abnormalities in the processing of eyes specific to paranoid schizophrenia. Perception 30, URL of the abstract: http://www.perceptionweb.com/abstract.cgi?id=v010280, (ECVP Abstract Supplement).

Sasayama, D., Hattori, K., Teraishi, T., Hori, H., Ota, M., Yoshida, S., Arima, K., Higuchi, T., Amano, N., Kunugi, H., 2012. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. Schizophrenia Research 139, 201–206.

Seeman, P., 1987. Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1, 133–152.

Scheele, D., Striepens, N., Güntürkün, O., Deutschländer, S., Maier, W., Kendrick, K. M., Hurlemann, R., 2012. Oxytocin modulates distance between males and females. Journal of Neuroscience 32, 16074–16079.

Striepens, N., Kendrick, K.M., Becker, B., Schäfer, L., Schwalba, K., Reul, J., Maier, W., Hurlemann, R., 2012. Oxytocin facilitates protective responses to aversive social stimuli in males. Proceeding of the National Academy of Sciences of the USA 109, 18144–18149.

Szeto, A., McCabe, P.M., Nation, D.A., Tabak, B.A., Rossetti, M.A., McCullough, M.E., Schneiderman, N., Mendez, A.J., 2011. Evaluation of enzyme immunoassay and radioimmunoassay methods for the measurement of plasma oxytocin. Psychosomatic Medicine 73, 393–400.

Tabak, B.A., 2013. Oxytocin and social salience: a call for gene-environment interaction research. Frontiers in Neuroscience 7, 199.

Yamasue, H., Yee, J.R., Hurlemann, R., Rilling, J.K., Chen, F.S., Meyer-Lindenberg, A., Tost, H., 2012. Integrative approaches utilizing oxytocin to enhance prosocial behaviour: from animal and human social behaviour to autistic social dysfunction. The Journal of Neuroscience 32, 14109–14117.