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Oxytocin reduces top-down control of attention by increasing bottom-up attention allocation to social but not non-social stimuli – A randomized controlled trial

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ABSTRACT

The neuropeptide oxytocin (OXT) may facilitate attention to social stimuli by influencing early stage bottom-up processing although findings in relation to different emotional expressions are inconsistent and its influence on top-down cognitive processing mechanisms unclear. In the current double-blind placebo (PLC) controlled between-subject design study we therefore recruited 71 male subjects (OXT = 34, PLC = 37) to investigate the effects of intranasal OXT (24IU) on both bottom-up attention allocation and top-down attention inhibition using a prosaccade and antisaccade paradigm incorporating social (neutral, happy, fearful, sad, angry faces) and non-social (oval shape) visual stimuli with concurrent eye movement acquisition. Results revealed a marginal significant interaction effect between treatment, condition and task ($p = 0.054$), with Bonferroni-corrected post-hoc tests indicating that OXT specifically increased antisaccade errors for social stimuli ($ps < 0.04$, effect sizes 0.46-0.88), but not non-social stimuli. Antisaccades are under volitional control and therefore this may indicate that OXT treatment reduced top-down inhibition. However, the overall findings are consistent with OXT acting to reduce top-down control of attention as a result of increasing bottom-up early attentional processing of social, but not non-social, stimuli in situations where the two systems are in potential conflict. Marked deficits in bottom-up attention allocation to social stimuli have been reported in autism spectrum disorder, within this context OXT may have the potential to increase early attention allocation towards social cues.

1. Introduction

The neuropeptide oxytocin (OXT) has been repeatedly demonstrated to facilitate early attentional processing of socio-emotional stimuli which may promote facial emotion recognition (Domes et al., 2007; Guastella et al., 2010; Luo et al., 2017). Specifically, the intranasal administration of OXT has been found to increase attention to the eye region (Guastella et al., 2008), to enhance detection of emotions in subliminal presented backward-masked facial stimuli (Schulze et al., 2011) and to augment early attentional orientation towards facial stimuli (Domes et al., 2013a; Tollenaar et al., 2013; Xu et al., 2015). Depending on the specific task paradigms employed, OXT has been found to enhance attentional bias towards positive (Domes et al., 2013b), positive and neutral (Xu et al., 2015), or positive and negative (Tollenaar et al., 2013) social stimuli. In another study OXT was found to promote switching of attention away from internal interoceptive cues towards external social ones (positive, negative or neutral expression faces) (Yao et al., 2018b). Together, these findings suggest a role for OXT in automatic, bottom-up attention processing of salient social-emotional stimuli. However, attention is a strongly limited cognitive resource and efficient allocation of this resource requires a balanced interplay between stimulus-driven bottom-up orientation towards salient stimuli in the environment and top-down goal-directed cognitive control of attention in response to task demands (Buschman and Miller, 2007; Corbetta et al., 2008). Despite an initial report on the modulatory influence of intranasal OXT on cognitive control during processing of non-social salient stimuli (Striepens et al., 2016), to date the effects of OXT on top-down control of attention towards social versus non-social stimuli have not been examined.

Antisaccade paradigms have been widely employed to investigate top-down (volitional) inhibitory control of attention in response to task demands. In this paradigm, a stimulus is presented in the peripheral

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region of the visual field and subjects are instructed to either look towards (prosaccade) or away from (antisaccade) the stimulus. The prosaccade eye gaze represents a stimulus-driven reflexive behavioral response towards a potentially salient stimulus in the environment. In contrast, a successful antisaccade requires the initial inhibition of the stimulus-driven automatic prosaccade as well as the subsequent volitional saccade away from the distractors, reflecting a top-down inhibitory attentional control mechanism (Munoz and Everling, 2004). In view of frequently reported social-specific effects of OXT (Shamay-Tsoory and Abu-Akel, 2016) the present study employed a social-emotional antisaccade paradigm including neutral, happy, sad, fearful and angry facial expressions as social and oval shapes as non-social stimuli to determine whether OXT generally modulates attention allocation or specifically modulates the processing of social stimuli.

Against this background the current study combined a randomized double-blind placebo controlled OXT administration protocol with an antisaccade eye-tracking paradigm to determine OXT effects on attention processing during stimulus-driven attention (prosaccade) and top-down inhibitory control of attention (antisaccade). Moreover, given previous reports on valence-specific (Xu et al., 2015) and emotion-specific effects of OXT on processing of social stimuli of different facial emotions were included to allow to further exploring emotion-specific effects of OXT on social attention allocation. Given that overarching hypotheses on the modulatory influence of OXT on social cognition suggest that its augmentation of social salience represents a core mechanism of action across different functional domains (Shamay-Tsoory and Abu-Akel, 2016) we hypothesized that OXT would specifically increase attentional bias for social stimuli as reflected by facilitated prosaccades in the context of impaired inhibition of volitional attentional control (impaired antisaccades). Based on our previous findings suggesting that OXT specifically enhances attention allocation towards neutral and positive facial stimuli (Domes et al., 2013b; Xu et al., 2015) we further hypothesized that OXT would particularly affect processing of neutral and positive (happy) faces rather than that of negative ones such as sad, fearful, and angry faces.

2. Materials and methods

2.1. Participants

71 healthy male students aged 18–30 years (mean ± sem = 21.85 ± 0.32 years) from the University of Electronic Science and Technology of China (UESTC) were recruited for the present randomized, placebo-controlled, double blind between-subject pharmaco-eye tracking study. Exclusion criteria were any previous or current neurological or psychiatric disorders, as well as current (30 days before the experiment) or regular use of any psychotropic substances, including nicotine. All participants were instructed to abstain from alcohol and caffeine during the 24 h before the pharmaco-eye tracking experiment. Participants were randomly assigned to receive either 24 International Units (IU) of intranasal OXT (n = 34, mean ± sem age = 21.88 ± 0.44 years) or placebo (PLC, n = 37, mean ± sem age = 21.81 ± 0.46 years). For allocation of the participants to the two treatment groups a computer-generated list of random numbers was used (groups, n = 2; numbers per group, n = 40; simple randomization), allocation was done by an experimenter not involved in data acquisition and analyses. All participants were Chinese native speakers, questionnaires, instructions and other study materials were provided in Chinese language.

Study protocols had full approval by the local ethics committee at the UESTC and experimental procedures were in accordance with the latest revision of the Declaration of Helsinki. All participants were provided informed consent before the experiment and received monetary compensation for participation (100RMB).

Study protocols and primary outcomes were registered at clinical trials.gov (https://clinicaltrials.gov/ct2/show/NCT03486925, Trial ID: NCT03486925) before enrollment. Enrollment started in April 2018, experiments were conducted between April and August 2018.

2.2. Experimental protocols and procedures

To control for confounding effects of between-group differences in variables that have previously been demonstrated to modulate the effects of intranasal OXT (Kendrick et al., 2017) potential confounders were assessed before treatment administration by means of validated scales (Chinese versions). Based on previous findings suggesting that individual variations in these variables modulate the effects of OXT, the following variables were assessed: childhood maltreatment (Childhood Trauma Questionnaire, CTQ) (Bernstein and Fink, 1998), social anxiety (Liebowitz Social Anxiety Scale, LSAS; Social Interaction Anxiety Scale, SIAS) (Mattick and Clarke, 1998; Heimberg et al., 1999), state anxiety (State-Trait Anxiety Inventory, STAI) (Barnes et al., 2002), depressive symptom load (Beck Depression Inventory, BDI-II) (Beck et al., 1996), autism traits (the Adult Autism Spectrum Quotient, ASQ) (Baron-Cohen et al., 2001) and mood (Positive and Negative Affect Schedule, PANAS) (Watson et al., 1988). In line with the focus of the study on cognitive control towards emotional stimuli, additional scales included the Action Control Scale (ACS) (Kuhl, 1994), Behavioral Inhibition System and Behavioral Activation System Scale (BIS/BAS) (Carver and White, 1994) and Emotion Regulation Questionnaire (ERQ) (Wang et al., 2015). Next, participants self-administrated either 24 IU of OXT (Oxytocin-spray, Sichuan Meike Pharmaceutical Co., Ltd; 3 puffs of 4IU per nostril with 30 s between each puff) or PLC (PLC – identical sprays with the same ingredients other than OXT). Administration adhered to standardized intranasal OXT protocols (Guastella et al., 2013), and in line with the pharmacodynamics of intranasal OXT in humans (Spengler et al., 2017) treatment was administered 45 min before the eye-tracking paradigm. Mood (PANAS) and state anxiety (STAI-S) were additionally assessed after the experiment to control for unspecific effects of treatment on these domains. After the experiment, subjects were asked to identify which treatment they had received and their responses indicated that in both groups they were not better than chance guessing the administered treatment (accuracy: PLC = 22, OXT = 18, $\chi^2 = 0.48$, $p = 0.49$, $\eta^2 = 0.08$), confirming successful double-blinding.

Individual differences in the behavioral inhibition system (BIS) and trait anxiety have been associated with both, attentional processing and top-down control of orientation towards social-emotional stimuli, including antisaccade performance (Dennis and Chen, 2009; Reinholdt-Dunne et al., 2012; Chen et al., 2014; Hepsomali et al., 2017). To determine whether OXT affects this association, correlations between individual variations in behavioral inhibition (as assessed by the BIS-scale), trait anxiety (as assessed by the TAI-scale) with eye gaze indices that showed OXT effects were further examined within the treatment groups.

2.3. Antisaccade paradigm

We employed a modified antisaccade paradigm (Chen et al., 2014) that included 5 social-emotional conditions (facial expressions from 4 male and 4 female actors: neutral, happy, fearful, sad, angry expressions) and a non-social control condition (oval shape, the shape was slightly varied to create 8 different shape stimuli). A total of 576 trials over 14 blocks were presented including 2 non-social control blocks (one anti- and one pro-saccade block) and 12 emotional blocks (6 anti- and 6 pro-saccade blocks). Each emotional block contained 40 trials in randomized order including 8 trials per emotional condition resulting in 48 trials in total per anti- and pro-saccade condition respectively. To avoid carry-over of emotion-specific effects of OXT the paradigm started with the shape blocks, which also contained 48 trials, followed by the emotional blocks. The order of anti- and pro-saccade blocks was randomized. Each block started with a 2000 ms visual Chinese

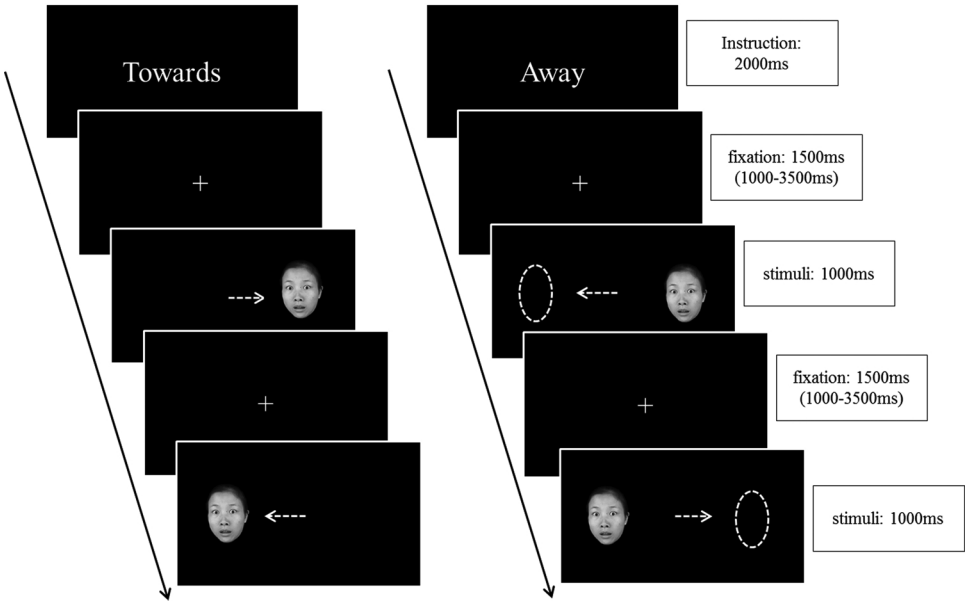

Fig. 1. The antisaccade paradigm Each block started with an instruction indicating whether a prosaccade ("Towards") or an antisaccade ("Away") response was required, followed by a fixation cross centered on the screen. A stimulus was presented at the left or right peripheral position after the fixation disappeared. For "Towards" blocks, subjects were asked to look at the stimulus (prosaccade) and for "Away" blocks they were instructed to look away from the stimulus to the opposite position (antisaccade). During the study the cues were presented in Chinese characters, to visualize the paradigm for the manuscript English words were used.

instruction ("Towards", "Away") indicating whether the subsequent block required a pro- or an anti-saccade response followed by a jittered fixation cross (random variation in the inter-stimulus interval to avoid anticipation effects, ranging from 1000 to 3500 ms with a mean duration = 1500 ms). Following the fixation period a stimulus was presented at 8° visual angle relative to the centered fixation cross to the left or right visual field for 1000 ms. The size of stimuli was 400 × 500 pixels. Participants were asked to direct their gaze as fast as possible towards the stimulus during the prosaccade ("Towards") blocks and away from it in the opposite direction during the antisaccade blocks ("Away") (Fig. 1).

Subjects completed the experiment in a dimly illuminated room. Stimuli were presented on a 17 inch monitor at a resolution of 1024 × 768 pixels. A chin rest was used to standardize the distance and position from the screen (57 cm away and centrally positioned relative to the monitor). The eye gaze data was acquired using an EyeLink 1000 Plus system (SR Research, Ottawa, Canada) in monocular mode at a sampling rate of 2000 Hz. Before each block a 9-point calibration was conducted, the experimental blocks were divided by brief rest periods to facilitate attentive processing throughout the experiment. The raw eye gaze data was initially exported and processed using the EyeLink DataViewer 3.1 (SR Research, Mississauga, Ontario, Canada) and effects of treatment were subsequently analyzed using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA).

Mean error rates for pro- and anti-saccade blocks and latencies for correct saccades served as primary outcomes to determine effects of treatment. Mixed ANOVA models and independent sample t-tests were employed to determine differences between the treatment groups. Post-hoc tests incorporated Bonferroni correction for multiple comparisons. Associations between individual variations in pre-treatment behavioral inhibition (BIS score) and trait anxiety (TAI score) with eye gaze behavior were examined using Pearson correlation. Differences in the correlations between the two treatment groups were assessed by Fisher' Z test with appropriate Bonferroni correction.

3. Results

3.1. Potential confounders

Examining the pre-treatment data on potential confounders using independent t-tests did not reveal significant differences between the two treatment groups (details see Table 1). Likewise, no significant post-treatment differences between the treatment groups were observed for mood. Together, these findings argue against potential confounding effects of pre-treatment differences or unspecific treatment effects.

Table 1
Questionnaire scores in PLC and OXT groups before and after treatment.

Measurements	PLC	OXT	*t-value*	*p-value*
Before treatment				
Positive and Negative Affect Schedule (PANAS)				
Positive	27.97 ± 0.83	27.82 ± 0.99	0.12	0.91
Negative	16.22 ± 0.92	15.91 ± 0.85	0.24	0.81
State-Trait Anxiety Inventory (STAI)				
State	37.84 ± 1.44	37.38 ± 1.56	0.22	0.83
Trait	40.41 ± 1.32	39.38 ± 1.32	0.55	0.59
Liebowitz Social Anxiety Scale (LSAS)				
Avoid	24.35 ± 2.20	20.21 ± 1.99	1.39	0.17
Fear	25.89 ± 2.32	22.35 ± 2.27	1.09	0.28
Beck Depression Inventory (BDI-II)	7.03 ± 1.00	6.41 ± 1.06	0.42	0.67
Adult Autism Spectrum Quotient (ASQ)	21.30 ± 0.85	21.88 ± 0.96	−0.46	0.65
Childhood Trauma Questionnaire (CTQ)	40.16 ± 1.38	39.88 ± 1.17	0.15	0.88
Social Interaction Anxiety Scale (SIAS)	55.24 ± 2.39	50.21 ± 2.34	1.50	0.14
Behavioral Inhibition/ Activation System Scale (BIS/BAS)				
BAS - Reward Responsiveness	6.97 ± 0.30	6.91 ± 0.30	0.16	0.87
BAS - Drive	7.76 ± 0.22	7.94 ± 0.35	−0.46	0.65
BAS - Fun Seeking	10.46 ± 0.30	10.09 ± 0.40	0.77	0.44
BIS - Behavioral inhibition	15.70 ± 0.47	15.88 ± 0.56	−0.26	0.80
Cognitive Emotion Regulation Questionnaire (CERQ)	47.16 ± 1.03	46.69 ± 1.36	0.29	0.77
Action Control Scale (ACS)				
Failure	5.24 ± 0.47	6.00 ± 0.61	−1.03	0.31
Decision	6.30 ± 0.46	6.88 ± 0.50	−0.88	0.38
Performance	9.05 ± 0.27	8.69 ± 0.34	0.88	0.38
After treatment				
Positive and Negative Affect Schedule (PANAS)				
Positive	22.97 ± 1.13	22.71 ± 1.41	0.15	0.88
Negative	12.78 ± 0.69	12.24 ± 0.58	0.60	0.55
State-Trait Anxiety Inventory (STAI) – State	37.64 ± 1.37	34.17 ± 1.30	1.84	0.07

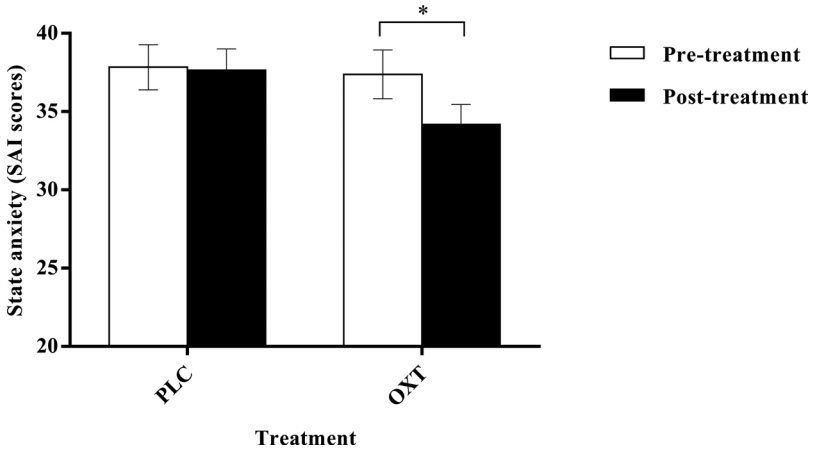

Fig. 2. Anxiety levels in the PLC and OXT group. State anxiety (SAI) scores assessed by State-Trait Anxiety Inventory (STAI) before and after treatment are displayed. OXT significantly decreased state anxiety after the experiment within the oxytocin-treatment group. Error bar refers to SEM, $*p < 0.05$, Abbreviations: PLC, placebo, OXT, oxytocin.

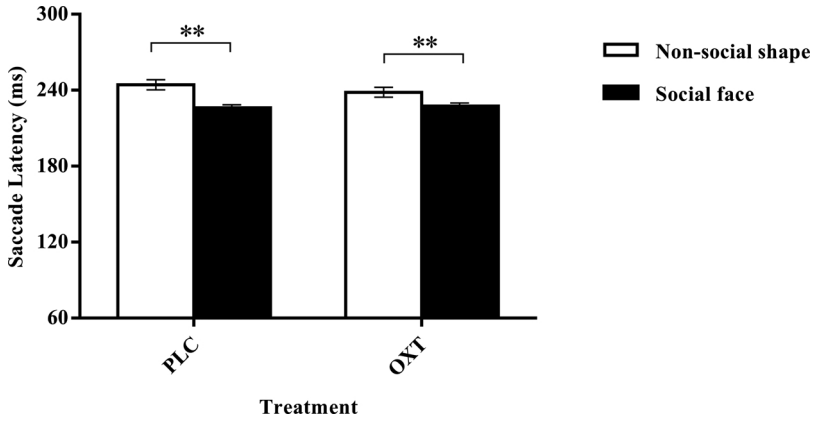

Fig. 3. Condition × treatment interaction in saccade latencies. Saccade latencies for shape and face stimuli in the placebo and oxytocin treated group are displayed. Error bar refers to SEM, $**p < 0.001$, Abbreviations: PLC, placebo, OXT, oxytocin.

While there were no significant post-treatment differences between the PLC and OXT groups for state-anxiety (independent t-test, PLC: mean ± sem = 37.64 ± 1.37, OXT = mean ± sem = 34.17 ± 1.30, $t = 1.84$, $p = 0.07$, Cohen's $d = 0.44$) there was a significant reduction in state anxiety in the OXT group when comparing pre vs post-treatment scores (paired t-test, pre: mean ± sem = 37.38 ± 1.56, post: mean ± sem = 34.17 ± 1.30, $t = 2.31$, $p = 0.027$, Cohen's $d = 0.27$), but not in the PLC group (paired t-test, pre: mean ± sem = 37.84 ± 1.44, post: mean ± sem = 37.64 ± 1.37, $t = 0.15$, $p = 0.882$, Cohen's $d = 0.02$, Fig. 2). This suggests that OXT treatment produced anxiolytic effects within the group treated with OXT.

3.2. Eye-tracking data

A valid saccade response was defined as gaze within 45° relative to the center of the visual target stimulus. Trials with saccade velocity < 30°/sec, latencies shorter than 70 ms (classified as anticipatory saccades) and longer than 700 ms were excluded (Mueller et al., 2010; García-Blanco et al., 2013). Data from subjects with > 75% excluded trials was discarded from further analysis (Reinholdt-Dunne et al., 2012). Based on these criteria a total of 5 subjects were excluded leading to a final sample size of PLC = 33 and OXT = 33 for the eye gaze data analyses. The percentage of trials excluded did not differ significantly between the treatment groups (independent t-test, PLC: mean ± sem = 91.38% ± 0.86, OXT: mean ± sem = 89.63% ± 0.80, $t = 1.49$, $p = 0.14$).

3.2.1. Saccade latency

A 2 (treatment: OXT/PLC) × 2 (condition: non-social shape/social-face) × 2 (task: anti-/pro-saccade) mixed ANOVA was conducted to examine saccade latencies. Results revealed significant main effects of task ($F_{1,64} = 812.96$, $p < 0.001$, $\eta_p^2 = 0.93$) reflecting longer anti-saccade than prosaccade latencies (antisaccade: mean ± sem = 275.91 ± 3.33 ms, prosaccade: mean ± sem = 191.62 ± 1.98 ms, $p < 0.001$). Moreover, a significant main effect of condition was observed ($F_{1,64} = 72.02$, $p < 0.001$, $\eta_p^2 = 0.53$) reflecting saccades for social-face stimuli being generally faster than those for shape stimuli (non-social, shape, mean ± sem = 241.34 ± 2.76 ms; social, face stimuli, mean ± sem = 226.18 ± 2.15 ms, $p < 0.001$). In addition, significant condition × treatment ($F_{1,64} = 4.20$, $p = 0.045$, $\eta_p^2 = 0.06$) and condition × task ($F_{1,64} = 63.88$, $p < 0.001$, $\eta_p^2 = 0.50$) interactions were observed. However, further examination of the interaction effect by means of post-hoc Bonferroni-corrected paired comparisons indicated that saccades for the social-face stimuli were faster in both treatment groups (PLC: non-social, shape, mean ± sem = 244.31 ± 3.91 ms, social, face stimuli, mean ± sem = 225.49 ± 3.03 ms, $p < 0.001$; OXT: non-social, shape, mean ± sem = 238.38 ± 3.91ms, social, face stimuli, mean ± sem = 226.88 ± 3.03ms, $p < 0.001$), suggesting that the interaction effect was mainly driven by the main effect of condition (see also Fig. 3). Post-hoc examination of the condition × task interaction effect indicated longer saccade latencies for shapes during prosaccade but not anti-saccade blocks (antisaccade: non-social, shape = 277.40 ± 3.80 ms, social, face stimuli = 274.42 ± 3.39 ms; $p = 0.28$; prosaccade: non-social, shape = 205.28 ± 2.58 ms, social, face stimuli = 177.95 ± 1.72 ms, $p < 0.001$). Together the results indicate that task instruction (pro- versus anti-saccade) and stimuli (social vs non-social) successfully modulated the behavioral response during the paradigm.

To further explore potential emotion-specific effects of OXT on latency, a 2 (treatment: OXT/PLC) × 6 (stimuli: shape/happy/angry/

neutral/sad/fear) × 2 (task: anti-/pro-saccade) mixed ANOVA was performed. Results revealed significant main effects of task ($F_{1,64}$ = 909.62, $p < 0.001$, $\eta_p^2 = 0.93$), reflecting longer antisaccades than prosaccades (antisaccade: mean ± sem = 274.92 ± 3.31 ms, prosaccade: mean ± sem = 182.51 ± 1.75 ms, $p < 0.001$), and stimuli ($F_{5,320} = 39.14$, $p < 0.001$, $\eta_p^2 = 0.38$), reflecting overall longer saccades for shapes compared to all emotions (all $ps < 0.001$). Moreover, a significant stimuli × treatment interaction effect was observed ($F_{5,320} = 3.08$, $p = 0.01$, $\eta_p^2 = 0.05$) with post-hoc comparisons indicating that for both treatment groups latencies for shapes were longer compared to all emotional stimulus categories (shape vs emotions, PLC: $ps < 0.001$, OXT: $ps < 0.01$). A significant stimuli × task interaction effect was observed ($F_{5,320} = 25.05$, $p < 0.001$, $\eta_p^2 = 0.28$) with post-hoc tests indicating that longer latencies for shapes were selectively observed during the prosaccade blocks (shape vs emotions, antisaccade: $ps > 0.9$, prosaccade: $ps < 0.001$). The stimuli × treatment × task interaction effect reached significance ($F_{5,320} = 2.39$, $p = 0.038$, $\eta_p^2 = 0.04$), however, post-hoc Bonferroni-corrected paired comparisons for the three way interaction demonstrated that the interaction effect was mainly driven by the main effects of task and stimuli (decomposing the interaction: compare drug: all $ps > 0.14$; compare task: longer anti- than prosaccade, all $ps < 0.001$; compare stimuli: longer latency for shape than emotions in prosaccade blocks, all $ps < 0.001$)

3.2.2. Saccade error rate

A 2 (treatment: OXT/PLC) × 2 (condition: non-social shape/social-face) × 2 (task: anti-/pro-saccade) mixed ANOVA was carried out including saccade error rates as dependent variable. Results revealed significant main effects of condition ($F_{1,64} = 25.57$, $p < 0.001$, $\eta_p^2 = 0.29$), task ($F_{1,64} = 149.10$, $p < 0.001$, $\eta_p^2 = 0.70$), and treatment ($F_{1,64} = 6.84$, $p = 0.01$, $\eta_p^2 = 0.10$) as well as significant task × treatment ($F_{1,64} = 6.59$, $p = 0.01$, $\eta_p^2 = 0.10$) and task × condition ($F_{1,64} = 33.13$, $p < 0.001$, $\eta_p^2 = 0.34$) interaction effects. Post-hoc Bonferroni-corrected comparisons demonstrated that the error rate for shapes was significantly lower compared to social-face stimuli (non-social, shape: mean ± sem = 6.65% ± 0.78, social, face stimuli: mean ± sem = 10.42% ± 0.78, $p < 0.001$) and the error rate for antisaccades was significantly higher compared to prosaccades (antisaccade: mean ± sem = 13.84% ± 1.02%, prosaccade: mean ± sem = 3.23% ± 0.54, $p < 0.001$). Overall, OXT significantly increased the error rate compared to PLC (PLC: mean ± sem = 6.74% ± 0.97, OXT: mean ± sem = 10.33% ± 0.97, $p = 0.01$). In addition, there was a marginal significant three-way treatment × condition × task interaction effect ($F_{1,64} = 3.85$, $p = 0.054$, $\eta_p^2 = 0.057$) and exploratory analyses revealed that OXT specifically increased error rates for antisaccades of social face stimuli (antisaccade: social, face stimuli: PLC = 13.73% ± 1.89, OXT = 21.43% ± 1.89, $p = 0.005$, Cohen's $d = 0.71$, Fig. 4a). In contrast, treatment effects on the prosaccade condition did not reach statistical significance (Bonferroni-adjusted, all $ps > 0.17$).

To further explore potential emotion-specific effects of OXT on saccade performance an additional 2 (treatment: OXT/PLC) × 6 (stimuli: shape/happy/angry/neutral/sad/fear) × 2 (task: anti-/pro-saccade) mixed ANOVA with saccade error rates as dependent variable was performed. Results revealed a main effect of stimuli ($F_{5,320} = 10.31$, $p < 0.001$, $\eta_p^2 = 0.14$, reflecting that the error rate for shape was significantly lower compared to all emotional conditions, all $ps < 0.01$), task ($F_{1,64} = 150.99$, $p < 0.001$, $\eta_p^2 = 0.70$, reflecting higher error rates for antisaccades compared to prosaccades, $p < 0.001$) and treatment ($F_{1,64} = 7.47$, $p = 0.008$, $\eta_p^2 = 0.11$) suggesting that OXT significantly increased overall saccade error rates compared to PLC (PLC = 7.79% ± 1.04, OXT = 11.79% ± 1.04, $p = 0.008$). Moreover, significant interaction effects between task × treatment ($F_{1,64} = 8.33$, $p = 0.005$, $\eta_p^2 = 0.11$) and task × stimuli ($F_{5,320} = 12.35$, $p < 0.001$, $\eta_p^2 = 0.16$) were observed. Post-hoc Bonferroni-corrected paired comparisons indicated that OXT significantly increased antisaccade errors compared to PLC (PLC = 12.80% ± 1.69, OXT = 19.87% ± 1.69, $p = 0.004$, Cohen's $d = 0.73$) and that lower errors rates for shapes specifically occurred during antisaccade blocks (shape vs emotions, antisaccade: $ps < 0.003$; prosaccade: $ps > 1$).The three-way interaction effect between treatment × stimuli × task did not reach significance ($F_{5,320} = 1.73$, $p = 0.1$, $\eta_p^2 = 0.03$), however exploratory post-hoc comparisons between the treatment groups revealed that OXT significantly increased antisaccade error rates for all facial stimuli but not for shape stimuli (OXT vs. PLC, face emotion conditions all $ps < 0.04$, shape $p = 0.07$, effect sizes for the post-hoc comparisons: angry: Cohen's $d = 0.56$; fearful: Cohen's $d = 0.67$; happy: Cohen's $d = 0.59$; neutral: Cohen's $d = 0.52$; sad: Cohen's $d = 0.88$; shape: Cohen's $d = 0.46$, Fig. 4b).

3.3. Effects of oxytocin on associations between eye gaze, trait behavioral inhibition and anxiety

To assess modulatory effects of OXT on the association between individual differences in pre-treatment behavioral inhibition, trait anxiety and cognitive control of attention, Pearson correlations between trait inhibition (BIS score), trait anxiety (TAS score) and antisaccade error rates were examined within each treatment group. No significant correlations were found (all $ps > 0.1$) and the correlations did not significantly differ between the treatment groups (BIS, $p = 0.16$; TAI: $p = 0.48$, Bonferroni-corrected).

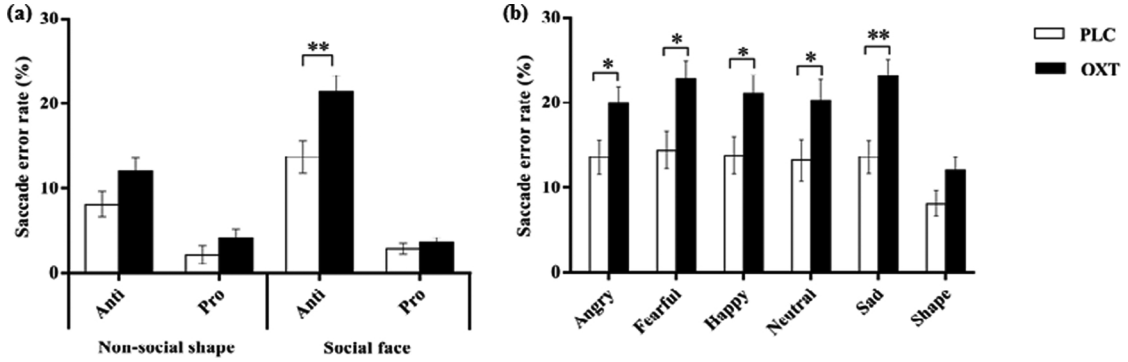

Fig. 4. Oxytocin effects on saccade error rates (a) Post-hoc comparisons comparing treatment effects on social and non-social stimuli suggesting that oxytocin increases the error rate in the social face but not the shape condition during antisaccade blocks; (b) Post-hoc comparisons for the emotion-specific effects of oxytocin on antisaccade performance suggesting that oxytocin generally increases the error rate for each face emotion but not for shapes during antisaccade blocks. Error bar refers to SEM, *$p < 0.05$, **$p < 0.005$ (post-hoc comparison) Abbreviations: PLC, placebo, OXT, oxytocin.

4. Discussion

Overall, the present pharmacological eye-gaze study employing a social-emotional pro- and anti-saccade paradigm revealed that participants respond to emotional faces faster than to shapes during pro-saccade blocks and are more prone to errors in the antisaccade blocks, indicating that social stimuli capture greater attention and are more difficult to inhibit responses towards. Examining modulatory effects of OXT demonstrated a marginal significant interaction effect between treatment, condition and task on saccadic accuracy, with exploratory post-hoc pair-wise comparisons indicating that OXT significantly increased antisaccade errors for social stimuli. Overall, this may reflect that OXT specifically decreased the ability to switch attention away from social stimuli, but not non-social stimuli compared with PLC treatment.

Our finding that OXT decreased the ability to switch attention away from emotional faces but not shapes is in line with previous studies reporting that it specifically increased attention towards social (neutral and positive expression faces) but not non-social stimuli in an attentional-blink task (Xu et al., 2015) and enhanced attention towards distracting external social stimuli (all face expressions) in an interoceptive awareness task (Yao et al., 2018b). Studies have increasingly demonstrated that OXT plays an important role in attention orientation and attention regulation to social cues (for review: Shamay-Tsoory and Abu-Akel, 2016). Rapid and accurate recognition of others' emotions from their facial expressions is critical for human social interactions (Adolphs, 2002) and OXT has been found to enhance this ability e.g. by increasing attention to the eye region of human faces (Domes et al., 2007; Guastella et al., 2008).

Effects of OXT were specifically observed on antisaccade performance, a gaze behavior that requires volitional inhibition of automatic attention allocation towards sudden-onset visual targets. Antisaccade performance is strongly modulated by the salience of the stimulus (Myers et al., 2011). The social salience hypothesis of OXT has proposed that OXT is of particular importance for regulating attention towards salient social cues (Shamay-Tsoory and Abu-Akel, 2016). This enhanced social salience effect of OXT might therefore have contributed to an increased difficulty in inhibiting saccades away from facial, but not shape, stimuli, resulting in higher error rates for antisaccadic eye-gaze behavior in the context of social stimuli.

Previous studies investigating the effects of OXT on attentional bias towards specific emotions revealed inconsistent findings. Some studies reported that OXT specifically enhanced attention allocation towards neutral or positive facial stimuli (Domes et al., 2013b; Xu et al., 2015) while other studies found that it reduced attentional bias towards negative emotion ones (Kim et al., 2014), increased attention orientation to faces expressing either positive and negative emotions (Tollenaar et al., 2013) or all faces irrespective of emotion (Yao et al., 2018). Although we hypothesized on the basis of these previous findings indicating that OXT can influence early attentional processing of salient social stimuli via acting on bottom-up processing, we failed in the current study to find supportive evidence in terms of either reduced latencies or errors rates when subjects made reflexive prosaccades towards face stimuli. One early study on OXT modulation of detection of social stimuli also failed to find evidence for effects on early perceptual stage processing using a visual search task (Guastella et al., 2009).

The robust effect of OXT (> 50% increase across face emotions, effect size Cohen's $d = 0.46$-0.88) on increasing antisaccade errors could either be interpreted as evidence for it selectively weakening top-down control processing, without influencing bottom-up control, or alternatively as it increasing bottom-up reflexive mechanisms resulting in impaired top-down control. While OXT only influenced antisaccade and not prosaccade errors, the net effect of this is that subjects under OXT made more prosaccades towards social stimuli so this can be considered as evidence of increased bottom-up processing. On the other hand, top-down attention inhibition is not biased by specific emotions and the effects of OXT on antisaccade errors occurred across all the face emotions. It is clear from previous studies that across different paradigms OXT often influences bottom-up processing of specific face emotions (Domes et al., 2013a; Kim et al., 2013; Tolenaar et al., 2013; Xu et al., 2015) although one study has shown OXT effects irrespective of the specific face emotion (Yao et al., 2018b). Interestingly, the latter study showing effects of OXT on bottom up processing across all face emotions was the only one where the paradigm involved potential conflict between top-down and bottom up processing and as such is similar to the antisaccade paradigm. Thus, it is possible that OXT does primarily influence bottom-up attentional processing of salient social stimuli such as faces but whether it alters attention towards specific face expressions or all of them may depend on the extent to which cognitive top-down control and bottom-up reflexive processing mechanisms are in conflict.

Accumulating evidence from neuroimaging studies suggests that intranasal OXT modulates activity in the salience and motivational processing circuits of the brain, including the insular cortex and striatum (Wigton et al., 2015). Previous neuroimaging OXT-administration studies reported modulatory effects on the insular cortex specifically during processing of salient cues in the environment (Striepens et al., 2012), particularly social ones (Yao et al., 2018a), and switching attention towards these cues (Yao et al., 2018b). An increasing number of OXT-administration studies additionally reported modulatory effects on reward-related striatal processing and associated networks (Scheele et al., 2013; Mickey et al., 2016; Zhao et al., 2019a, b). Furthermore, recent evidence suggests that the striatum exhibits particularly high expression of OXT-receptors (Bethlehem et al., 2017; Quintana et al., 2019). Previous studies have demonstrated that OXT increases activation in the striatal reward-pathways in response to facial stimuli irrespective of valence suggesting that it may generally increase the salience of social cues, probably via interactions with the dopaminergic reward system (Shamay-Tsoory and Abu-Akel, 2016). In the context of these previous findings the present results may suggest that modulatory effects on salience and reward processing circuits may mediate an OXT-induced bottom-up attention orientation towards social stimuli as observed in the present study.

In a clinical context exaggerated anxiety and marked impairments in the preferential bottom-up processing of social stimuli have been reported in individuals with autism spectrum disorders (Dawson et al., 1998; Amso et al., 2014; Kou et al., 2019), particularly in the context of competing top-down attentional control demands (Wang et al., 2014). As such the present findings may indicate that OXT-treatment may have the potential to decrease anxiety and concomitantly increase attention allocation for social stimuli in autism spectrum disorders.

In conclusion, the current study has demonstrated that OXT may primarily function to increase bottom up processing of attention to salient social stimuli and that - where there is a context of conflicting top-down cognitive processing - the influence of the latter over bottom-up processing is weakened, leading to more errors in the cognitive task component.

There are several limitations in the current study. First, oval shapes were employed as non-social stimuli to differentiate effects of OXT on social versus non-social processing. However, compared to faces these stimuli have a lower visual complexity and thus we cannot exclude that the social specific effects of OXT may (partly) reflect interactions between OXT and stimulus complexity. Specifically, within the context of a previous overarching hypothesis postulating that OXT may modulate approach-avoidance motivation across social and non-social domains (Harari-Dahan and Bernstein, 2014) findings may alternatively be explained by the higher salience inherent to the visually more complex facial stimuli. Second, to avoid the task being too long and fatiguing for the participants (which might impair saccadic performance) only two blocks of non-social stimuli were included. Third, based on previous studies suggesting social-specific effects of OXT (Norman et al., 2011; Rimmele et al., 2009) the paradigm started with the presentation of the

non-social stimuli to avoid carry over effects of potential social-specific effects of OXT. However, we cannot fully exclude carry over effects in the other direction. Fourth, the sample size was based on previous OXT administration studies of OXT (e.g. Zhao et al., 2019a,b) reporting medium to large effect sizes. Although no a priori sample size estimation was employed, a sensitivity calculation revealed the sample number used in the study achieved 80% power to detect a primary treatment effect with an effect size of 0.7 (alpha = 0.05 two-tailed).

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