Intranasal oxytocin decreases fear generalization in males, but does not modulate discrimination threshold

Haoran Dou 1,2,3 · Liye Zou 4 · Benjamin Becker 5 · Yi Lei 1,2

Received: 18 May 2020 / Accepted: 13 November 2020 / Published online: 25 November 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

Abstract
Background A previously acquired fear response often spreads to perceptually or conceptually close stimuli or contexts. This process, known as fear generalization, facilitates the avoidance of danger, and dysregulations in this process play an important role in anxiety disorders. Oxytocin (OT) has been shown to modulate fear learning, yet effects on fear generalization remain unknown.

Methods We employed a randomized, placebo-controlled, double-blind, between-subject design during which healthy male participants received either intranasal OT or placebo (PLC) following fear acquisition and before fear generalization with concomitant acquisition of skin conductance responses (SCRs). Twenty-four to 72 h before the fear learning and immediately after the fear generalization task, participants additionally complete a discrimination threshold task.

Results Relative to PLC, OT significantly reduced perceived risk and SCRs towards the CS+ and GS1 (the generalization stimulus that is most similar to CS+) during fear generalization, whereas the discrimination threshold was not affected.

Conclusions Together, the results suggest that OT can attenuate fear generalization in the absence of effects on discrimination threshold. This study provides the first evidence for effects of OT on fear generalization in humans and suggests that OT may have therapeutic potential in anxiety disorders characterized by dysregulated fear generalization.

Keywords Oxytocin · Fear generalization · Discrimination threshold · Skin conductance responses (SCRs)

Introduction
Fear generalization refers to the expression of a fear response to a neutral stimulus (light, tone, or smell) that is similar to a previously conditioned fear-associated stimulus. High perceptual similarity between the fear-associated stimulus and the neutral event promotes the generalization of fear (Pavlov 1927; Desiderato and Wassarman 1967; Dunsmoor and Paz 2015). The generalization of fear represents an adaptive mechanism that promotes survival by facilitating defensive responses towards a potential danger. Maladaptive dysregulations in this mechanism have been increasingly recognized as an important contributor to the development and maintenance of exaggerated fear and anxiety and represent a key diagnostic feature of a range of debilitating psychiatric disorders (Dymond et al. 2015), particularly generalized anxiety disorder (GAD) (Lissek et al. 2014; Greenberg et al. 2013a, b), panic disorder (Lissek et al. 2009), post-traumatic stress disorder (Kaczkurkin et al. 2016), and social anxiety disorder (Ahrens et al. 2016). Thus, understanding the neurobiological basis of fear generalization and identifying effective behavioral and pharmacological interventions that inhibit fear generalization is of significant translational and clinical interest. Moreover, fear conditioning and generalization is an evolutionary highly preserved mechanism that can be examined by means of the Pavlovian fear-conditioning paradigm across species, thus promoting translational determination of
averse learning mechanisms across species and facilitating the translation from basic research to clinical application (Bowers and Ressler 2015).

The evolutionary highly conserved hypothalamic neuropeptide oxytocin (OT) has been increasingly studied as a potential treatment for enhancing the regulation of fear and anxiety (Kendrick et al. 2017; Neumann and Slattery 2016). Previous studies combining the intranasal administration of OT with functional MRI in humans have demonstrated repeatedly an attenuation of amygdala reactivity towards threatening social cues. Several previous studies reported that a single dose of intranasal OT induced robust downregulation of amygdala responses to threatening faces (Domes et al. 2007; Grace et al. 2018; Kirsch et al. 2005; Petrovic et al. 2008). Even in the patients with generalized social anxiety disorder, such that Labuschagne et al. (2010) found that OT attenuated hyper-reactivity of the amygdala towards fearful faces in patients with this disorder. Furthermore, a dose-response study (Spengler et al. 2017) demonstrated pronounced effects of a single dosage of 24 IU OT on attenuating amygdala threat reactivity to ambiguous fearful faces (35% emotional intensity). Together, results from these previous studies indicate that OT can effectively attenuate amygdala threat reactivity and shift the perception of ambiguous fearful faces towards neutral.

Based on convergent evidence for a role of OT in the regulation of fear and amygdala threat responses, initial studies have employed Pavlovian fear conditioning and extinction paradigms to examine effects on aversive learning; yet effects on fear generalization have not been examined. OT is produced primarily in the hypothalamic brain regions and released via the pituitary in the periphery and various brain regions (Donaldson and Young 2008), especially amygdala, hippocampus, and medial prefrontal cortex (mPFC). These regions highly overlap with the fear generalization network (Dunsmoor et al. 2011; Greenberg et al. 2013a). Taken together, it is reasonable to assume that OT may be able to reach fear-associated brain areas to inhibit fear generalization. OT may exert its effects on fear generalization via different mechanisms. One possible path is that OT promotes the extinction of fear generalization, such that it decreases the behavioral and physiological responses to fear generalization stimuli. Previous studies explored the effect of OT on fear extinction in both human and animal studies. In healthy male humans, OT administered following threat conditioning and prior to immediate extinction training facilitated extinction in the context of increased activation of the prefrontal cortex and attenuated amygdala activity (Eckstein et al. 2015). In rodents, OT effects on fear extinction are highly regional-specific and depend on the time of the administration (before or after the fear conditioning) (Lahoud and Maroun 2013). More specifically, OT acted as an enhancer of the fear response during extinction following local infusions in the dorsal raphe nucleus or intracerebroventricular regions (Kovács et al. 1979; Toth et al. 2012), whereas OT infusion into the central amygdala or the dorsolateral septum facilitated the extinction of fear (Viviani and Stoop 2008; Zoicas et al. 2014). A second possible pathway via which OT may modulate fear generalization is through reducing the discrimination threshold. Holt et al. (2014) tested discrimination thresholds of human faces and non-social control stimuli before participants underwent a Pavlovian fear conditioning procedure with concomitant acquisition of the psychophysiological fear response as assessed by skin conductance responses (SCRs). Results have indicated that in humans, the SCR—an autonomic threat detection index—is highly sensitive to a small perceptual difference between stimuli. Furthermore, Tuominen et al. (2019) also provided neural evidence that fear generalization responses were influenced by perceptual discrimination thresholds. They found that when the stimuli were under the discrimination thresholds, specific regions of the anterior insula and superior frontal cortex were activated. More importantly, a recent animal study by Ferretti et al. (2019) demonstrated that oxytocinergic projections from the paraventricular nucleus (PVN) of the hypothalamus to the central amygdala (CeA) are crucial for the discrimination of both positively and negatively valence emotional stimuli.

Against this background, the present study aimed at examining the effects of OT on fear generalization and the underlying pathways. To this end, 24 IU of OT was intranasally administered to healthy male participants following fear acquisition to determine effects on subsequent fear generalization. Considering that changes in the discrimination threshold may modulate fear generalization, discrimination thresholds were assessed before and after the experiment by means of the previously validated just notice differences (JNDs) procedure (Holt et al. 2014; Tuominen et al. 2019). Additionally, OT has been proposed to specifically modulate the salience of social stimuli (Shamay-Tsoory and Abu-Akel 2016), whereas an increasing number of studies reported effects on fear learning and salience processing independent of social context (Eckstein et al. 2015; Yao et al. 2018a). To additionally examine whether OT effects on fear generalization are limited to social stimuli, we therefore included both social (face morphs between two different female faces) and non-social (circle with different size) fear generalization stimuli. We hypothesized that OT would reduce shock expectations during fear generalization and the psychophysiological fear response (SCR) thus facilitating the extinction of fear generalization. Furthermore, given that a review by the Shahrestani et al.
(2013) indicated the intranasal OT promoted emotion recognition of facial stimuli, we expected that OT could alternatively modulate fear generalization by reducing the discrimination threshold relative to the PLC group.

Methods

Participants

Male university students with age ranging from 18 to 25 years were recruited via advertisements and flyers on the campus. To account for previously reported sex differences of OT on salience and social threat processing as well as brain regions involved in threat generalization (Ma et al. 2018; Luo et al. 2017), only male participants were included in this study. All volunteers were pre-screened in telephone interviews and were excluded if they (1) had no normal or corrected to normal vision; (2) were previously diagnosed with a neuropsychological disorder; (3) had rhinitis or common cold; (4) were using medication or underwent therapy; and (5) reported substance abuse. According to the aforementioned criteria, eight volunteers were excluded (7 reported rhinitis or common cold and one declined participation in the experiment). In total, 63 eligible university students underwent the experiment following randomization into either an experimental group (oxytocin treatment) or a control (placebo treatment) group. Notably, data from one participant in the control group was removed because of a technical failure during SCR acquisition. Participants received compensation of 100 RMB. Each participant provided written informed consent, and all the study protocol contributing to this work complied with the ethical standards of the local ethical council of Shenzhen University and with the Helsinki Declaration of 1975, as revised in 2008.

Design

A randomized, placebo-controlled, double-blind, between-subject trial was conducted during which 63 eligible males were randomly assigned to either an experimental group \((n = 30)\) or a control group \((n = 33, \text{ see Fig. 1})\). We adopted posteriori power calculation after the data analysis and found that the power was sufficient to support the hypothesis (see more details in the Supplementary information). Randomization was conducted via a computer-based random number generator. Participants in the experimental group received 24 International Units (IU) OT via intranasal administration of Syntocinon spray (ProSpec, Israel). Participants were asked to administer 3 puffs per nostril with 4 IU per puff. Participants were asked to wait for 1 min between the puffs to ensure that OT was fully absorbed once each puff was completed. In case the Syntocinon spray came out of the nostril cavity or was swallowed, additional puffs would be added. Participants in the placebo-controlled group (PLC) were delivered intranasally with equivalent volumes of 0.9% NaCl per nostril. To ensure double-blinding of the experimenter and participants, the bottom of bottles for OT and PLC were labeled with blue and dark color, respectively, by a research assistant who was not involved in the administration. Another research assistant blinded for the color coding was specifically responsible for distribution and recording the color code of the bottle for each participant.

Procedure

Participants were asked to visit the lab two times on different days throughout this research project (see Supplementary Fig. 1).

During the first visit, subjects were required to perform the forced-choice discrimination task (FCDT). To minimize the practice effect of FCDT, participants were arranged to come back to the lab after approximately 24 h. For the second visit, all participants initially completed three questionnaires (the Beck Depression Inventory II, BDI-2; State-Trait Anxiety Inventory, STAI; Liebowitz Social Anxiety Scale, LSAS). Given that variations in depressive and anxiety symptom load have been associated with fear generalization, we decided to control for between-group differences. Next, participants underwent the fear learning task that lasted approximately 15 min. Once the fear learning stage was completed, participants were administered either OT or PLC and waited for 40 min to maximize the treatment effect of OT on the subsequent fear generalization task that lasted approximately 20 min. Finally, all participants were retested with the FCDT.

Stimuli

Social stimuli included two pictures of neutral female faces selected from the Chinese Affective Face System (CAFS, Gong et al. 2011) which served as threat (CS+) and safety cues (CS−). A face-morphing software (Squirlz morph Version 2.1; Xiberpix, Solihull, UK) was used to create four stimuli for generalization (GS) by morphing the two faces in 20% steps (Schiele et al. 2016), with the GS most similar to the CS+ referred to as GS1 and the GS most similar to the CS− as GS4 (see Supplementary Fig. 2). Non-social stimuli included 6 circles of varying sizes. Conditioned and generalization stimuli were circles of different sizes. The smallest ring was 2 in. Circles increased successively in size by 20%. The face
stimuli were the same as the circle stimuli; half of the participants received the face A as CS+, while the other half received the face B as the CS+. The task was present using the E-prime 2 software and a 22-in. Lenovo monitor with 60 Hz resolution.

**Conditioned generalization paradigm**

The conditioned generalization paradigm used in our research was a modified version compared with that used in a previous study (Lissek et al. 2008; 2014, see Supplementary Fig. 2). The conditioned stimuli included 10 circles of varying sizes, while the unconditioned stimulus was a mild electric shock (50 ms) delivered to the right wrist. The latter was produced by a multichannel electrical stimulator (type: SXC-4A, Sanxia Technique Inc., China) and was delivered through a pair of Ag/AgCl surface electrodes. Before the experiment, we tested the participants’ pain threshold and adjusted the potency of the electric shock to a level that the participants described as “highly uncomfortable but not painful.” The paradigm consisted of two different phases: learning and generalization. The learning phase linked the conditioned fear response (shock) to the conditioned stimuli. The largest circle was the conditioned fear cue (CS+), which was paired with an uncomfortable electric stimulation. This phase presented the CS+ 12 times, of which nine included an electric stimulation (reinforcement rate, 75%). The smallest circle was the conditioned safety stimulus (CS-) and was never paired with an electric shock across its 12 presentations. The participants were required to rate their perceived likelihood of receiving an electric shock once the CS+ or CS− was presented on a 9-point scale: 1 indicated no risk; 5, moderate risk; and 9, high risk. The assignments of the large and small circles to the CS+ and CS− were counter-balanced across subjects. Each stimulus was presented for 6 s, followed by a 50-ms electric shock in the case of a CS+. The inter-trial-interval (ITI) consisted of a fixation cross-presented for a random time frame of 8–12 s (Guhn et al., 2014). Each type of the circle and face was presented in 12 trials, respectively (total, 72 trials). The sequence of the stimuli was pseudo-randomized such that maximally, three same type of stimuli followed each other. To avoid fear extinction, the reinforcement rate of CS+ was 50% in the generalization phase. The participants’ task was the same as that in the learning phase. When the participants had finished 20 trials, they were permitted to take a break. The same assignment of the largest and smallest circle to the CS+ and CS− in the learning phase was applied to the generalization phase; thus, half of the participants received the largest circle as the CS+, while the other half received the smallest circle as the CS+.

Three questions were sequentially presented to the participants immediately following both fear learning and generalization tasks: (1) valence rating: how much pleasure do you feel when this stimulus was presented? (1 very unhappy to 9
very happy). (2) Arousal rating: how much arousal do you feel when this stimulus was presented? (1 very calm to 9 very excited). We added the valence and arousal rating is to test whether the OT can reduce fear generalization by modulating the subjective emotional rating. (3) Attractiveness rating: how much attractiveness do you feel when this stimulus was presented? (1 no attractive to 9 very attractive). We defined the attractiveness in our study is that an attractive stimuli (face and circle) attract the participant, and the participant can make a judgment about them, tends to look at them. The three questions were answered on a 9-point Likert scale.

**Discrimination thresholds—forced-choice task**

The forced-choice task was used to measure perceived discrimination threshold as reflected by the just noticeable difference (JND) in psychology (Holt et al. 2014; Tuominen et al. 2019). JNDs were calculated by testing the accuracy of distinguishing the changed stimulus (morphs from face A and face B, or different size squares between square A and square B) from the initial stimulus by using a 2 alternative forced-choice (2-AFC) discrimination task (see Supplementary Fig. 3). This 2-AFC task consisted of three runs of 80 trials each. A stimulus was shown for 500 ms. After a 500-ms inter-trial interval, subjects were presented with the stimulus A and a morph stimulus side by side and asked to select which stimulus they had previously seen by pressing the left or right key; the response time was unlimited. The positions of the stimulus A and the morph stimulus were pseudo-randomized across trials. The morph stimuli used in this task were 6, 12, 24, 48, and 100 physical steps from the stimulus A. Responses were followed by a 1-s inter-trial interval. A Weibull function was fitted to the responses: $y = \frac{1}{a} 
 - e^{-(x/a)^b}$, in which $y$ is the proportion of correct responses, $x$ is the morph level, and $a$ and $b$ are the parameters for scale and shape, respectively. The JND corresponded to the morph level at which the subject achieved 75% accuracy on the 2-AFC task (Fig. 2a) (Clementz et al. 2007; Holt et al. 2014; Parkes et al. 2001; Tuominen et al. 2019). An example of this morph continuum is shown in Fig. 3a.

**SCR recording**

SCR was measured using an 8-Slot BioNex (Mindware, Model 50-3711-08) (https://www.mindwaretech.com/product_detail.asp?ItemID=1512) device. We recorded the SCR data with the BioLab Acquisition Software 3.2.1 with a 1000-Hz sample rate in our experiment by electrodermal activity (EDA) channel. Before the experiment, we asked the participants to wash their hands with clean warm water without using alcohol or liquid soap with alcohol. Then, the Ag/AgCl electrodes with 0.5% chloride wet gel were placed on the thenar and hypothenar eminence of the participants’ left palms. The date was calculated using the Basic Signal Analysis (BAS) 3.2.4 software. We calculated the difference of the mean value of 3 s before the stimulus onset as baseline and the maximum values within 6 s after the stimulus onset. If a trial lacked an SCR peak, it was recorded as a zero-response trial; specifically, if the max-baseline amplitude for any trial was below 0.02 μs, the trial was scored as a zero-response trial (Boucsein et al., 2012).

**Data analysis**

Behavioral data and SCR data were analyzed using SPSS 21.0. Behavioral data and SCR were examined by means of repeated-measures ANOVA. The ratings of valence, arousal, and attractiveness of the stimuli after the fear learning and generalization were also examined with repeated-measures ANOVA. We calculated the partial eta-square as a measure of the effect size and accessed the assumption of sphericity with Mauchly’s test. Besides, non-sphericity was corrected by Greenhouse-Geisser correction, and Bonferroni correction was adopted when pairwise comparisons were conducted. Significance threshold was set to $p < 0.05$ with two-tailed tests.

**Results**

**Demographics data**

No significant between-group differences were observed on all neuropsychological indices (anxiety trait, anxiety state, depression, social anxiety, and avoidance) and mean age (see Table 1).

| Table 1 Baseline data on age, anxiety, depression, and social anxiety in two groups |
|-----------------------------------------------|----------|----------------|----------|
| Age(year) | 19.96 ± 1.65 | 19.75 ± 1.13 | 0.61 | 0.55 |
| STAI_Trait | 39.33 ± 7.64 | 38.15 ± 10.32 | 0.51 | 0.61 |
| STAI_State | 35.20 ± 7.52 | 35.62 ± 9.28 | −0.20 | 0.84 |
| BDI_II | 7.43 ± 6.95 | 7.59 ± 5.91 | −0.10 | 0.92 |
| LSAS_FA | 21.93 ± 9.92 | 21.88 ± 9.09 | 0.02 | 0.98 |
| LSAS_A | 24.90 ± 11.41 | 23.78 ± 7.07 | 0.46 | 0.65 |

|M mean, SD standard deviation  
†State-Trait Anxiety Inventory  
‡ Beck Depression Inventory-II  
§ LSAS_FA Liebowitz Social Anxiety Scale_Fear/Anxiety subscale  
¶ LSAS_A Liebowitz Social Anxiety Scale_Avoidance subscale
Perceived risk score

Fear learning

During the fear acquisition phase, a significant main effect of stimuli was observed \((F(1, 60) = 405.344, p < 0.001, \eta_p^2 = 0.871)\). The perceived risk of the CS+ was significantly higher than that of CS−. In addition, a significant main effect of stimulus material was also observed \((F(1, 60) = 11.222, p = 0.001, \eta_p^2 = 0.158)\); participants perceived the facial CS with higher risk relative to the non-social (circle) CS. However, we did not observe significant results in terms of a main effect of group \((F(1, 60) = 0.000, p = 0.988, \eta_p^2 = 0.000)\), group × stimuli interaction effect \((F(1, 60) = 0.382, p = 0.539, \eta_p^2 = 0.006)\), group × material interaction effect \((F(1, 60) = 2.434, p = 0.124, \eta_p^2 = 0.039)\), and material × stimuli interaction effect \((F(1, 60) = 0.511, p = 0.477, \eta_p^2 = 0.008)\). Likewise the stimuli × material × group interaction effect was not significant \(F(1, 60) = 0.431, p = 0.514, \eta_p^2 = 0.007)\). The results of the fear learning task are displayed in Fig. 2a. Collectively, the findings suggest a successful acquisition of the fear response in both groups.

Fear generalization

For the fear generalization, a significant main effect of stimuli was observed \((F(2.6, 156.5) = 265.753, p < 0.001, \eta_p^2 = 0.816)\). Results from post hoc test indicated that the perceived risk of CS+ was higher than that of other GS and CS− \((p < 0.001)\): GS1 > GS2→, CS− \((p < 0.001)\); GS3 > GS4, CS− \((p < 0.001)\); GS4 > CS− \((p = 0.073)\). Moreover, a significant main effect of group was observed \((F(1, 60) = 6.819, p = 0.011, \eta_p^2 = 0.102)\), suggesting that the OT group showed a considerably lower perceived risk relative to PLC group. Moreover, a group × stimuli interaction effect was also significant \((F(2.6, 156.5) = 4.301, p = 0.009, \eta_p^2 = 0.067)\), and results from simple-effect analyses indicated significantly higher perceived risk of CS+ \((F(1, 60) = 14.197, p < 0.001, \eta_p^2 = 0.191)\) and GS1 \((F(1, 60) = 5.427, p = 0.023, \eta_p^2 = 0.083)\) in the PLC group as compared to those in the OT group. However, we did not observe significant results in terms of a main effect of materials \((F(1, 60) = 2.809, p = 0.099, \eta_p^2 = 0.045)\), material × group interaction effect \((F(1, 60) = 1.759, p = 0.190, \eta_p^2 = 0.028)\), material × generalization stimuli interaction effect \((F(3.0, 183.9) = 1.560, p = 0.200, \eta_p^2 = 0.025)\), material × generalization stimuli × group interaction effect \((F(3.0, 183.9) = 1.560, p = 0.200, \eta_p^2 = 0.025)\), and a main effect of generalization stimuli \((F(3.0, 183.9) = 1.560, p = 0.200, \eta_p^2 = 0.025)\).

During extinction of fear generalization, the placebo group exhibited a higher SCR for GS1 in Block2 \((p = 0.019)\) and Block3 \((p = 0.019)\) higher than that compared to the oxytocin group. e The SCR of CS+ was larger than that of CS− in fear learning \((p < 0.001)\) for both face and circle. And there was no significant difference between the oxytocin and placebo groups. f The SCR of CS+ \((p = 0.041)\) and GS1 \((p = 0.041)\) in the placebo group was significantly higher than that in the oxytocin group, and GS2 showed a marginal significant difference \((p = 0.067)\) for both face and circle materials. g During the extinction of fear generalization, the SCR of CS+ in Block1 \((p = 0.011)\) and Block2 \((p = 0.059)\) was higher in the placebo group as compared to that in the oxytocin group. h During the extinction of fear generalization, the placebo group exhibited a higher SCR for GS1 in Block2 \((p = 0.059)\) and Block3 \((p = 0.045)\) compared to that in the oxytocin group.
\( F(3.1, 183.9) = 0.990, p = 0.400, \eta_p^2 = 0.016 \). Results of the fear generalization task are displayed in Fig. 2b.

To determine the effect of OT on extinction of fear generalization between the two groups, the presentation of each generalization stimulus was segmented into three parts (Block1, Block2, Block3) according to the phase of the extinction procedure based on time frame. We found a significant main effect of time in the perceived risk of CS+ \((F(2, 120) = 8.894, p < 0.001, \eta_p^2 = 0.129)\). Pairwise comparison showed that the perceived risk of Block1 was much higher than those of Block2 \((p = 0.053)\) and Block3 \((p = 0.001)\). A significant time \(\times\) group interaction effect was observed on CS+ \((F(2, 120) = 3.148, p = 0.046, \eta_p^2 = 0.050)\). Results from simple-effect analyses indicated that the OT group was rated the perceived risk of the CS+ lower as compared to that in the PLC group. An interaction effect of time and group was not significant \((\eta_p^2 = 0.019, \eta_p^2 = 0.014, \eta_p^2 = 0.021)\) (Fig. 2c).

In the GS1, a significant main effect of time \((F(2, 120) = 21.923, p < 0.001, \eta_p^2 = 0.259)\) was observed. The perceived risk of Block1 \((6.155, 0.196)\) was significantly higher than that of Block2 \((4.945, 0.243, p < 0.001)\) and Block3 \((4.808, 0.241, p < 0.001)\). A main effect of group was significant \((F(1, 60) = 5.727, p = 0.020, \eta_p^2 = 0.087)\). However, an interaction effect of time and group was not significant \((F(2, 120) = 0.732, p = 0.483, \eta_p^2 = 0.012)\). Although the interaction effect was not significant, we exploratively calculated the simple effect and found that the OT group rated the perceived risk of the GS1 lower as compared to the PLC group in Block2 \((F(1, 60) = 3.350, p = 0.072, \eta_p^2 = 0.053)\) and Block3 \((F(1, 60) = 5.826, p = 0.019, \eta_p^2 = 0.089)\). Results for extinction of fear generalization are displayed in Fig. 2d.

### SCR data during fear learning

A significant main effect of stimuli \((F(1, 60) = 14.529, p < 0.001, \eta_p^2 = 0.195)\) was observed, but no main effect of group \((F(1, 60) = 0.679, p = 0.413, \eta_p^2 = 0.011)\) or stimuli \(\times\) group interaction effect \((F(1, 60) = 0.626, p = 0.432, \eta_p^2 = 0.010)\). With regard to the SCRs, results of stimuli main effect indicated that CS+ was significantly higher than CS−. However, no significant results for material \((F(1, 60) = 1.506, p = 0.225, \eta_p^2 = 0.024)\), material \(\times\) group interaction \((F(1, 60) = 0.011, p = 0.918, \eta_p^2 = 0.000)\), material \(\times\) stimuli interaction \((F(1, 60) = 1.019, p = 0.317, \eta_p^2 = 0.017)\), and material \(\times\) stimuli \(\times\) group interaction \((F(1, 60) = 0.017, p = 0.898, \eta_p^2 = 0.000)\) were observed (see Fig. 2e).

### SCR data during fear generalization

Examination of the SCR data during fear generalization revealed a marginal significant effects of group \((F(1, 60) = 3.276, p = 0.075, \eta_p^2 = 0.052)\). The SCR in the OT group was considerably lower than that in the placebo group. An interaction effect of generalization stimulus and group was significant \((F (2.1, 127) = 4.412, p = 0.013, \eta_p^2 = 0.069)\). Results from simple-effect analyses indicated that the SCRs of CS+ and GS1 in the OT group were lower as compared to those in the placebo group \((CS+: F(1, 60) = 4.351, p = 0.041, \eta_p^2 = 0.068; GS1: F(1, 60) = 0.041, \eta_p^2 = 0.068)\). The SCR of GS3 was marginally significantly different between the two groups \((F(1, 60) = 3.490, p = 0.067, \eta_p^2 = 0.055)\), with the OT group exhibiting lower score as compared to the PLC group. However, no significant effect of materials \((F(1, 60) = 0.099, p = 0.754, \eta_p^2 = 0.002)\), material \(\times\) group interaction \((F(1, 60) = 0.303, p = 0.857, \eta_p^2 = 0.001)\), material \(\times\) generalization stimulus interaction \((F(3.4, 205) = 0.990, p = 0.424, \eta_p^2 = 0.016)\), and material \(\times\) generalization stimuli \(\times\) group interaction \((F(3.4, 205) = 1.300, p = 0.274, \eta_p^2 = 0.021)\) was observed (see Fig. 2f).

To determine the treatment effects on extinction of fear generalization, each generalization stimulus was segmented into three parts (Block1, Block2, Block3) based on the presentation time frame. The main effect of time was marginal significant on CS+ \((F(1.7, 101) = 2.667, p = 0.084, \eta_p^2 = 0.043)\). A significant main effect of group on the CS+ \((F(1, 60) = 4.276, p = 0.043, \eta_p^2 = 0.067)\) was also observed. Although the time \(\times\) stimuli interaction effect was not significant \((F(1.7, 101) = 1.623, p = 0.202, \eta_p^2 = 0.026)\), results of an exploratory simple-effect analysis indicated that CS+ in OT showed a lower SCR than that in the placebo group in Block1 \((F(1, 60) = 6.910, p = 0.011, \eta_p^2 = 0.102)\), and a marginal significantly lower SCR than that in PLC in Block2 \((F(1, 60) = 3.707, p = 0.059, \eta_p^2 = 0.058)\) (Fig. 2g). In GS1, the main effect of the group was significant \((F(1, 60) = 4.380, p = 0.41, \eta_p^2 = 0.068)\). But we did not find the significant main effect of time \((F(1.7, 100) = 1.452, p = 0.239, \eta_p^2 = 0.024)\). Although the time \(\times\) group interaction effect of SCR in GS1 was non-significant \((F(1.7, 100) = 0.207, p = 0.772, \eta_p^2 = 0.003)\), results of simple-effect analysis revealed that GS1 in OT showed a lower SCR than that in PLC in Block3 \((F(1, 60) = 4.182, p = 0.045, \eta_p^2 = 0.065)\), a marginal significantly lower SCR than that in PLC in Block2 \((F(1, 60) = 3.711, p = 0.059, \eta_p^2 = 0.058)\) (see Fig. 2h).

### Discrimination threshold

The FCDT was conducted before and after the experiment to explore whether OT influenced discrimination thresholds. We adopted 2 materials (face, square) \(\times\) 2 time (pretest, posttest) \(\times\) 2 group (OT, PLC) repeated-measures ANOVAs. The results suggested that the main effect of the material was significant \((F(1, 60) = 27.825, p = 0.001, \eta_p^2 = 0.317)\) suggesting that the JND for face stimuli \((21.1, 2.008)\) was considerably higher than for the non-social (circle) stimuli \((10.909, 0.828)\). The main effect of time was also significant \((F(1, 60) = 5.988, p = 0.017, \eta_p^2 = 0.091)\). The JND of the posttest \((14.842, 1.201)\)
was much lower than that of the pretest (17.688, 1.375). However, neither the main effect of the group \((F(1, 60) = 0.375, \eta_p^2 = 0.006)\) nor the group \(\times\) time interaction effect \((F(1, 61) = 0.004, p = 0.952, \eta_p^2 = 0.000)\) reached a significance. Moreover, the analysis revealed a non-significant material \(\times\) group interaction effect \((F(1, 60) = 0.079, p = 0.780, \eta_p^2 = 0.001)\), non-significant material \(\times\) time \((F(1, 60) = 0.977, p = 0.327, \eta_p^2 = 0.0106)\), and a non-significant material \(\times\) time \(\times\) group interaction effect \((F(1, 60) = 0.240, p = 0.626, \eta_p^2 = 0.004)\) for the JND (see Fig. 3b).

**Emotional ratings of the generalization stimuli**

**Valence rating**

For the valence rating after fear learning, a significant main effect of the stimuli was observed \((F(1, 60) = 97.211, p < 0.001, \eta_p^2 = 0.618)\). The valence of the CS+ was significantly lower than that of the CS−. A significant main effect of material was also observed \((F(1, 60) = 7.728, p = 0.007, \eta_p^2 = 0.114)\). The valence of the facial stimuli was much lower than that of the circle stimuli. Furthermore, a non-significant main effect of group \((F(1, 60) = 0.479, p = 0.492, \eta_p^2 = 0.008)\), non-significant stimuli \(\times\) group interaction effect \((F(1, 60) = 0.967, p = 0.329, \eta_p^2 = 0.016)\), non-significant material \(\times\) stimuli interaction effect \((F(1, 60) = 0.304, p = 0.583, \eta_p^2 = 0.005)\), and non-significant the material \(\times\) group \(\times\) stimuli interaction effect \((F(1, 60) = 1.600, p = 0.211, \eta_p^2 = 0.026)\) were observed in the valence rating following the fear learning phase. The results of valence score after the fear learning are displayed in Fig. 4a.

For the valence rating after fear generalization, a significant main effect of the stimuli was observed \((F(2.3135) = 50.368, p < 0.001, \eta_p^2 = 0.456)\). The interaction effect of the stimuli \(\times\) group was significant \((F(4.2, 251) = 5.136, p < 0.001, \eta_p^2 = 0.079)\); results of simple effect showed that the valence scores of CS+ \((F(1, 60) = 12.824, p = 0.001, \eta_p^2 = 0.177)\) and GS1 \((F(1, 60) = 9.326, p = 0.003, \eta_p^2 = 0.135)\) in the facial stimuli were much lower than that in the circle stimuli. However, the main effect of the group \((F(1, 61) = 0.279, p = 0.599, \eta_p^2 = 0.005)\), the interaction effect of material \(\times\) group \((F(1, 60) = 0.989, p = 0.324, \eta_p^2 = 0.016)\), and the material \(\times\) stimuli \(\times\) group interaction effect \((F(4.2, 251) = 1.806, p = 0.125, \eta_p^2 = 0.029)\) did not reach statistical significance (see Fig. 4b).

**Arousal rating**

For the arousal rating after fear learning, the main effect of the stimuli was significant \((F(1, 60) = 46.665, p < 0.001, \eta_p^2 = 0.437)\); indicating that the arousal of CS+ was higher than the arousal of CS−. A non-significant main effect of group was observed \((F(1, 60) = 1.079, p = 0.303, \eta_p^2 = 0.018)\). Likewise, a non-significant group \(\times\) stimuli interaction effect \((F(1, 60) = 0.081, p = 0.777, \eta_p^2 = 0.001)\), a non-significant group \(\times\) material interaction effect \((F(1, 60) = 0.060, p = 0.808, \eta_p^2 = 0.001)\), and a non-significant group \(\times\) stimuli \(\times\) material interaction effect \((F(1, 60) = 1.156, p = 0.287, \eta_p^2 = 0.019)\) were observed. Besides, the main effect of material \((F(1, 60) = 2.193, p = 0.144, \eta_p^2 = 0.035)\) and the interaction effect of the material and stimuli \((F(1, 60) = 0.943, p = 0.335, \eta_p^2 = 0.015)\) were not significant (see Fig. 4c).

For the arousal rating after fear generalization, a significant main effect of the stimuli \((F(2.8, 169) = 35.973, p < 0.001, \eta_p^2 = 0.446)\) was observed. However, neither the main effect of the group \((F(1, 60) = 0.019)\) were observed. Besides, the main effect of material \((F(1, 60) = 0.019)\) were observed. Moreover, the analysis revealed a non-significant material \(\times\) group interaction effect \((F(1, 60) = 0.125, p = 0.543)\) and the interaction effect of the material and group \((F(2.3135) = 4.517, p < 0.001, \eta_p^2 = 0.020)\) were not significant.
In the fear learning task, a main effect of the material was observed (F(1, 60) = 11.566, p = 0.001, ηp² = 0.162). The facial stimuli showed higher arousal than the circle stimuli. However, the main effect of the group (F(1, 60) = 0.221, p = 0.640, ηp² = 0.004), the group × stimuli interaction effect (F(2.8, 169) = 0.633, p = 0.675, ηp² = 0.010), the group × material interaction effect (F(1, 60) = 0.280, p = 0.599, ηp² = 0.005), and the group × material × stimuli interaction effect (F(4.1, 245) = 0.470, p = 0.761, ηp² = 0.008) were all non-significant (see Fig. 4d).

Rating of attractiveness

For the attractiveness rating after the fear learning, the main effect of the stimuli was significant (F(1, 60) = 16.222, p < 0.001, ηp² = 0.213); the attractiveness score of the CS− was higher than that of the CS+. A significant main effect of material (F(1, 60) = 6.307, p = 0.015, ηp² = 0.095) was found suggesting that the facial stimuli rated higher than the non-social (circle) stimuli. However, a non-significant main effect of the group (F(1, 60) = 0.386, p = 0.537, ηp² = 0.006), non-significant group × stimuli interaction effect (F(1, 60) = 0.088, p = 0.768, ηp² = 0.001), non-significant material × group interaction effect (F(1, 60) = 1.431, p = 0.236, ηp² = 0.023), non-significant material × stimuli interaction effect (F(1, 60) = 0.696, p = 0.408, ηp² = 0.011), and non-significant material × stimuli × group interaction effect (F(1, 60) = 1.599, p = 0.211, ηp² = 0.026) were observed for the attractiveness ratings (see Fig. 4e).

In the fear generalization task, the main effect of the stimuli was significant (F(2, 124) = 6.097, p = 0.003, ηp² = 0.092); GS1 was less attractive than GS4 (p < 0.05). We also found a significant interaction effect of material × stimuli (F(3.9, 233) = 2.889, p = 0.024, ηp² = 0.046); results of simple effect indicated that GS2 (F(1, 60) = 4.128, p = 0.047, ηp² = 0.064), GS3 (F(1, 60) = 11.769, p = 0.001, ηp² = 0.164), and GS4 (F(1, 60) = 6.203, p = 0.016, ηp² = 0.094) was observed. The main effect of the material was also significant (F(1, 60) = 11.566, p = 0.001, ηp² = 0.162). The facial stimuli showed higher arousal than the circle stimuli. However, the main effect of the group (F(1, 60) = 0.221, p = 0.640, ηp² = 0.004), the group × stimuli interaction effect (F(2.8, 169) = 0.633, p = 0.675, ηp² = 0.010), the group × material interaction effect (F(1, 60) = 0.280, p = 0.599, ηp² = 0.005), and the group × material × stimuli interaction effect (F(4.1, 245) = 0.470, p = 0.761, ηp² = 0.008) were all non-significant (see Fig. 4d).
material (F(1, 60) = 0, p = 0.985, \eta^2_p = 0.000), the group \times stimuli interaction effect (F(2.1, 124) = 0.747, p = 0.480, \eta^2_p = 0.012), and the group \times stimuli \times material interaction effect (F(3.9, 233) = 1.482, p = 0.210, \eta^2_p = 0.024) failed to reach statistical significance (see Fig. 4f).

Discussion

The present experiment revealed the first evidence that intranasal OT has the potential to modulate fear generalization in the healthy humans. More specifically, the results of the present study suggest that during a fear generalization paradigm, intranasal OT reduced the perceived risk of CS+ and GS1 accompanied by an attenuated SCR to both, CS+ and GS1, in the OT relative to the PLC group. Moreover, we additionally found that during the fear generalization task, OT facilitated the decrease of the perceived risk of CS+ during time. Notably, the interaction of materials \times group or materials \times group \times stimuli was not significant, suggesting that OT did not differentially modulate processing of different materials, and the observed effects of OT generalize across social and non-social contexts of fear generalization. Additionally, the discrimination threshold assessed after fear generalization was not affected by OT, suggesting that effects of OT on the discrimination threshold may not have contributed to its effects on fear generalization. Finally, no effects of OT were observed on the perceived pleasantness, arousal, and attractiveness of the stimuli after fear generalization, which argues against unspecified effects of OT on stimulus perception.

We found that OT attenuated the behavioral and physiological response to CS+ and GS1 during fear generalization. These findings indicate that OT does not only reduce the response to conditioned fear stimuli but may also have the ability to modulate fear generalization. Fear learning and generalization are neurally mediated by limbic-prefrontal circuits, including the amygdala and (medial) prefrontal regions (Lopresto et al. 2016). Previous studies reported modulatory effects of intranasal OT on these circuits, such that several previous studies observed that OT attenuated amygdala reactivity in response to threatening social stimuli, including fearful faces (Kirsch et al. 2005). Moreover, OT has been shown to attenuate amygdala threat reactivity in patients with exaggerated amygdala responsivity such that it attenuated elevated amygdala responses to fearful faces in generalized anxiety disorders (Labuschagne et al. 2010). Previous studies furthermore reported effects on ambiguous threatening faces, such that Quintana et al. (2015) reported decreased anger ratings for ambiguous faces, and Spengler et al. (2017) reported that ambiguous fearful stimuli (35% emotional intensity) were judged more neutral in the context of decreased amygdala reactivity following OT. In addition, previous studies reported that OT does not only attenuates amygdala reactivity but also strengthens the connectivity of the amygdala with medial prefrontal regions engaged in emotion regulation and suppression of a previously learned fear responses (e.g., Eckstein et al. 2017).

With respect to the different pathways that may explain the effects of OT on fear generalization, we found that OT did not modulate extinction of fear generalization, but promoted the decrease of the perceived risk of CS+ in the fear generalization. In the present study, the OT significantly modulated the reduction during time on the perceived risk of CS+ rather than SCR of CS+. This might be due to the different time courses of the two fear indices and the different brain systems mediating these processes. For instance, previous studies reported that SCRs towards threat-associated stimuli precede the conscious awareness of threat contingency (Knight et al. 2003). Moreover, threat effects on autonomous responses including the SCR are mediated by limbic and brainstem regions (Becker et al. 2012; Mangina and Beuzeron-Mangina 1996), while risk assessments and threat anticipation additionally require the engagement of prefrontal regions (Kirkic et al. 2017; Nitschke et al. 2006). A previous study examining the effects of OT on extinction revealed a general reduction of amygdala activation, yet a threat-stimulus specific enhancement of prefrontal activation following OT (Eckstein et al. 2015) during threat extinction, suggesting differential effects on brain systems engaged in autonomous threat reactivity and risk evaluation. Moreover, it should be pointed out that in our fear generalization task, CS+ was also paired with shock with a 50% chance, whereas fear extinction procedures in other studies did not pair the CS+ with a shock during extinction. Therefore, CS+ in fear generalization phase was not the standard extinction. This reduction effect with time might be due to the decrease of reinforcement rate (75% in fear learning and 50% in fear generalization). In brief, we found the main effect of time that the perceived risk of CS+ reduced with time and OT promoted this reduction effect in the fear generalization phase.

Our results showed that OT did not affect discrimination thresholds. This argues against the second potential pathway via which OT may affect fear generalization, specifically that OT may decrease the discrimination threshold of the generalized stimuli and in turn attenuates fear generalization. Although several previous studies reported that OT enhanced emotion recognition in faces (Shahrestani et al. 2013), most of these studies examined motion recognition using unambiguous emotional faces and did not sensitively assess the threshold of discrimination using ambiguous faces. Moreover, Domes et al. (2013) demonstrated that intranasal OT did not have an impact on discrimination performance in both healthy adults and individuals with autism spectrum disorder (ASD) when facial and non-social stimuli (house) were used. Together, despite the lack of apparent OT effects on the
discrimination threshold, we cannot fully exclude that the combination with the fear generalization task may have influenced the sensitivity to determine OT effects on the discrimination threshold, and future studies are needed to confirm the lack of OT effects on the discrimination threshold.

Furthermore, the present design does not allow us to exclude alternative pathways by which OT may have affected fear generalization. For instance, ambiguity-based uncertainty played a critical role in fear generalization and might be also influenced by OT (Onat and Büchel 2015). Several previous studies reported effects of OT on insula activation in healthy subjects, including modulated insular responses to potentially threatening stimuli (Striepens et al. 2012) and salient cues in the environment independent of social context (Yao et al. 2018a, b). Our results did not test the value of the accurate uncertainty, but the fearful response to fear generalization was inhibited by OT. We inferred that OT might also be able to decrease the feeling of uncertainty during fear generalization. In line with these results, Spengler et al. (2017) reported that intranasal OT made the ambiguous fearful stimuli (35% emotional intensity) more neutral, which might inhibit the ambiguity-based uncertainty. However, some other researchers have found that OT enhanced startle reflex responses in the unpredictable threat condition in the conditioned fear learning task (Grillon et al. 2013). Because we did not directly assess levels of uncertainty in our study, it remains more evidence to clarify the details.

At the end of the fear learning and generalization, we tested the valence, arousal, and attractiveness of each stimulus. We found that no effect of OT on the ratings of valence, arousal, and attractiveness was observed, arguing against the notion that unspecific effects of OT on stimulus perception may have affected effects on fear generalization. Alternatively, the lack of effects might be due to the fear generalization paradigm that contained several trials and took nearly 20 min. The emotional rating was after repeated presentation of the stimuli during the fear generalization task. Although the reinforcement rate of CS+ in the fear generalization was 50%, we still found the reduction of perceived risk of CS+ in time in fear generalization stage. We inferred that no OT effect in the emotional rating after the fear generalization was due to this decrease with time. Of course, another possibility was due to the distinguishing of physiological reactions and subjective emotional feeling after the fear generalization, which required more evidence. Besides, in this experiment, we found no significant effect between the social stimuli and non-social stimuli. Although previous studies reported that oxytocin specifically modulated processing of social information (face stimulus) (Gorka et al. 2015; Xu et al. 2019), studies in animals and healthy humans also reported that OT affected basal emotional processes, including fear extinction, independent of social context (Eckstein et al. 2015; Onaka et al. 2012; Yao et al. 2018a; Yoshida et al. 2009). Therefore, our results indicated that OT modulates fear generalization function in healthy humans across social and non-social stimuli.

Our research provides the first preclinical evidence for a potential of OT to modulate fear generalization in humans. Our data resonates with previous findings in animals and humans suggesting a role of OT on threat and stress-related processes including fear-related learning. Overgeneralization is not only the important symptom of GAD (Lissek et al. 2014; Greenberg et al. 2013b) but also fear memory-related disorders, such as panic disorder (Lissek et al. 2009) and posttraumatic stress disorder (Kaczkurkin et al. 2016). Therefore, the present results suggest a potential therapeutic application of OT in disorders associated with dysregulated fear generalization.

The present study has some limitations. First of all, we recorded only behavioral data and physiological data without any functional neuroimaging data, and therefore, the neural mechanism underlying the effects of OT on fear generalization in human remains to be determined. Furthermore, future research employing clinical trial designs is needed to determine the therapeutic potential effect of intranasal oxytocin in anxiety disorders. More specifically, overgeneralization showed an abnormal gradient in fear generalization, especially less degradation of fear response to GS, which played an important role in many anxiety disorders (Laufer et al. 2016; Lissek et al. 2009; Lissek et al. 2014). OT may be able to recover the over intensity of fear response to GS by inhibiting the activity of amygdala. In addition, in this experiment, in order to rule out the extra variable evoked by the female menstrual cycle and account for previously reported sex differences in the effects of OT, we only recruited male adults. Accumulating evidence suggests that OT may exert different or even opposing effects in men and women during early social threat perception (Luo et al. 2017) as well as social evaluation and interaction (Ma et al. 2018; Gao et al. 2016).

Besides, the present study was not pre-registered. Pre-registration is a good method to improve the quality of the study by controlling for publication bias and selective reporting, and future studies can use this method.

**Conclusion**

The present study found that OT decreases fear generalization but did not affect the discriminate threshold. This research helps to elucidate novel evidence on the effects of OT on fear generalization and suggests that OT may have beneficial effects in disorders with dysregulated fear generalization and exaggerated fear reactivity.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00213-020-05720-8.
Funding The work was supported by the National Natural Science Foundation of China (NSFC, Grant Numbers, 31871130, 31571153, 91632117), the National Key Research and Development Program of China (Grant Number 2018YFA0701400), and the Science, Innovation and Technology Department of the Sichuan Province (2018JY0001). Guangdong Key Project in “Development of new tools for diagnosis and treatment of Autism” (2018B030355001), National Natural Science Foundation of China (31671150), Innovative Team Program in Higher Education of Guangdong, China (2015KCXTD009), Major Program of Guangdong, China (2016KZDXM009), Shenzhen Basic Research Scheme (JCYJ20150729104249783), Shenzhen Peacock Plan (KQTD2015033101604926), Investigation and evaluation of neural mechanisms associated with development of language, emotion, and cognitive disorders, 2019SHIBS0003.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Ahrens LM, Pauli P, Reif A, Mühlberger A, Langs G, Aaldertink T, Wieser MJ (2016) Fear conditioning and stimulus generalization in patients with social anxiety disorder. J Anxiety Disord 44:36–46
Becker B, Mihov Y, Scheele D, Kendrick KM, Jentsch A et al (2012) Fear processing and social networking in the absence of a functional amygdala. Biol Psychiatry 72(1):70–77
Bowers ME, Ressler KJ (2015) An overview of translational informed treatments for posttraumatic stress disorder: animal models of Pavlovian fear conditioning to human clinical trials. Biol Psychiatry 78(5):E15–E27
Clementz BA, McDowell JE, Dobkins KR (2007) Compromised speed discrimination among schizophrenia patients when viewing smooth pursuit targets. Schizophr Res 95(1–3):61–64
Desiderato O, Wasserman ME (1967) Incubation of anxiety: effect on generalization gradients. J Exp Psychol 74(4p1):506
Domes G, Heinrichs M, Gläscher J, Büchel C, Braus DF, Herpertz SC (2007) Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol Psychiatry 62(10):1187–1190
Domes G, Heinrichs M, Kumbier E, Grossmann A, Hauenstein K, Herpertz SC (2013) Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. Biol Psychiatry 74(3):164–171
Donaldson ZR, Young LJ (2008) Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322(5903):900–904
Dunsmoor JE, Paz R (2015) Fear generalization and anxiety: behavioral and neural mechanisms. Biol Psychiatry 78(5):336–343
Dunsmoor JE, Prince SE, Murtyp VP, Kragel KA, LaBar KS (2011) Neurobehavioral mechanisms of human fear generalization. Neuroimage 55(4):1878–1888
Dyndol SD, Dunsmoor JE, Vervliet B, Roche B, Hermans D (2015) Fear generalization in humans: systematic review and implications for anxiety disorder research. Behav Ther 46(5):561–582
Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE, Grinevich V, Kendrick KM, Maier W, Hurlemann R (2015) Oxytocin facilitates the extinction of conditioned fear in humans. Biol Psychiatry 78(3):194–202
Eckstein M, Markett S, Kendrick KM, Ditzen B, Liu F, Hurlemann R, Becker B (2017) Oxytocin differentially alters resting state functional connectivity between amygdala subregions and emotional control networks: inverse correlation with depressive traits. Neuroimage 149:458–467
Ferretti V, Maltese F, Contarini G, Nigro M, Bonavia A, Huang H et al (2019) Oxytocin signaling in the central amygdala modulates emotion discrimination in mice. Curr Biol 29:1938–1953.e6
Gao S, Becker B, Luo L, Geng Y, Zhao W, Yin Y et al (2016) Oxytocin, the peptide that bonds the sexes also divides them. Proc Natl Acad Sci 113(27):7650–7654
Gong X, Huang Y-X, Wang Y, Luo Y-J (2011) Revision of the Chinese facial affective picture system. Chin Ment Health J 25(1):40–46
Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, Phan KL (2015) Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. Neuropsychopharmacology 40(2):278–286
Grace SA, Rossell SL, Heinrichs M, Kordschach A, Labuschagne I (2018) Oxytocin and brain activity in humans: a systematic review and coordinate-based meta-analysis of functional MRI studies. Psychoneuroendocrinology 96:66–24
Greenberg T, Carlson JM, Cha J, Hajcak G, Mujica-Parodi LR (2013a) Neural reactivity tracks fear generalization gradients. Biol Psychol 92(1):2–8
Greenberg T, Carlson JM, Cha J, Hajcak G, Mujica-Parodi LR (2013b) Ventromedial prefrontal cortex reactivity is altered in generalized anxiety disorder during fear generalization. Depress Anxiety 30(3):242–250
Grillon C, Kirmisky M, Charney DR, Vytal K, Ernst M, Cornwell B (2013) Oxytocin increases anxiety to unpredictable threat. Mol Psychiatry 18(9):958–960
Holt DJ, Boeke EA, Wolthusen RP, Nasr S, Milad MR, Tootell RB (2014) A parametric study of fear generalization to faces and non-face objects: relationship to discrimination thresholds. Front Hum Neurosci 8:624
Kaczurkin AN, Burton PC, Chazin SM, Manbeck AB, Espensen-Sturges T, Cooper SE, Sponheim SR, Lissek S (2016) Neural substrates of overgeneralized conditioned fear in PTSD. Am J Psychiatr 174(2):125–134
Kendrick KM, Guastella AJ, Becker B (2017) Overview of human oxytocin research. In: Behavioral pharmacology of neuropeptides: oxytocin. Springer, Cham, pp 321–348
Kirlic N, Aupperle RL, Misaki M, Kuplicki R, Alvarez RP (2017) Recruitment of orbitofrontal cortex during unpredictable threat among adults at risk for affective disorders. Brain Behav 7(8):e00757
Kirsch P, Esslinger C, Chen Q, Mier D, Las S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A (2005) Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci 25(49):11489–11493
Knight DC, Nguyen HT, Bandettini PA (2003) Expression of conditional functional connectivity between amygdala subregions and emotional control networks: inverse correlation with depressive traits. Neuroimage 149:458–467
Kovacs GL, Bohus B, Versteeg DH, De Kloe ER, De Wied D (1979) Effect of oxytocin and vasopressin on memory consolidation: sites of action and catecholaminergic correlates at local microinjection into limbic-midbrain structures. Brain Res 175(2):303–314
Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, Stout JC, Nathan PJ (2010) Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. Neuropsychopharmacology 35(12):2403–2413
Lahoud N, Maroun M (2013) Oxytocinergic manipulations in corticolimbic circuit differentially affect fear acquisition and extinction. Psychoneuroendocrinology 38(10):2184–2195
Laufer O, Israelie D, Paz R (2016) Behavioral and neural mechanisms of overgeneralization in anxiety. Curr Biol 26(6):713–722
Lissek S, Biggs AL, Rabin SJ, Cornwell BR, Alvarez RP, Pine DS, Grillon C (2008) Generalization of conditioned fear-potentiated
Quintana DS, Westlye LT, Rustan ØG, Tesli N, Poppy CL, Smevik H, Petrovic P, Kalisch R, Singer T, Dolan RJ (2008) Oxytocin attenuates Pavlov IP (1927) Conditioned reflexes: an investigation of the physiology and treatment of posttraumatic stress disorder. Neurosci Biobehav Rev 68:31–42
Luo L, Becker B, Geng Y, Zhao Z, Gao S, Zhao W et al (2017) Sex-dependent neural effect of oxytocin during subliminal processing of negative emotion faces. Neuroimage 162:127–137
Ma X, Zhao W, Luo R, Zhou F, Geng Y, Xu L, Gao Z, Zheng X, Becker B, Kendrick KM (2018) Sex-and context-dependent effects of oxytocin on social sharing. Neuroimage 183:62–72
Mangina CA, Beuzeron-Mangina JH (1996) Direct electrical stimulation of specific human brain structures and bilateral electrodermal activity. Int J Psychophysiol 22(1–2):1–8
Neumann ID, Slattery DA (2016) Oxytocin in general anxiety and social fear: a translational approach. Biol Psychiatry 79(3):213–221
Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ (2006) Functional neuroanatomy of aversion and its anticipation. Neuroimage 29(1):106–116
Onaka T, Takayanagi Y, Yoshida M (2012) Roles of oxytocin neurones in the control of stress, energy metabolism, and social behaviour. J Neuroendocrinol 24(4):587–598
Onat S, Büchel C (2015) The neuronal basis of fear generalization in humans. Nat Neurosci 18(12):1811–1818
Parkes L, Lund J, Angelucci A, Solomon JA, Morgan M (2001) Compulsory averaging of crowded orientation signals in human vision. Nat Neurosci 4(7):739–744
Pavlov IP (1927) Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex (trans: Anrep, GV). Oxford University Press, London
Petrovic P, Kalisch R, Singer T, Dolan RJ (2008) Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. J Neurosci 28(26):6607–6615
Quintana DS, Westlye LT, Rustan ØG, Tesli N, Poppy CL, Smevik H et al (2015) Low-dose oxytocin delivered intranasally with Breath Powered device affects social-cognitive behavior: a randomized four-way crossover trial with nasal cavity dimension assessment. Transl Psychiatry 5(7):e602
Schiele MA, Reinhard J, Reif A, Domshchke K, Romanos M, Deckert J, Pauli P (2016) Developmental aspects of fear: comparing the acquisition and generalization of conditioned fear in children and adults. Dev Psychobiol 58(4):471–481
Shahrestani S, Kemp AH, Guastella AJ (2013) The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38(10):1929–1936
Shamay-Tsoory SG, Abu-Akel A (2016) The social salience hypothesis of oxytocin. Biol Psychiatry 79(3):194–202
Spengler FB, Schultz J, Scheele D, Essel M, Maier W, Heinrichs M, Hurlemann R (2017) Kinetics and dose dependency of intranasal oxytocin effects on amygdala reactivity. Biol Psychiatry 82(12):885–894
Striepens N, Scheele D, Kendrick KM, Becker B, Schäfer L, Schwabka K et al (2012) Oxytocin facilitates protective responses to aversive social stimuli in males. Proc Natl Acad Sci 109(44):18144–18149
Toth I, Neumann ID, Slattery DA (2012) Central administration of oxytocin receptor ligands affects cued fear extinction in rats and mice in a time-dependent manner. Psychopharmacology 223(2):149–158
Tuominen L, Boeke E, DeCross S, Wolthusen RP, Nasr S, Milad M, Vangel M, Tootell R, Holt D (2019) The relationship of perceptual discrimination to neural mechanisms of fear generalization. Neuroimage 188:445–455
Viviani D, Stoop R (2008) Opposite effects of oxytocin and vasopressin on the emotional expression of the fear response. Prog Brain Res 170:207–218
Xu X, Li J, Chen Z, Kendrick KM, Becker B (2019) Oxytocin reduces top-down control of attention by increasing bottom-up attention allocation to social but not non-social stimuli-a randomized controlled trial. Psychoneuroendocrinology 108:62–69
Yao S, Becker B, Zhao W, Zhao Z, Kou J, Ma X, Geng Y, Ren P, Kendrick KM (2018a) Oxytocin modulates attention switching between interoceptive signals and external social cues. Neuropsychopharmacology 43(2):294–301
Yao S, Zhao W, Geng Y, Chen Y, Zhao Z, Ma X, Xu L, Becker B, Kendrick KM (2018b) Oxytocin facilitates approach behavior to positive social stimuli via decreasing anterior insula activity. Int J Neuropsychopharmacol 21(10):918–925
Yoshida M, Takayanagi Y, Inoue K, Kimura T, Young LJ, Onaka T, Nishimori K (2009) Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. J Neurosci 29(7):2259–2271
Zoicas I, Slattery DA, Neumann ID (2014) Brain oxytocin in social fear conditioning and its extinction: involvement of the lateral septum. Neuropsychopharmacology 39(13):3027–3035

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.