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Neurobiobehavioral responses to virtual social rejection in females—exploring the influence of oxytocin

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Abstract

In recent years, especially adolescents and young adults interact frequently via social media and digital communication. Mimicking an online communication platform where participants could initiate short conversations with two computerized interlocutors, the Verbal Interaction Social Threat Task (VISTTA) was used to induce feelings of social rejection. Motivational and physiological reactions were investigated in 43 healthy young women undergoing functional magnetic resonance imaging (fMRI), of which 22 received 24 international units (IU) intranasal oxytocin and 21 received placebo. Replicating previous findings, social rejection entailed a lower willingness to cooperate with the two peers. Increased activation in the anterior cingulate cortex and bilateral insula/inferior frontal gyrus was observed when receiving negative feedback from others, and in the precuneus when subsequently rating one's willingness to cooperate with them in the future. Oxytocin did not seem to alter responses to social rejection. The current findings provide validation of the VISTTA for examining consequences of rejection in a virtual social interaction that bears a strong resemblance to online communication platforms.

Key words: social rejection; verbal communication; VISTTA; fMRI; oxytocin

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Introduction

In recent years, especially adolescents and young adults interact more and more frequently via social media and online communication. Accordingly, negative interactions involving social exclusion or rejection are also experienced in digital environments. Whereas *exclusion* means simply being kept apart from others, *rejection* is a more explicit declaration of dislike or expulsion from the group (Williams, 2007). Following latest developments, the effects of these phenomena have been experimentally investigated in contexts of social media and chat rooms. For example, participants were excluded by reducing the number of opportunities for interaction with others in a chat room (Donate *et al.*, 2017) or by receiving fewer 'likes' on their profile than others (Wolf *et al.*, 2015). In addition to exclusion, receiving fewer "likes" also includes social judgment and thereby ties into the concept of rejection. Still, both exclusion and rejection elicit increased anger as well as feeling hurt (Donate *et al.*, 2017) and sad (Wolf *et al.*, 2015).

In a prior behavioral study (Tops *et al.*, 2019), we induced feelings of social rejection by disapproving feedback on personal views and preferences from others. This Verbal Interaction Social Threat Task (VISTTA) mimics an online communication platform where participants can initiate short conversations with two computerized interlocutors. Reinforced by the belief that the two others are real, receiving unexpected negative comments concerning one's opinions and choices led to increased feelings of anger and surprise along with decreased happiness and a decreased willingness to cooperate with the other two peers. Building upon these findings, the current study targeted neural correlates of social rejection using the VISTTA.

Neuroimaging studies indicate that social exclusion and rejection reliably engage the anterior insula and the anterior cingulate cortex (ACC), often extending to inferior frontal gyrus (IFG) and posterior medial frontal cortex (pMFC), respectively, as well as the precuneus and caudate (Cacioppo *et al.*, 2013; Radke *et al.*, 2018; van Schie *et al.*, 2018), which may relate to the affective component of being excluded (Eisenberger *et al.*, 2003), to the processing of unexpected, salient events (e.g. Perini *et al.*, 2018) and to updating one's self-image (Bolling *et al.*, 2011; van Schie *et al.*, 2018). Threats to one's self-esteem, in turn, contribute to behavioral reactions, such as retaliation against the sources of exclusion (Will *et al.*, 2016; Walasek *et al.*, 2019). Selectively punishing the exclusion perpetrators was accompanied by increased activity in the insula and pre-supplementary motor area/ACC in adolescents (Moor *et al.*, 2011; Will *et al.*, 2015, 2016).

Social norm enforcement, particularly in-group cooperation, has been linked to the neuropeptide oxytocin (De Dreu, 2012; Israel *et al.*, 2012; Ten Velden *et al.*, 2014). Increased cooperation and prosocial tendencies after oxytocin administration may be confined to male samples; however, recent research in females signifies opposite effects: during reciprocated cooperation in incentivized games, oxytocin reduced activation of the caudate and the ventral tegmental area in females (Feng *et al.*, 2015; Chen *et al.*, 2017), while it did not affect the insula response to unreciprocated cooperation (Chen *et al.*, 2016) or cooperative behavior itself (Feng *et al.*, 2015; Chen *et al.*, 2017). Also in a female sample, oxytocin increased nucleus accumbens activation in a cooperative, but not in an ambivalent, decision context in which it shifts attention to other social cues (Lambert *et al.*, 2017).

Here, following our behavioral study (Tops *et al.*, 2019), we expected to evoke a decreased willingness to cooperate with the others after being rejected. To conceptually replicate previous neuroimaging findings with the VISTTA, we expected increased engagement of the insula, ACC and precuneus due to social rejection. Compared to established imaging paradigms like *Cyberball* (Eisenberger *et al.*, 2003; Cacioppo *et al.*, 2013; Radke *et al.*, 2018), the VISTTA includes verbal and interactive components that are intended to make the rejection experience more targeted and personal. Moreover, the current study explored whether oxytocin might influence the desire to cooperate, and to which extent it might buffer the negative experience particularly in terms of rejection-related brain activation. We focused on females due to the relative paucity of oxytocin administration studies in women.

Material and methods

Subjects

Forty-three healthy women ($M_{age} = 22.8$ years, s.d. = 3.1; range 18–30) participated for financial compensation. All were right-handed, fluent in German, had (corrected-to-)normal vision and used monophasic oral contraceptives for at least 3 months. Duration of use and current brand name of the pill were registered, and participants were tested during the regular 3 weeks of active pill intake. Exclusion criteria were endocrine diseases, mental disorders, medication, drug or alcohol abuse, application of other hormonal preparations, magnetic resonance imaging (MRI) contraindications and (allergic) rhinitis (hay fever) on the test day. The sample was further characterized by a set of personality measures (see Supplementary Material).

All participants gave written informed consent. The study was approved by the ethics committee of the Medical Faculty of RWTH Aachen (EK105/15). One participant already knew the paradigm and was excluded from all analyses. For the analysis of neuroimaging data, three more women were excluded (two for excessive head movement of >4 mm and one due to technical failure, yielding $n = 39$ for the imaging data). Moreover, one participant was excluded from analyses of the cortisol data due to very high cortisol values (>59 nmol/l), according to Kobayashi *et al.* (2017), which leaves 41 participants for these analyses. All other analyses are based on a sample size of $n = 42$. Originally, the study had been planned for a sample of $n = 80$, but several practical factors limited data collection to the current sample size.

Oxytocin administration

Following a randomized, placebo-controlled, double-blind cross-sectional design, 22 participants received 24 IU intranasal oxytocin and 21 received placebo. Production of the nasal sprays and randomization were performed by the pharmacy of the University Hospital Heidelberg, Germany. Under the supervision of the experimenter, participants self-administered the nasal spray with six puffs per nostril (each with 2 IU or 0.05 ml). For a better uptake of the substance, participants were asked to wait 10 s and switch to the other nostril after each puff. The VISTTA was carried out after a waiting period between 45 and 60 min, a time window derived from earlier oxytocin and related peptide nasal spray studies (Born *et al.*, 2002; Israel *et al.*, 2012).[1] The VISTTA was performed at the same time for both groups.

[1] According to the planned protocol, the VISTTA was to start 45 min after substance administration. The small variability of the actual starting time was only due to unforeseen practical issues at the scanner, such as when participants needed some additional time for slight visual corrections (i.e. they could not see the screen properly upon first positioning).

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Substance administration did not entail any adverse events or any effects based on either participants' or experimenters' belief on which substance had been administered.

Paradigm and cover story

The VISTTA simulates an online communication environment to induce social evaluative threat and feelings of rejection. In a simplified chat interface, participants initiate 30 short conversations on different topics to which two computerized interlocutors provide mostly negative feedback. Topics had high relevance to student life—e.g. studying, going out and sports—and were evaluated in a pilot as well as a prior behavioral study (see Tops *et al.*, 2019). Participants initiated the conversation by selecting one of four opening sentences that would fit their views or preferences best (e.g. 'I sometimes play computer games, but not very often.'). Afterward, the chat interface appeared, followed by reactions from the two peers, which were both either negative (20 conversations) or neutral (10 conversations). Negative feedback directly targeted the participants' point of view (e.g. 'I don't like computer games at all, I never ever play them, only nerds play those kinds of games.')

One of two pseudorandom orders of topics was randomly presented using the Presentation software package (Neurobehavioral Systems, Inc., Albany, California). These orders were created in such a way that (i) the first and the last conversations were not negative and (ii) the conversations would not switch from the most positive to the most negative ones and vice versa. These measures were taken to strengthen the credibility of the ostensible interaction and to keep participants engaged and interested. Several additional measures were taken to reinforce the cover story that the other two peers were real, such as variation of the time it took them to 'type' while chatting, but also emphasizing the necessity to be punctual for the test session as it was conducted with two others. Ostensibly, the aim of the study was to investigate brain activation while getting to know new people in a virtual environment, without having a first impression. Therefore, participants could not meet the other participants, who were said to be sitting in separate rooms nearby, beforehand. However, participants were told they will meet them afterward to do a cooperation task together. At the end of the experiment, participants were queried about the existence of the other two participants, which 37 of them (=88%) did not doubt, before being debriefed in detail.

As a manipulation check, participants rated how much they wanted to cooperate with the two others after each conversation in the VISTTA on a scale from 1 to 5 (1 = not at all, 5 = very much).

Procedure and repeated measures

Participants abstained from alcohol for 24 h before, from caffeine for 3 h before, and from eating and drinking (except water) for 2 h before substance administration as well as from smoking and exercise on the test day. All sessions began between 12:30 and 16:00 to control for circadian rhythms and took approximately 3 h during which affective and hormonal measures were repeatedly assessed at four timepoints (T1: 20 min after study onset, T2: 60 min after study onset = before the VISTTA in the scanner-room, T3: 120 min after study onset = immediately after the MRI session, T4: 160 min after study onset; i.e. the nasal spray was administered 45 min after study onset, i.e. 25 min after T1, and the MRI session took place between T2 and T3; Figure 1). Saliva samples were taken using SaliCaps (IBL international, Hamburg, Germany) and stored at −30°C until they were analyzed by the Dresden LabService. Cortisol concentrations

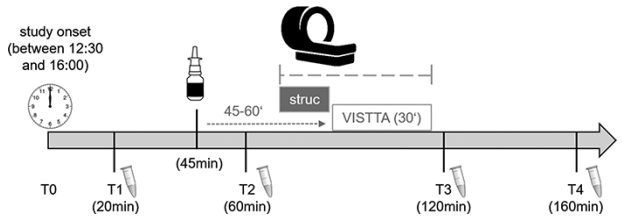


Fig. 1. Experimental timing. Black numbers refer to time after study onset; gray numbers refer to duration. The onset of the VISTTA was 25–30 min after T2, corresponding to 45 min after substance administration. The time elapsed between the onset of the VISTTA and T3 was about 35 min. Struc = structural scan (5 min; not to scale) plus VISTTA (30 min) amount to 35 min 'net' scan time. Participants spent about 45 min in the MR scanner due to task instructions, technical checks and measurement preparation.

were measured using Luminescence Immunoassays with high sensitivity (Immuno-Biological Laboratories GmbH, Hamburg, Germany), with intra-assay and inter-assay coefficients of less than 9%. Samples were analyzed in duplicate. The average was used in further analyses. Affective measures are reported in the Supplementary Material.

Statistical analyses of behavioral and physiological data

All analyses of behavioral and physiological data were performed using SPSS 23 (Armonk, New York; IBM Corp.). The alpha level was set to 0.05. When necessary Greenhouse–Geisser correction was applied and *post-hoc* pairwise comparisons were Bonferroni corrected. If data were transformed, all analyses were computed based on the transformed data. Please note that we have retained the between-subjects factor substance, although the effects involving this factor are likely underpowered for some analyses and should be considered preliminary due to the smaller sample size than originally planned.

Manipulation check: motivational responses. Values of cooperation ratings were averaged for negative and neutral reactions separately and, showing normal distribution, were entered into a 2 × 2 analysis of variance (ANOVA) with valence (negative, neutral) as within-subject factor and substance (oxytocin, placebo) as between-subjects factor.

Physiological responses. Cortisol data were transformed by computing the reciprocal value to reach normal distribution. A repeated measure ANOVA with *post-hoc* pairwise comparisons was conducted with time (T1, T2, T3, and T4) as within-subject factor and substance (oxytocin, placebo) as between-subjects factor.

Neuroimaging data acquisition and processing

All neuroimaging data were acquired on a 3T Siemens Prisma scanner (Siemens Medical Solutions) located in the Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University. Stimuli were projected onto a screen behind the participant, which could be viewed via a mirror mounted on the head coil. During the VISTTA (duration: 30 min), T_2-weighted images (34 slices) were collected in an ascending interleaved fashion using an echo planar imaging (EPI) sequence with the following imaging parameters: time of repetition (TR) = 2000 ms, echo time (TE) = 28 ms, flip-angle = 77°, and slice thickness = 3.1 mm. Before the VISTTA, high-resolution

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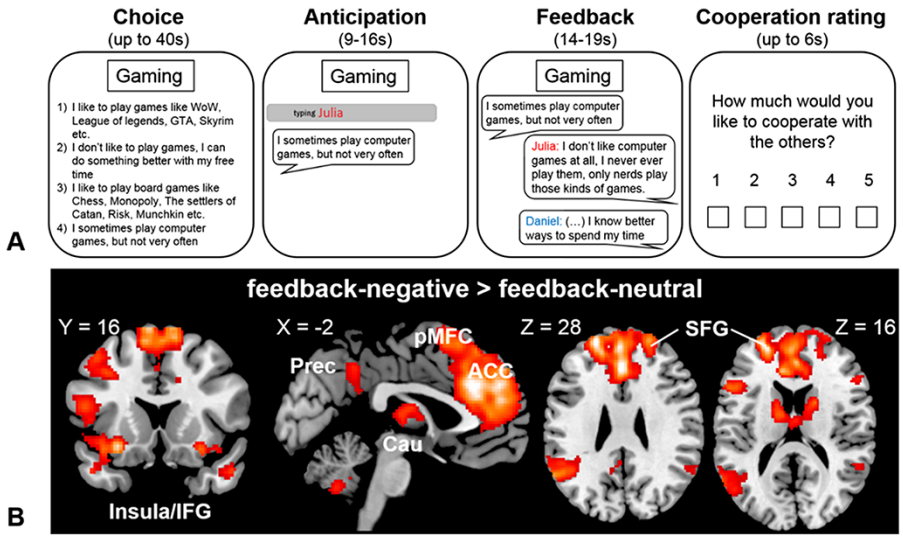


Fig. 2. Social rejection task and brain activation. (A) Overview of one trial in the VISTTA, with the four phases of choice, anticipation, feedback and cooperation rating (from left to right). The reactions from the two interlocutors were presented one after the other, i.e. here, first Julia's response, then Daniel's, but were modeled as the same regressor/event in the fMRI analyses. Also not depicted is the inter-trial interval after the cooperation rating, during which a fixation cross was shown for 4–8 s. (B) Negative compared to neutral feedback elicited increased activation in bilateral IFG and the left ACC, extending to pMFC, SFG and middle frontal gyrus. Clusters in precuneus (Prec) and caudate (Cau) can also be seen, all with $P_{FWE} < 0.05$ (FWE-corrected at the cluster level).

T_1-weighted anatomical images were acquired using a 3D magnetization-prepared rapid gradient-echo sequence (5 min) with a TR of 2000 ms, a TE of 3.03 ms and a flip-angle of 9°. The voxel size was 1 mm^3. While the 'net' scan time amounted to 35 min, participants spent about 45 min in the MR scanner due to task instructions, technical checks and measurement preparation. There were no other tasks administered (neither inside nor outside the scanner).

Preprocessing and analyses of the imaging data were performed with statistical parametric mapping (SPM12, Wellcome Department of Imaging Neuroscience, London) implemented in Matlab 2013 (MathWorks Inc., Natick, Massachusetts, USA) using standard algorithms and parameters unless specified differently. Functional images were realigned to correct for head movement, slice time corrected, co-registered to the T_1-weighted anatomical image, spatially normalized to Montreal Neurological Institute (MNI) stereotactic space and finally smoothed with a 6 mm full-width-at-half-maximum Gaussian kernel.

Each trial consisted of four phases (compare Figure 2A): choice, anticipation, feedback and cooperation rating. Feedback and cooperation were further divided based on the content of the conversation, i.e. negative (20) or neutral (10), yielding the four regressors of interest to the experimental question, modeled in the GLM-analysis: feedback-negative (rejection), feedback-neutral (non-rejection), cooperation-negative (cooperation after rejection) and cooperation-neutral (cooperation after non-rejection). Choice and anticipation were not further divided as no conceptual differences were assumed, yielding one regressor each. The seventh task-related regressor included the practice trial at the beginning of the session. To minimize residual head movement effects, additional regressors were derived from incorporating the realignment parameters and the percent signal change value as covariates of no interest. A high-pass filter with a cutoff of 190 s was used to exclude low-frequency signals.

On the group level, two full factorial models were computed, corresponding to the two phases of interest to the experimental question, i.e. feedback and cooperation rating. For each ANOVA, the resulting contrast images of each participant were entered with valence (negative, neutral) as a within-subject factor and substance (oxytocin, placebo) as between-subjects factor. All effects were tested using a whole-brain approach, with $P < 0.05$ at cluster-level, family-wise-error-corrected for multiple comparisons ($P_{FWE} < 0.05$), with an underlying voxel-level threshold of $P < 0.001$, uncorrected. The SPM anatomy toolbox (Version 2.0; Eickhoff *et al.*, 2005) was used for anatomical localization.

Results

Manipulation check

The ANOVA on the cooperation rating yielded a significant effect of valence, $F(1,41) = 279.76$, $P < 0.001$, partial $\eta^2 = 0.88$, but neither a significant effect of substance nor a significant valence × substance interaction ($Fs < 0.04$, $Ps > 0.846$). Consequently, in both groups, the willingness to cooperate was significantly lower after receiving negative feedback ($M_{OXT} = 2.34$, s.d. = 0.53; $M_{PLC} = 2.33$, s.d. = 0.45) than after neutral responses ($M_{OXT} = 3.9$, s.d. = 0.40; $M_{PLC} = 3.86$, s.d. = 0.43).

Cortisol

For salivary cortisol, there was neither a main effect of substance ($F(1,39) = 0.12$; $P = 0.74$) nor a substance × time interaction ($F(1,39) = 0.32$ $P = 0.66$). The main effect of time, $F(3117) = 31.00$,

Table 1. Mean scores with standard deviations of cortisol levels (based on $n = 41$; see Section 2.1) at all four timepoints (T1 = 20 min, T2 = 60 min, T3 = 120 min and T4 = 160 min after study onset) per group

	OXT ($N = 20$)	PLC ($N = 21$)
Cortisol (nmol/l)	T1: 4.49 (2.49)	T1: 5.11 (3.72)
	T2: 3.79 (2.39)	T2: 3.69 (2.30)
	T3: 3.13 (1.65)	T3: 3.45 (2.67)
	T4: 2.96 (1.82)	T4: 2.81 (1.73)

OXT = oxytocin; PLC = placebo

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$P < 0.001$, partial $\eta^2 = 0.44$, was due to a general decline over time. Pairwise comparisons revealed significant differences between all timepoints, i.e. decreases from T1 to T2 ($P < 0.001$), T1 to T3 ($P < 0.001$), T1 to T4 ($P < 0.001$), T2 to T3 ($P = 0.004$), T2 to T4 ($P < 0.001$) and T3 to T4 ($P = 0.003$) (Table 1).

Neural effects of exclusion (feedback). Contrasting rejection to non-rejection (feedback negative > feedback neutral) yielded increased activation in the left ACC (cluster extending to superior and middle frontal gyri; Figure 2B) and bilateral insula/IFG. Increased activation was further observed in bilateral caudate, bilateral angular gyrus, bilateral cerebellum, bilateral middle temporal gyrus, left precuneus and right medial temporal pole (Table 2).

For the reverse contrast (non-rejection > rejection), there was increased activation in bilateral inferior parietal lobule, bilateral inferior temporal gyrus and right lingual/calcarine gyrus, left middle occipital gyrus and bilateral insula lobe (Table 2).

As a formal main effect of substance, the oxytocin group showed enhanced activation in right cuneus and lingual gyrus compared to the placebo group. Neither opposite effects nor interactions were observed.

Neural after-effects of exclusion (on cooperation decisions). Contrasting post-rejection cooperation decisions (cooperation-negative) to post-non-rejection decisions (cooperation-neutral) yielded increased activation in the right rectal gyrus, extending to superior medial gyrus and left ACC; precuneus, left angular gyrus, right superior frontal gyrus (SFG), right middle temporal gyrus, bilateral cerebellum and right precentral gyrus (Table 3). The opposite contrast did not reveal any suprathreshold activation.

Two clusters in the left and right cerebellum showed increased activation in the context of a formal substance × valence interaction, i.e. (oxytocin > placebo) > (rejection > non-rejection; Table 3). This effect was due to significant differences in the placebo group for post-non-rejection cooperation than post-rejection cooperation in the left cerebellar cluster, in the absence of any other suprathreshold activation in this region. There was no main effect of substance.

Table 2. Differences in whole-brain activation during feedback, all with $P < 0.05$ (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and T-values. Only significant effects are listed. For each cluster, the maximum peak in gray matter is reported

Contrast region	k	Side	MNI x	MNI y	MNI z	T-value
Valence						
Rejection > non-rejection						
Anterior cingulate cortex	8132	L	−2	32	28	8.73
Insula lobe	1642	L	−28	16	−12	7.66
Caudate nucleus	1142	R	18	6	16	5.73
Angular gyrus	1133	L	−58	−58	26	7.04
Cerebellum	917	R	26	−78	−34	7.32
Middle temporal gyrus	653	L	−52	−26	−8	6.57
Cerebellum	636	L	−24	−80	−34	7.40
Inferior frontal gyrus (p. orbitalis)	614	R	48	24	−6	6.77
Middle frontal gyrus	603	L	−44	14	48	5.64
Cerebellar vermis (9)	601	R	6	−58	−40	5.19
Middle temporal gyrus	354	R	48	−32	−2	6.39
Precuneus	350	L	−10	−50	42	6.21
Medial temporal pole	303	R	42	4	−32	7.59
Angular gyrus	233	R	48	−46	22	4.42
Valence						
Non-rejection > rejection						
Inferior parietal lobule	1136	R	46	−38	50	5.40
Inferior parietal lobule	800	L	−46	−38	46	4.52
Inferior temporal gyrus	336	R	56	−46	−10	6.06
Lingual gyrus	311	R	16	−76	−6	4.65
Inferior temporal gyrus	269	L	−52	−52	−12	5.19
Middle occipital gyrus	242	L	−28	−70	40	4.40
Insula lobe	241	L	−38	−4	14	4.66
Insula lobe	227	R	38	−2	6	4.34
Substance						
Oxytocin > placebo						
Cuneus	204	R	14	−90	14	5.84
Lingual gyrus	178	R	14	−78	−10	4.12
Cuneus	170	L	−12	−92	14	4.75

Discussion

The current study investigated the neural correlates of social rejection induced by the VISTTA, a newly developed task to investigate social rejection via mimicking an online communication platform. Our female participants exhibited a lower willingness to cooperate after being rejected, which was accompanied by an enhanced activation of the insula, ACC and the precuneus when receiving negative feedback and when deciding whether to cooperate. However, partially in line with previous findings, the VISTTA did not elicit a cortisol response. Furthermore, our preliminary findings provide no evidence for an influence of oxytocin.

Effects of social rejection

As expected, processing social rejection was characterized by involvement of frontal areas, like the ACC and the insula/IFG, consistent with a large body of studies investigating the effects of social exclusion (Eisenberger *et al.*, 2003; Cacioppo *et al.*, 2013; Wagels *et al.*, 2017; Radke *et al.*, 2018) as well as social rejection (Woo *et al.*, 2014; Hsu *et al.*, 2015). Feeling socially rejected, whether caused by exclusion or by receiving offending responses, constitutes a negative affective experience. Therefore, the subsequent need for emotional control and

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Table 3. Differences in whole-brain activation during the cooperation rating, all with $P < 0.05$ (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and T-values. Only significant effects are listed. For each cluster, the maximum peak in gray matter is reported

Contrast	k	Side	MNI			T-value
region			x	y	z	
Cooperation after Rejection > non-rejection						
Rectal gyrus	2941	R	2	48	−16	5.60
Precuneus	2578		0	−72	40	6.08
Angular gyrus	636	L	−46	−56	28	5.05
Superior frontal gyrus	376	R	16	32	52	5.33
Middle temporal gyrus	318	R	62	−8	−22	5.07
Cerebellum	230	R	30	−76	−34	4.51
Precentral gyrus	165	R	34	−22	54	4.78
Cerebellum	147	L	−28	−82	−32	5.09
Oxytocin > placebo Rejection > non-rejection						
Cerebellum	450	L	−16	−64	−30	5.13
Cerebellum	155	R	22	−62	−32	3.95

the regulation of negative affect may recruit particularly the insula/IFG (Dedovic *et al.*, 2009; Wagels *et al.*, 2017). Engagement of the ACC has been related to the perception and the self-reported distress during social pain (Rotge *et al.*, 2015). According to Eisenberger and Liebermann (2003), the ACC may also act as a neural 'alarm system' monitoring automatic responses that are in conflict with current aims. Receiving mostly negative comments during the VISTTA is in conflict with the goal of getting along with the others in order to perform well in the ostensible cooperation task. Moreover, participants' expectations about the interaction were likely violated, underlined by heightened reports of surprise after the VISTTA (Tops *et al.*, 2019). However, although participants probably did not expect to be rejected in general, no prefrontal activation was observed when contrasting the actually less frequent neutral feedback to negative feedback. After all, ACC activation does not seem to merely reflect the detection of atypical events.

Compared to other paradigms in which participants are represented by standardized, impersonal avatars (e.g. Cyberball), rejections in the VISTTA are based on subjective preferences and choices, and may therefore be perceived as more personal. Along these lines, participants were less motivated to cooperate with the others after having received rejecting responses, replicating Tops *et al.* (2019) and underscoring that social rejection leads to decreased prosocial behavior (Bossi *et al.*, 2018). Reflecting upon the motives of the others from a first-person perspective is critical for understanding the causes of social behavior (Freton *et al.*, 2014). Deciding whether to cooperate after negative vs. neutral feedback was primarily associated with enhanced activation in the precuneus and superior medial gyrus/ACC, which have been linked to self-referential processing and attribution (e.g. Cabanis, 2013), also in the context of social exclusion (Radke *et al.*, 2018).

Hormonal influences

In contrast to previous findings (Tops *et al.*, 2019), the VISTTA did not entail stable cortisol levels, let alone an increase in salivary cortisol. Although both studies relied on a similar sample, i.e. women using oral hormonal contraceptives, the constant cortisol levels in women could not be replicated in the current study. Instead, the general decrease of cortisol levels resembles the circadian rhythm of cortisol, peaking early in the morning and declining throughout the day (Kobayashi *et al.*, 2017). This pattern is commonly observed when investigating social exclusion (Zoller *et al.*, 2010; Zwolinski, 2012; Seidel *et al.*, 2013; Gaffey and Wirth, 2014; Radke *et al.*, 2018) and may be amplified by attenuated responses to psychosocial stressors due to hormonal contraceptives (Roche *et al.*, 2013; Liu *et al.*, 2017).

Exploring oxytocin-related influences on subjective and hormonal responses yielded no effects. For example, oxytocin did not appear to enhance the willingness to cooperate after negative comments, which is in line with other studies revealing no effect of oxytocin on cooperative behavior (Feng *et al.*, 2015; Chen *et al.*, 2017). Instead, a lower motivation for social interaction after being rejected was evident in both groups. This fits with antisocial behavior and selective punishment toward the perpetrators (Will *et al.*, 2016; Walasek *et al.*, 2019), fueled by increased anger about being excluded or even rejected (Chow *et al.*, 2008). Even more, the absence of oxytocin effects on cortisol is not surprising given the overall declining cortisol levels and the absence of any cortisol response in the placebo group, which likely precludes any additional buffering effect of oxytocin.

Exploring oxytocin-related influences on a neural level increased activation in the cuneus and lingual gyrus during the feedback phase appeared in the oxytocin group. Although meta-analyses on pharmacoimaging studies mention single findings in some of these regions (Wigton *et al.*, 2015; Leppanen *et al.*, 2018), they are not further discussed in detail. Therefore, they are likely not key areas of oxytocinergic modulation. Along these lines, the threatening stimuli summarized in Leppanen *et al.* (2018) refer almost exclusively to facial expressions or disorder-related pictures. In contrast, the VISTTA is more complex in a variety of ways and involves more cognitive tasks than the processing of threatening pictures. Participants first have to read and understand possible opening sentences, reflect personal points of view and actively decide which opening sentence corresponds best to their own opinion. While receiving responses, they process and interpret the statements to receive an impression of the other two participants. After each conversation, they have to evaluate the virtual communication and rate the extent to which the want to interact with both interlocutors. These increased social-cognitive demands are likely to recruit brain regions beyond the amygdala and insula (Wigton *et al.*, 2015).

Conclusions

The main limitation of the current study is the small number of participants to investigate the effects of oxytocin, particularly in light of the concerns of statistical power in this research field (Walum *et al.*, 2016). While the current findings may be informative for future oxytocin research with larger samples, they need to be regarded as preliminary. Moreover, although the intranasal route is well-established, assessing oxytocin may provide additional validation of its administration and uptake. As most oxytocin studies have been conducted with men, we consider the investigation of a female sample as a strength of the current study.

Task-related neural and behavioral effects across the whole sample seem robust and align with previous findings on social exclusion (Eisenberger *et al.*, 2003; Cacioppo *et al.*, 2013; Wagels

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et al., 2017; Radke et al., 2018) and rejection (Woo et al., 2014; Hsu et al., 2015; Tops et al., 2019). Lower cooperation ratings after negative reactions clearly underscore lower willingness to cooperate after being rejected. Conceptually replicating previous engagement of the insula, ACC and precuneus due to social rejection, the VISTTA is a useful addition to investigate the effects of social rejection. Designed as a realistic yet highly controlled experimental procedure, the VISTTA bears a strong resemblance to online communication platforms and continuously involves participants in the interaction, thus presents a more 'active' task than previous options for investigating social rejection or exclusion. It offers high ecological validity by focusing on recent developments in the increasing use of social media.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary data

Supplementary data are available at *SCAN* online.

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