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Reduced eye gaze during facial emotion recognition in chronic depression: Effects of intranasal oxytocin

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ABSTRACT

Chronic depression disorders (CDD) are characterized by impaired social cognitive functioning. Visual attention during social perception is altered in clinical depression and is known to be sensitive to intranasal treatment with oxytocin (OT). The present study thus investigated potential alterations in gaze preferences during a standardized facial emotion recognition (FER) task using remote eye tracking in patients with CDD and the effect of a single dose of intranasal OT (compared to placebo). In emotion recognition, CDD patients were not more impaired than healthy controls, and there was no OT effect. However, CDD patients (with placebo) demonstrated less attentional preference for the eye region during FER than healthy controls, which was not apparent in the CDD group after OT treatment. Our results suggest that despite largely preserved basic facial emotions recognition, attention in social perception may be altered in CDD, and that this bias may be sensitive to OT treatment. These findings highlight OTs potential as a means of augmenting psychotherapy.

1. Introduction

Depressive disorders are among of the most frequent psychiatric disorders causing severe harm to affected individuals. Lifetime and the 12-month prevalence of major depression disorder (MDD) has been estimated at 20% and 10%, respectively (Kessler et al., 2005). Aside from the affective symptoms, depression is associated with impairments in the social domain such as social withdrawal and social interaction deficits (Hirschfeld et al., 2000). A review summarized the social cognitive and behavioral alterations in depression, including altered social decision making, empathy and theory of mind (Kupferberg et al., 2016). The ability to decode social cues like facial expressions and accurately recognize facial expressions of emotions is considered a fundamental cognitive function in adaptive social behavior (Leppänen and Nelson, 2006), and a deficient performance in this function might therefore contribute to social impairments in other laboratory tasks and everyday life.

About 25% of all depressive disorders become chronic, that is, they last more than two years without remission longer than two months (Rubio et al., 2011). Patients with chronic depressive disorders (CDD) are more severely affected than those with episodic depression. CDD is associated with higher rates of psychiatric and somatic comorbidity, more impaired psychosocial and interpersonal functioning, more frequent suicide attempts, hospitalizations, and healthcare utilization, and an earlier onset, often after early adversities (Klein, 2008; Murphy and Byrne, 2012). In addition, patients with CDD have been reported to show pronounced impairments in social cognitive functioning, especially cognitive aspects of empathy (Domes et al., 2016c; Mattern et al., 2015; McCullough Jr., 2003; Zobel et al., 2010).

1.1. Facial emotion recognition in depression

Many studies have yielded evidence over the past decades, after explicitly investigating emotion recognition performance in depression. Most thereof reported generally impaired emotion recognition, while others showed no significant impairments compared to unaffected controls (Bourke et al., 2010). In sum, meta-analyses support the impression of an overall recognition impairment, and report an overall small effect of Hedges' $g = -0.16$ (Dalili et al., 2015) and Hedges' $g = -0.21$ (Krause et al., 2021). While some studies demonstrated specific effects for distinct emotions such as sadness or happiness (Gur et al., 1992; Rubinow and Post, 1992), others revealed general impairments

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(Asthana et al., 1998). Krause et al. (2021) conclude in their recent meta-analysis that recognition impairments might be more pronounced in inpatients and patients with high symptom severity. Accordingly, one might expect that patients with CDD might be even more impaired than MDD in emotion recognition. Unfortunately, many studies do not distinguish between episodic and chronic depression, or report no data on the chronicity of depression. To our knowledge, no study has yet been conducted to investigate emotion recognition performance specifically in patients with CDD.

1.2. Processing of facial expressions and social cognition in depression

Aspects of face processing other than emotion recognition performance have also been investigated in depression, i.e., attention allocation to specific emotions, or biased responding when evaluating ambiguous faces. Although it is difficult to develop a coherent understanding given the methodological differences between studies, Bourke and colleagues conclude in their review that there is reasonably consistent evidence of a negative response bias and increased vigilance towards sadness in individuals with MDD (Bourke et al., 2010). Several eye tracking studies reviewed in recent meta-analyses (Armstrong and Olatunji, 2012; Suslow et al., 2020) have provided evidence that depressed patients show increased attention towards negative/dysphoric stimuli while being less attentive to positive/happy stimuli. Their pattern of attentional preferences is distinguishable from that reported in patients with anxiety disorders, and might thus be considered specific for clinical depression (Armstrong and Olatunji, 2012).

1.3. Effects of oxytocin on emotion recognition and social attention

There is considerable evidence that oxytocin (OT) regulates social cognition and behavior in different mammal species (Donaldson and Young, 2008; Neumann and Landgraf, 2012). In humans, many experimental studies have been conducted over the last three decades, delivering evidence that OT is also a modulator of social functioning in health and mental disease (Chen et al., 2011; Heinrichs et al., 2003, 2009; Kosfeld et al., 2005; Meyer-Lindenberg et al., 2011). In particular, OT has been found to improve social cognitive functioning in psychiatric conditions such as borderline disorder (Bertsch et al., 2013; Domes et al., 2019), social phobia (Gorka et al., 2015; Labuschagne et al., 2010), and autism spectrum disorders (Domes et al., 2014; Guastella and Hickie, 2016; Kanat et al., 2017). Given that CDD overlaps somewhat with ASD in terms of social cognitive impairments (Domes et al., 2016c) and that OT in ASD has had a positive impact on emotion recognition, we might expect OT in CDD to reveal positive effects in this domain as well. Furthermore, lower OT concentrations in cerebrospinal fluid (CSF) have been detected in women with a history of childhood adversities, especially after emotional abuse, which is also frequently reported by CDD patients (Brakemeier et al., 2018; Heim et al., 2009). In a previous study with CDD patients, we provided first evidence that OT reduced the allocation of attention to aversive social signals, and increased adherence to positive social signals based on reaction times in a dot-probe paradigm (Domes et al., 2016b).

Accordingly, applying eye tracking to measure overt visual attention, OT has been reported to modulate attention to social stimuli and to alter the allocation of attention to the eye region during face perception (Domes et al., 2013; Guastella et al., 2008; Marsh et al., 2021). Especially individuals exhibiting a low preference for the eye region in face perception show increased attention to the eye region after a single intranasal application of OT (Auyeung et al., 2015).

The present study was planned to investigate differences between CDD and healthy control participants in emotion recognition performance via a dynamic facial emotion recognition task (FERT). In addition, we tested for potential effects of a single dose of OT on recognition performance in a double-blind placebo-controlled trial. Finally, we explored OT effects on attention allocation to facial features during emotion recognition. We hypothesized that OT would compensate for a general emotion recognition deficit in patients with CDD, and modulate social attention towards the eye region.

2. Methods

2.1. Participants

Patients with a CDD were recruited from the psychiatric in-patient and out-patient units of University Medical Center Freiburg, Germany. Patients were included if they met criteria for persistent depressive disorder (300.4), double depression (300.4 + 296.2x), or chronic major depression (296.2x) lasting more than two years according to DSM-V. Patients were excluded if they presented one of the following comorbidities: bipolar I disorder, psychotic disorders, mental retardation or organic affective disorders, borderline personality disorder, or substance abuse or addiction with under three months of abstinence (excluding nicotine).

In all, 46 patients (19 men/27 women) passed our screening for inclusion and exclusion criteria. Patients were allocated to either a group receiving a single dose of 24 IU OT (Syntocinon, Novartis, Switzerland) intranasally, or a group given a placebo which included all ingredients except for the peptide. After excluding seven patients because of technical difficulties during data acquisition or low data quality (see below), $n = 20$ remained in the OT condition, and $n = 19$ in the placebo condition. Of our total patient sample, 87% ($n = 33$) were taking psychoactive medication ($n = 11$ SNRI, $n = 10$ SSRI, $n = 9$ tri-/tetracyclic antidepressants, $n = 8$ neuroleptic, $n = 16$ others psychoactive medication).

In addition, a healthy control (HC) group (8 men/11 women) was recruited by on-campus advertisement. Healthy participants were given neither OT nor a placebo, and were recruited as a comparison group. HC were screened for psychiatric disorders according to the DSM-IV and fulfilled none of those diagnostic criteria for axis-I or axis-II disorder during the past 12 months.

All participants gave written informed consent prior to participation. The study was approved by the University of Freiburg Ethics Committee and registered as part of a clinical trial: EUDRA-CT 2010-020,956-69; date registered: February 23, 2011.

2.2. Psychological measures

To approximate verbal intelligence, the vocabulary test (Wortschatztest, WST) was employed. The WST has good reliability (Split-half-reliability $r = 0.95$) and is a good predictor of verbal intelligence assessed with full-scale IQ-tests (Schmidt and Metzler, 1992). The Autism-Spectrum Quotient (AQ, Baron-Cohen et al., 2001), Interpersonal Reactivity Index (IRI, Davis, 1983), the Social Interaction Anxiety Scale (SIAS, Stangier et al., 1999), and the 20-item version of the Toronto Alexithymia Scale (TAS-20, Bagby et al., 1994) were used to assess autistic traits, empathy, social anxiety, and alexithymia for study group description and comparison. The Montgomery-Åsberg Depression Rating Scale (MADRS, Montgomery and Åsberg, 1979) and Childhood Trauma Questionnaire (CTG, Bernstein et al., 1994) were administered to further characterize the CDD patient population and depression severity. With a few exceptions, participants completed the questionnaires either during or after the diagnostic session, which took place before the testing session.

2.3. Experimental task and procedures

At the beginning of each testing session, participants self-administered the nasal spray containing 4 IU OT, or a placebo in each nostril alternately under supervision by the experimenter. A total of three puffs per nostril were administered, resulting in a total dose of 24 IU OT. The application occurred 45 min before the start of the FERT.

During this waiting period participants rested. Afterwards, the participants completed an adaptation of a dynamic FERT as previously used to assess emotion recognition performance (Domes et al., 2008; Hysek et al., 2014; Matzke et al., 2014). The experiment was presented on a computer screen (Dell 22 ", visible display area: 47.5 × 27.5 cm; 50.8 × 30.7° visual angle at a viewing distance of 50 cm) controlled by a personal computer running Presentation (Version 12.1, Neurobehavioral Systems, Albany CA, USA). Participants sat on a comfortable chair and placed their head on a chin rest to reduce head movements and ensure a constant viewing distance of 50 cm.

The FERT consisted of a brief written instruction and six training trials, two blocks of 36 trials each were presented. The 36 stimuli (female: #03, #07, #08; male: #20, #34, #36) with the six basic emotions (anger, disgust, fear, joy, sadness, and surprise) were taken from the NimStim Face database (Tottenham et al., 2009) and morphed with Winmorph (Version 3.01) to reveal picture sets with 1% increments from a neutral to a fully expressed emotional expression. Facial stimuli were converted to gray scale images, cropped to remove hair and clothing, rescaled to approx. 350 × 500 px (11.5 × 14.9° visual angle at a viewing distance of 50 cm) and put on a light gray background.

In each trial, facial stimuli were presented for 80 ms, resulting in the impression that the faces developed the emotion in a continuous, dynamic fashion with increasing intensity. Participants were asked to "stop the presentation as soon as they became aware which particular emotion the face was expressing" by pressing a button. Afterwards, participants were asked to choose the emotion from a list of six basic emotions: anger, disgust, fear, joy, sadness, and surprise. The level of intensity (in percent) at which they stopped the presentation, as well as the emotion chosen were recorded during each trial. The FERT lasted approx. 15–20 min.

2.4. Eye tracking

Overt visual attention was assessed during the FERT with a remote infrared eye tracker (SMI, RED250, Teltow, Germany) attached below the display running at 250 Hz. Before recording gaze data in the main experiment, a 9-point calibration procedure was employed. During a subsequent validation, three targets were presented at the approximate location of the eyes and mouth of the faces presented in the following experiment and participants were instructed to fixate on these targets for 2 s. Calibration and validation were repeated until the mean accuracy reached 1.0 ° visual angle (or better) for the validation targets.

Data quality check. As the first step, data were segmented for further analysis based on the sequences with facial representations. For the segmented data, the percentage of lost data (due to blinks, gaze outside tracking area, loss of tracking for other reasons) was estimated by dividing the total number of available data points by the expected number of data points. In addition, the root-mean-square (RMS) of successive datapoints was calculated to estimate the amount of high-frequency noise (imprecision) in the gaze data (Holleman et al., 2020). Data on five participants were excluded from further analyses because their data loss exceeded 10% or because RMS exceeded 2 SD of the average for the entire group (see Fig. 1). Two additional data sets were removed because of extreme outliers in the frequency of eye or mouth gaze (>4 SD above the mean of the entire group).

Definition *of Areas of Interest (AOIs).* For gaze analysis, facial AOIs were created for each stimulus and each frame of the presentation based on a Limited-Radius Voronoi-Tessellation method (LRVT; Hessels et al., 2016; Vehlen et al., 2021, 2022). Therefore, relevant facial landmarks were detected on each frame with OpenFace (Amos et al., 2016) to define both eyes, the nose, mouth, and face shape. These landmarks were used to define the AOI center points for the LRVT algorithm with a limited radius of approx. 3 ° visual angle. With the given viewing distance and stimulus size (see above), this procedure revealed stimulus-specific AOI mosaics comprising "eyes", "nose", "mouth", "rest of face" and "surrounding area" used to classify the gaze location (see Fig. 2).

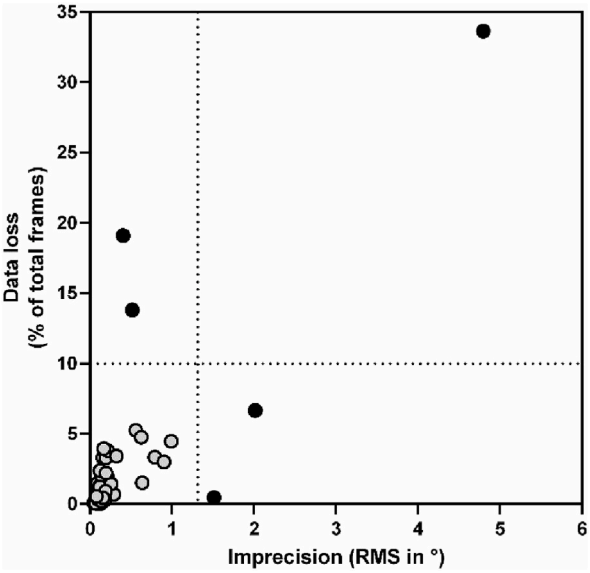

Fig. 1. Five participants were excluded because of data loss and imprecision.

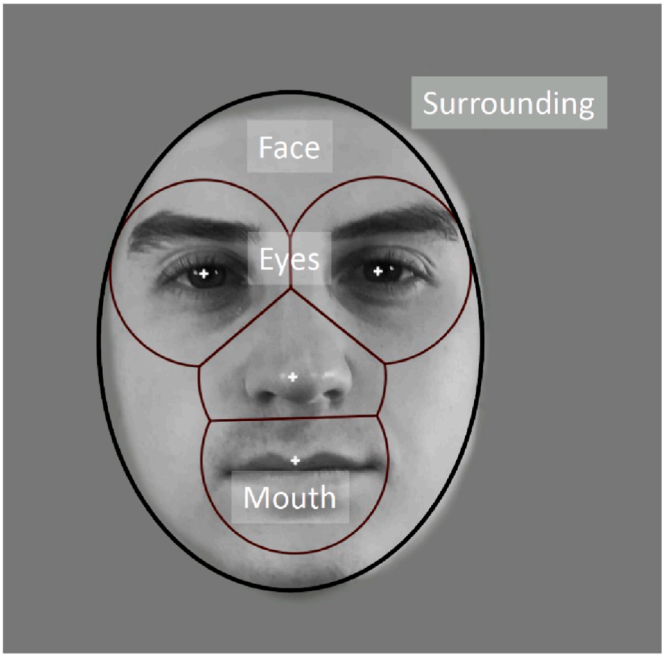

Fig. 2. Location and size of the Areas of Interest (AOIs) based on Limited-Radius Voronoi-Tessellation method (LRVT; Hessels et al., 2016) method used for gaze analyses. White crosses represent the AOI center points. The radius was set to 3° visual angle at 50 cm viewing distance. *Note.* The face depicted here is not part of the NimStim Set and was used for an illustrative purpose only. This person has agreed to publication.

Gaze quantification. For each segment (trial), the position of each gaze point (total dwell time: metric including all gaze events, e.g., fixations, saccades etc.) was classified according to whether it was located within one of the AOIs or on the stimulus-surrounding or missing (i.e., invalid data frames due to tracking failure). Then, for each trial, gaze duration was summed up for each AOI and used to calculate the percentage of total dwell time on the eyes vs. the mouth region relative to valid dwell times for the whole face. Finally, to assess the eyes attentional preferences compared to the mouth region, we calculated a preference score by subtracting dwell times on the mouth from dwell

times on the eyes. Thus, positive values reflect a preference for the eye, while negative values reflect a preference for the mouth region. Preference scores were averaged for each emotional category in the FERT.

2.5. Statistical analyses

Emotion recognition performance (intensity thresholds and correct responses in the FERT) and gaze behavior (preference scores for the eyes vs. mouth region) for the different emotion categories in the FERT were tested with separate MANOVAs, with subsequent multivariate single group comparison using discriminant analyses as implemented in SPSS. In other words, three separate MANOVAs were conducted for the dependent variables intensity threshold and correct responses in the FERT as well as gaze preference. In each analysis, the respective emotion categories (anger, disgust, fear, joy, sadness, and surprise) were additionally added as dependent variables and group affiliation as a between-subjects factor. The a priori hypotheses regarding group differences were tested with planned univariate contrasts reflecting the impaired performance of the CCD group with placebo compared to the healthy control group and the expected normalization of the CDD group receiving OT, resulting in the following contrast weights: HC vs. CDDplac vs. CDDoxy: [0.5–1.0 0.5]. Significance level was set at $p < .05$ (uncorr.). All calculations were done with SPSS (Version 26.0.1.1 for Windows).

3. Results

3.1. Sample characteristics

Descriptive demographic and psychometric data are found in Table 1. The three study groups did not differ in sex distribution. However, the patient groups were significantly older, achieved lower verbal intelligence scores on the WST, and reported fewer years of schooling. Additionally, MADRS ratings in these groups reflected a severe depressive syndrome, and we noted high rates of childhood maltreatment. The extent of such maltreatment was reported as moderate to severe, particularly in the areas of emotional abuse and neglect. As expected, the two CDD groups reported higher levels of autistic traits (AQ), social anxiety (SIAS), and alexithymia (TAS-20), but no differences in empathy (IRI) (see Table 1). The demographic and psychometric characteristics of the study participants correspond to prior reports in CDD patient populations (Brakemeier et al., 2015, 2018; Schramm et al., 2015).

3.2. Emotion recognition performance

The MANOVA for group differences regarding the intensity threshold at which the presentation was stopped in the FERT was not significant: F (12,102) = 1.443, $p = .159$, $\eta^2_{part} = 0.145$ (Fig. 3a). Accordingly, there was no multivariate group effect for the number of correct responses in the FERT: F (12,102) = 0.736, $p = .713$, $\eta^2_{part} = 0.080$ (Fig. 3b), indicating that there was neither a difference between CDD patients and controls, nor an OT treatment effect on emotion recognition performance in the FERT (see Fig. 4).

3.3. Gaze preference

The MANOVA for group differences in gazing at the eye vs. the mouth region (preference scores) revealed a significant multivariate effect: F (12,102) = 2.259, $p = .014$, $\eta^2_{part} = 0.210$. This effect was still significant after controlling for age, IQ, and education (F (12,96) = 2.075, $p = .026$, $\eta^2_{part} = 0.206$). However, none of the multivariate contrasts (HC vs. CDDplac; HC vs. CDDoxy; CDDplac vs. CDDoxy) reached significance (all $p > .10$). Based on the specific hypotheses regarding group differences, we calculated planned univariate contrasts for the three groups [0.5–1.0 0.5] to test for OT's expected compensation for avoiding eye gaze. The planned contrast was significant only for happy facial expression (t (55) = 2.084; $p = .042$), which is in accordance with the prediction of lower eye preference for CDD receiving placebo compared with HC and CDD receiving OT.

4. Discussion

Taken together, the present study revealed no deficit in CDD patients' emotion recognition performance compared to a healthy control group. In addition, a single dose of OT given intranasally to CDD patients revealed no effect on their sensitivity and accuracy in recognizing facial emotions. However, our results do reveal differences in gaze patterns during facial emotion recognition in line with the predicted pattern: While CDD patients in the placebo group showed a lower tendency of eye gaze while evaluating facial expressions than healthy controls, OT treatment in CDD shifted this tendency towards the pattern observed in healthy controls. Notably, this effect was strongest for happy facial expressions.

The lack of differences in emotion recognition performance between HC and CDD patients we observed was unexpected given previous findings in major depression (Krause et al., 2021) and the presence of autistic traits in CDD (Domes et al., 2016c; Radtke et al., 2019). Moreover, clinical descriptions of CDD patients suggest severe psychosocial impairment based on dysfunctional emotion recognition, which is

Table 1
Demographic and psychometric data of the study samples.

	HC ($n = 19$)	CDDplac ($n = 19$)	CDDoxy ($n = 20$)			
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	F/X^2	*p*	
Sex (male/female)	7/12	7/12	10/10	0.94	.626	
Age	38.1 (10.4)	47.9 (9.7)	45.6 (11.8)	4.42	.017	a<b
Verbal IQ (WST)	35.4 (1.4)	32.1 (4.1)	33.7 (3.1)	5.50	.007	a>b
Years in School	12.6 (0.8)	11.2 (2.1)	11.3 (1.7)	4.92	.011	a>b,c
Medication (yes/no)	–	16/3	17/3	<0.01	.946	
Childhood adversities (CTQ)	n.d.	52.8 (19.9)	59.0 (27.6)	0.56	.459	a<b,c
Depressive Symptoms (MADRS)	n.d.	24.0 (7.6)	27.7 (11.1)	1.41	.242	a<b,c
Autism Traits (AQ)	10.5 (5.9)	25.0 (6.2)	24.1 (7.0)	30.52	<.001	a<b,c
Empathy (IRI)	57.2 (8.2)	59.6 (10.6)	59.0 (13.0)	0.269	.765	
Social Anxiety (SIAS)	13.8 (8.9)	37.0 (15.7)	37.9 (19.0)	15.41	<.001	a<b,c
Alexithymia (TAS-20)	35.1 (9.3)	52.9 (12.4)	57.0 (15.2)	16.37	<.001	a<b,c

Note. Except for sex differences and medication, all group comparisons were conducted with separate ANOVAs. Sex differences and medication were compared by means of a χ^2-Test. HC = healthy control group, CDDplac = chronic depressed patients in the placebo group, CDDoxy = chronic depressed patients in the oxytocin group.

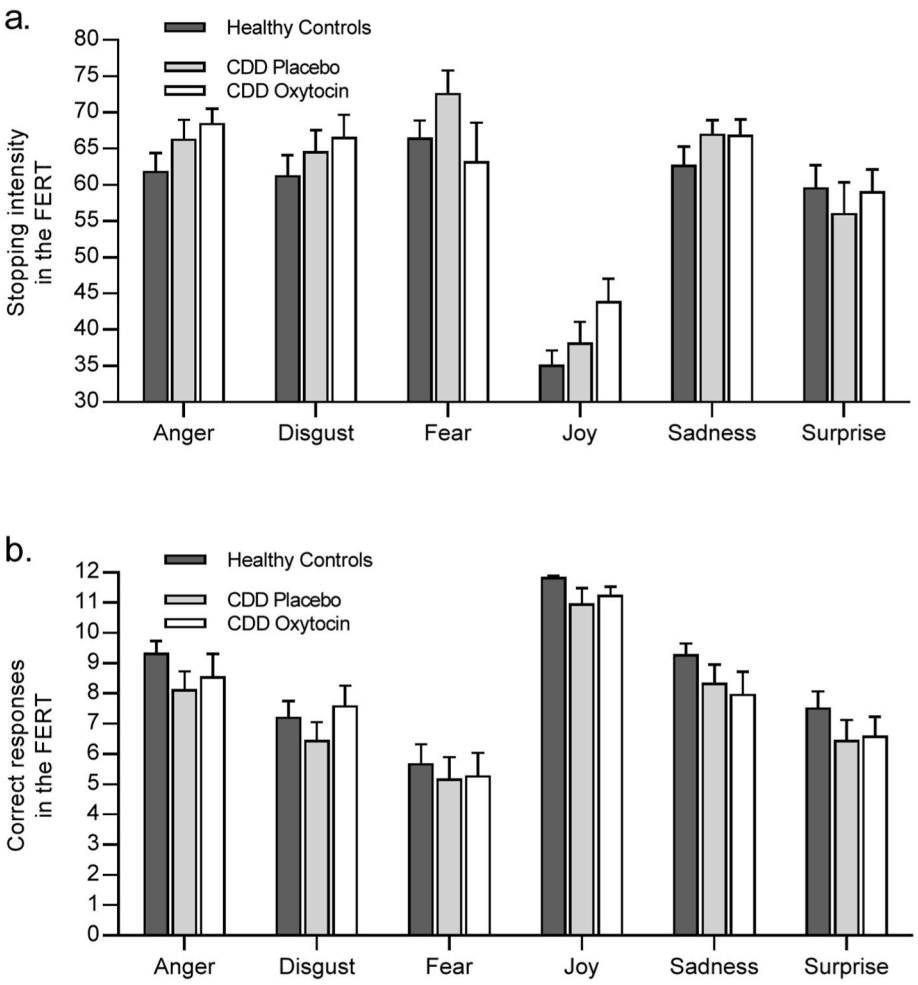

Fig. 3. Emotion recognition performance in the facial emotion recognition task as a function of group. a. Intensity at which presentations were stopped, b. Percentage of correct answers. *Note*. Error bars represent SE. CDD = chronic depressive disorders, FERT = facial emotion recognition task.

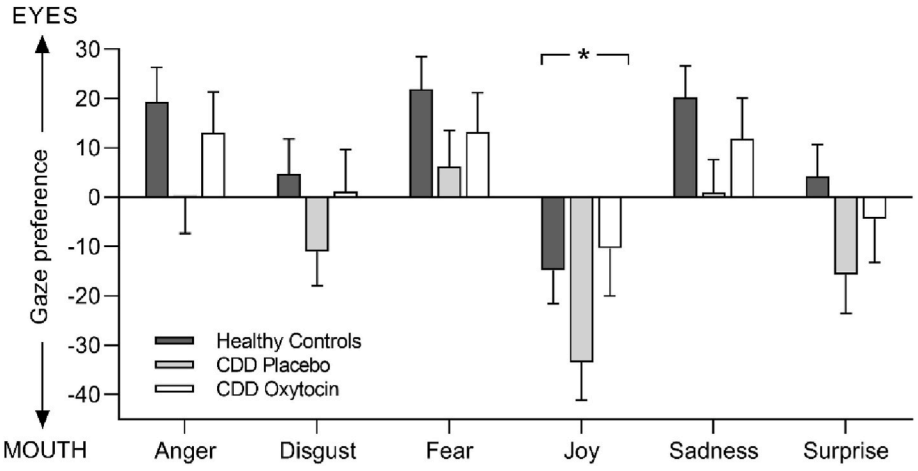

Fig. 4. Gaze preference for eye vs. the mouth region as a function of group. Positive values indicate a relative preference for the eye region. *Note*. Asterisk indicates significant planned contrast ($p < .05$). Error bars represent SE. CDD = chronic depressive disorders.

specifically addressed when these patients undergo psychotherapeutic therapy (McCullough Jr., 2003). However, detecting impairments experimentally when investigating social cognitive function in CDD patients is difficult even using different paradigms, and has likely been hampered by this patient populations' cognitive deficits (Mattern et al., 2015; Zobel et al., 2010). In our study, we observed a small trend towards better emotion recognition performance in HC vs. CDD that failed to reach significance. One possible explanation for this finding might be a paradigm-specific ceiling effect. To avoid such effects in the future and to circumvent potential speed-accuracy trade-offs, future studies could use emotion recognition tasks based on signal detection theory (Domes and Zimmer, 2019; Pessoa et al., 2005; von Dawans et al.,

2020). As a major advantage, such experimental paradigms could help provide differentiated information about the effects of OT on participants' sensitivity to emotional signals and response bias. Furthermore, Guhn et al. (2018) reported that mood reactivity in CDD depends on the individual relevance to the subject, such that a general mood induction was less effective than a personalized mood induction involving autobiographical content. Future research should consider similar individualized approaches to investigating emotion recognition in CDD. Gaze avoidance during social interactions has been frequently reported in individuals with ASD and in those scoring high in autistic traits (Hessels et al., 2018; von dem Hagen and Bright, 2017) and social anxiety (Rubo et al., 2019; Wieser et al., 2010). In addition, OT has been found to increase eye gaze and compensate for gaze avoidance in several studies (Auyeung et al., 2015; Guastella et al., 2008; Kanat et al., 2017). The present finding of lower eye gaze in CDD compared to controls, as well as (partially) increased eye gaze after OT treatment could be interpreted as reflecting these previously reported effects in other clinical conditions which partially overlap with CDD symptomatology (Domes et al., 2016c). Our observation that besides a generally increased attentional preference for the eye region after OT treatment (especially for happy (positive) facial expressions) concurs with our earlier finding that OT shifted attention towards positive social cues in the facial dot probe task (Domes et al., 2016b). It particular, this evidence suggests that OT might be also a significant modulator of social perception during the intentional evaluation of social cues, signaling positive social interaction.

The main limitations of our study are its small sample size, heterogeneous concomitant medication, and the inability of the chosen experimental paradigm to account for baseline differences between HC and CDD in emotion recognition performance, thereby masking potential OT treatment effects. In addition, potential sex differences in the responsiveness to OT as suggested by previous studies in healthy women (Domes et al., 2010; Lieberz et al., 2020; Rilling et al., 2014), could not be tested adequately in the present study due to the small sample size and the limited statistical power. Nevertheless, OT's ability to partially correct a decreased attentional preference for the eye region in CDD has potential clinical relevance. Gaze anxiety and avoidance can be reliably and validly assessed by applying self-reported questionnaires (Domes et al., 2016a) and might help plan behavioral treatment and facilitate the development of innovative treatment strategies in CDD.

Dysfunctional emotion recognition and its resultant impairment of adaptive social behavior are a key feature of chronic depression, and an important target for its specific psychotherapeutic treatment (McCullough Jr., 2003). Although we did not find differences in emotion recognition performance between patient and control groups, OT administration appeared to normalize gaze patterns in the patient group compared to placebo. Future studies should further investigate different doses and durations of OT administration in study designs that account for sexual dimorphism, using a wide range of social-emotional outcome measures to better understand the potential effects (including dysfunctional) of OT in different clinical populations. In particular, OT's potential to alleviate symptoms or augment psychotherapy in CDD might be a subject of future research.

Author contributions

Claus Normann, Markus Heinrichs and Gregor Domes designed the study, Antonia Kellner performed the data collection, Antonia Vehlen and Gregor Domes analyzed the data, and all authors contributed to the interpretation of the results and writing of the manuscript. All authors approved the final version of the article.

Data statement

The datasets collected and analyzed in the current study are available in the Open Science Framework (OSF): https://osf.io/48vqn/?view_only=97273c2829f54ea49373fb567143785c.

Declaration of competing interest

None.

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