



Oxytocin administration and emotion recognition abilities in adults with a history of childhood adversity

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ABSTRACT

Adverse childhood experience such as neglect or abuse can lead to long-term deficits in emotion processing abilities. Animal studies indicate that oxytocin production and/or sensitivity are influenced by variation in early nurturing experiences. The goal of this study was to test whether emotion recognition abilities and empathy might be improved via intranasal oxytocin administration in adults with a history of childhood maltreatment. We assessed a total of 80 healthy participants, half with and half without a history of childhood adversity. Participants performed the Reading the Mind in the Eyes Test (RMET) and an emotion recognition task under 24 IU intranasal oxytocin and placebo, using a double-blind crossover study design. In the first of two sessions, both groups profited equally from oxytocin administration and showed greater accuracy under oxytocin compared to placebo in the RMET ($p = .049$). In the emotion recognition task, only the early adversity group benefited significantly from oxytocin administration in the first session ($p = .035$), mainly due to more accurate recognition of angry and fearful facial expression. Our findings show that emotion processing abilities might be improved via oxytocin administration in adults reporting adverse childhood experiences.

1. Introduction

It is well established that adverse early life experiences can predispose individuals to mental and physical disease in adulthood (Gilbert et al., 2009; Repetti et al., 2002) raising the question of how the long-lasting health consequences of unfavorable early environments are sustained. A large body of research has shown that early adversity can lead to altered regulation of the hypothalamus-pituitary-adrenal (HPA) axis (Heim et al., 2008) and to deficits in social behavior and social cognitive skills such as emotion processing (Young and Widom, 2014). Facial emotion recognition is essential for social cognition and the early learning environment plays an important role in how facial expressions are interpreted and which expressions are particularly relevant to the individual (Pollak and Kistler, 2002). Several studies with maltreated children have reported increased sensitivity for negative emotions (Curtis and Cicchetti, 2011; Masten et al., 2008; Pollak et al., 2000). Furthermore, impairments in emotion recognition in clinical samples of adults reporting childhood trauma have been reported (Nicol et al., 2014; Russo et al., 2015). A potential neurobiological mechanism underlying the link between childhood adversity and social and emotional

difficulties observed in adulthood involves the central oxytocin system (Heim et al., 2008): the neuropeptide oxytocin modulates the activity of various brain areas (including limbic structures such as the amygdala, hippocampus, striatum, and midbrain; (Meyer-Lindenberg et al., 2011) involved in social behavior and cognition. Intranasal application of oxytocin in humans has been shown to have beneficial effects on complex social cognitive functions (Heinrichs et al., 2009; Kanat et al., 2014). There is evidence suggesting that adverse experiences in childhood, like maltreatment or neglect, can have long-lasting effects on the developing oxytocin system. Due to its role in mediating caregiver-child attachment and trust (Feldman, 2015; Rilling and Young, 2014), disruptions in the relationship to attachment figures during early-life – a phase of heightened plasticity – may influence the development of the oxytocin system (Heim et al., 2008). Animal studies revealed that central oxytocin receptor expression was influenced by early nurturing experiences in rats, and that these changes persisted over time (Francis et al., 2000). In rhesus monkeys, a lower concentration of oxytocin in cerebrospinal fluid (CSF) was found in nursery-reared male monkeys than in mother-reared controls (Winslow et al., 2003). In humans, children raised in deprived orphanages showed less responsiveness of the

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oxytocin system after physical interaction with their adoptive mothers as compared to family-reared control children (Fries et al., 2005). Meinschmidt and Heim (2007) reported a decreased sensitivity to intranasally applied oxytocin in men who experienced early life stress in the form of parental separation. A lower concentration of oxytocin in CSF was observed in women with a history of childhood abuse or neglect, most notably in those who experienced emotional abuse (Heim et al., 2009).

Given the evidence of deficits in social cognitive skills in adults with adverse childhood experiences, and given the association between childhood adversity and alterations in the oxytocin system, we sought to test in adults with early adverse experiences whether intranasal oxytocin administration might lead to an improvement in the performance of tasks involving the recognition of basal emotions and complex mental states. We hypothesized that the ability to recognize basic emotions as well as complex mental states would improve after oxytocin administration in adults reporting childhood adversity.

2. Methods and materials

2.1. Participants

A total of 80 healthy adults (54 females, 26 males) were recruited from the Freiburg (Germany) region. We used articles in local newspapers as well as community-posted flyers to advertise a study looking for adults with adverse childhood experiences. The control group was recruited by the same means, advertising a study on „Stress and Emotions“. Inclusion criteria were age between 40 and 60 years, and experience of childhood adversity for the early adversity group (and absence thereof for the control group). The German 28-item version of the Childhood Trauma Questionnaire (CTQ, Bernstein et al., 1994, 2003; Rodewald, 2005) was used to assess five categories of childhood adversities (sexual, physical and emotional abuse, as well as physical and emotional neglect). In order to classify subjects as positive for a history of childhood adversity, CTQ cut-off scores for moderate to severe exposure to traumatic experiences were used (> 12 for emotional abuse; > 9 for physical abuse; > 7 for sexual abuse; > 14 for emotional neglect; and > 9 for physical neglect). Experience of adversity was validated in a structured interview with the Early Trauma Inventory (ETI, Bremner et al., 2000; Heim, 2000). Acute mental disorders were screened for by a psychologist using the German version of the Structured Clinical Interview for DSM-IV Disorders (SKID I & II; Wittchen et al., 1996). None of the participants fulfilled the criteria for mental disorders at the time of assessment or during the preceding twelve months. The control group participants scored below cut-off on all CTQ subscales, and were matched using a matched-pair procedure to the early adversity group according to sex, age, and socioeconomic status (SES) at present, and SES during childhood. Current and childhood SES were assessed in reference to current and childhood family income as well as the participants' and their parents' educational level. The Brief Symptom Inventory (Franke, 2000) was used to assess subclinical psychopathological symptoms at the time of testing. For both groups, the use of psychoactive medication or hormone intake (e.g. oral contraceptives) led to study exclusion. The participants gave written informed consent to the study procedures, approved by the Ethics Committee of the Albert-Ludwigs University of Freiburg (183/11). The study was part of a larger project investigating the long-term consequences of childhood adversity, which also included the assessment of hormonal and genomic responses to stress (Schwaiger et al., 2016). Experiments reported here were conducted at least one week after the stress session.

2.2. Study procedure

A double-blind, placebo-controlled, within-subject design was used to investigate the effect of a single dose of intranasal oxytocin on social

cognitive abilities. Participants first completed a multidimensional mood-questionnaire (MDBF, Steyer et al., 1997) at each experimental session, followed by the intranasal application of the oxytocin or placebo spray via self-administration. In accordance with a standardized protocol and under investigator supervision, the participants administered three puffs of oxytocin (Syntocinon-Spray Novartis, Switzerland; 4 IU oxytocin per puff, total dose of 24 IU oxytocin) or placebo (containing all ingredients except for the neuropeptide) per nostril (Spengler et al., 2017). After a 45 min loading period, during which the participants watched a movie with non-social content, the MDBF was completed a second time and then the tests were carried out. Dosage and test latency were chosen based on the results by Spengler et al. (2017) who systematically varied dose-test latencies and doses of oxytocin and identified a time window between 45 and 70 min after administration of a dose of 24 international units as most effective. After each experimental session, participants were asked if they thought they had received oxytocin or placebo. The self-report indicated that they were unable to guess beyond the chance level. Two tests were applied to assess emotion processing ability, the “Reading the Mind in the Eyes Test” (RMET, Baron-Cohen et al., 2001) and a “Gradual Emotion Recognition Test” (Chen et al., 2015; based on Lischke et al., 2012). Whereas the RMET calls for high sensitivity to emotional cues and requires the participant to infer complex mental states from solely the eye region, the “Gradual Emotion Recognition Test” requires the individual to swiftly and accurately detect basic emotions from naturalistic, animated stimuli. Both tests were conducted twice on two separate sessions, with the RMET preceding the emotion recognition task on both sessions. Block randomization was used to ensure that an equal number of participants in the two groups would receive oxytocin and placebo in the two sessions. The experimental sessions took place in the afternoon and lasted about two hours. Tests were implemented on a computer and each participant was seated in an individual cubicle. At any given time, there was a maximum of four subjects participating in the experiments. Participants did not communicate with each other before, during or after the experimental sessions.

To account for fluctuations in gonadal steroids over the menstrual cycle and their possible interactions with exogenous oxytocin, female participants with regular menstrual cycles were tested in the mid-luteal phase. The cycle-phase was assessed as a self-report by participants and validated by saliva assays of estradiol and progesterone taken on both sessions. All values were in the typical range for the second cycle phase for both hormones. To take the menstrual cycle phase into account and reduce learning effects, there was a four-week time period between the two experimental sessions for all participants. After completion of the second sessions, subjects received monetary compensation for study participation (total of 100 €).

2.2.1. Experiment 1: reading the mind in the eyes test

The RMET was used to assess participants' ability to infer complex mental states from the eye region. During the test, 36 pictures of the eye region are shown on a computer screen with four alternative labels describing what the person is thinking or feeling. Participants have to decide which of the four labels accurately describes the person's mental state (Baron-Cohen et al., 2001). Performance on the RMET was calculated as the percentage of items rated correctly.

2.2.2. Experiment 2: emotion recognition task

The task to determine emotion recognition ability of the subjects corresponds to the task used by Chen et al. (2015). The task requires that subjects evaluate a person's emotional state from the display of a face gradually changing from a neutral expression towards one of the emotions sadness, anger, happiness or fear. Participants were instructed to respond as quickly and accurately as possible. As soon as they recognized the displayed emotion, they were supposed to press a stop button. After stopping the presentation, they had to indicate which of the four emotions they had identified. There were 24 test trials

preceded by four practice trials. The same trials were used in both sessions, but in two different pseudo-randomized sequences. For each trial, accuracy (i.e., percentage correct) and detection threshold were recorded. The detection threshold was measured as the intensity level at which the participant had stopped the presentation, ranging from 0 (neutral) to 100 (fully expressed emotion).

2.2.3. Non-social control task

To control for non-specific group differences and oxytocin effects on general object recognition, participants additionally completed a non-social control task (Chen et al., 2015), where participants had to identify four different types of car models (Smart car, pickup truck, box truck and VW Beetle). As neutral stimulus, they were shown a common car model (a small hatchback), which then morphed into one of the four models. Again, participants were instructed to press a stop button as soon as they identified the car type. Participants completed four practice trials before the 16 test trials. The same test trials were used in both sessions in one of two pseudo-randomized testing orders. Accuracy and detection thresholds were recorded for each trial.

2.3. Statistical analysis

Analyses of variance for repeated measures (session 1 vs session 2) were computed with group (early adversity vs. control) and substance (oxytocin vs. placebo) as factors. Because of sex differences in emotion recognition (e.g. Baron-Cohen et al., 2001) and due to differences in circulating oxytocin levels (females tend to respond differently to oxytocin administration than males; Bakermans-Kranenburg and van Ijzendoorn, 2013) sex was included in all analyses as a covariate. Because of the regulatory influence of sex hormones on the oxytonergic system (Bos et al., 2012; Rilling and Young, 2014), women's estradiol and progesterone levels were entered as covariates in a subsequent analysis of the female subsample to ascertain that results were stable after inclusion of this potential confounder. The level of significance for all analyses was set at $p < .05$ and effect sizes were reported as η^2 . Greenhouse-Geisser corrections were applied whenever the Mauchly test of sphericity indicated heterogeneity of covariance in repeated-measures analyses. IBM SPSS Version 23 for Windows was used for statistical analyses of the data.

For the emotion recognition task, preliminary analyses revealed a significant substance by order of substance administration interaction for both accuracy ($F_{1, 74} = 4.82, p = .031, \eta^2 = .061$) and detection threshold ($F_{1, 74} = 8.23, p = .005, \eta^2 = .10$). As the effects of substance and order of substance administration cannot be disentangled from the time effect, we also report results from the first session only. Follow-up analyses for session 1 were performed with ANOVA with group and substance as between-subject factors. For the emotion recognition task, emotions were included as an additional factor to uncover potential valence specific effects.

3. Results

3.1. Sample characteristics

The control group was matched to the group of adults reporting childhood adversity in terms of sex, age, current socioeconomic status (SES) and SES in childhood (see Table 1A for details). As shown in Table 1A, there were no significant differences between the two groups regarding age and sex. Table 1A also shows participants' total scores on the Childhood Trauma Questionnaire (CTQ) and the number of participants who scored above cut-off scores for moderate to severe exposure of the five CTQ categories. Table 1B indicate that 47.5% of the early adversity group met the criteria for four or more, 65% for three or more categories of childhood abuse and neglect.

Table 1A

Demographic characteristics, total CTQ scores, number and percentage of participants meeting moderate to severe cutoff criteria for CTQ categories, psychopathological history and current symptoms.

	Early Adversity (n = 40)	Control (n = 40)	P
Age; mean \pm SD	52.00 \pm 6.01	49.98 \pm 5.22	0.112
Sex; number of females (%)	27 (67.5)	27 (67.5)	1
CTQ total score; mean \pm SD	63.73 \pm 16.48	35.28 \pm 5.58	< .001
CTQ categories; n (%)			
Sexual abuse	18 (45.0)	–	
Physical abuse	17 (42.5)	–	
Emotional abuse	26 (65.0)	–	
Emotional neglect	35 (87.5)	–	
Physical neglect	25 (62.5)	–	
Family net income during childhood			0.36
Up to 2000€	33	32	
Up to 3000€	4	6	
> 3000€	3	3	
Current Family net income			0.426
Up to 2000€	25	24	
Up to 3000€	7	10	
> 3000€	8	8	
History of mental disorder n (%)	24 (60)	11 (27.5)	0.003
BSI global severity index	0.47 \pm 0.41	0.33 \pm 0.27	0.071

Table 1B

Number of CTQ categories which were met by participants (cutoff criteria for moderate to severe exposure).

	Number of endorsed CTQ Categories n (%)					
	0	1	2	3	4	5
Early Adversity Group	–	9 (22.5)	5 (12.5)	7 (17.5)	14 (35.0)	5 (12.5)
Control Group	40 (100)					

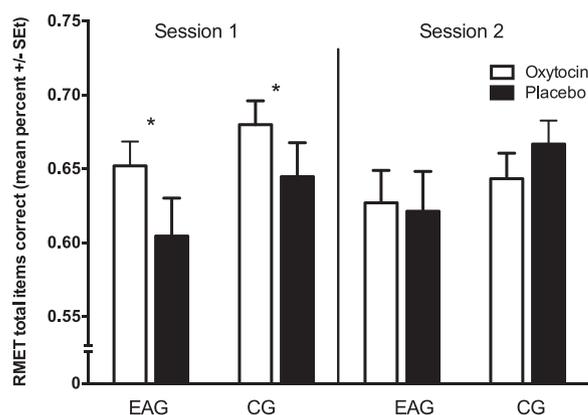


Fig. 1. Performance on the RMET total items (mean \pm SE) for each group, separated per trial and as a function of substance administration. Abbreviations: SE, standard error; RMET, Reading the Mind in the Eyes Test; EAG, early adversity group; CG, control group. * $p < 0.05$.

3.2. Effects of oxytocin on theory of mind

Overall, the control group was marginally better at identifying the states of mind depicted in the RMET as compared to the group reporting childhood adversity ($F_{1, 77} = 3.43, p = .068, \eta_p^2 = .043$; see Fig. 1). No oxytocin effect was observed when the two sessions were analyzed together ($F_{1, 77} = .98, p = .326, \eta_p^2 = .013$), nor was any oxytocin by

group interaction ($F_{1, 77} = .96, p = .330, \eta_p^2 = .012$) found. To eliminate sequence effects from our analysis, data from both sessions were analyzed separately. For the first session, a main oxytocin effect ($F_{1, 75} = 4.02, p = .049, \eta_p^2 = .051$) was found for the total score on the RMET, indicating that the participants who received oxytocin performed better than those who received placebo. Both the main effect of group ($F_{1, 75} = 2.62, p = .109, \eta_p^2 = .034$) and the oxytocin by group interaction effect were non-significant ($F_{1, 75} = 0.06, p = .811, \eta_p^2 = .001$). For the second session, there were no significant effects for substance ($F_{1, 75} = 0.28, p = .598, \eta_p^2 = .004$), group ($F_{1, 75} = 2.15, p = .147, \eta_p^2 = .028$) or the substance by group interaction ($F_{1, 75} = 0.62, p = .435, \eta_p^2 = .008$).

3.3. Effects of OT on emotion recognition

There were no main effects of group or substance and no group by substance effects when the two sessions were analyzed together (all $F < 1.94$, all $p > .168$). Analyses of the first session revealed a significant oxytocin by group interaction ($F_{1, 75} = 4.62, p = .035, \eta_p^2 = .058$). In participants with a history of early adversity, emotion recognition was more accurate under oxytocin compared to placebo (post-hoc comparison: $p < .019$), whereas there was no significant difference in the control group (Fig. 2). The main oxytocin ($F_{1, 75} = 1.45, p = .233, \eta_p^2 = .019$) and group effects ($F_{1, 75} = 0.00, p = .951, \eta_p^2 = .000$) were non-significant.

Next, we analyzed emotion recognition separately for the four emotions in session 1 (Fig. 3). There was a significant main effect of substance for fear ($F_{1, 75} = 4.54, p = .036, \eta_p^2 = .057$), and a significant substance by group effect for anger ($F_{1, 75} = 4.287, p = .042, \eta_p^2 = .054$). Post-hoc analyses showed that the early adversity group showed significantly better performance under oxytocin compared to placebo for fear ($p = .017$) and anger ($p = .039$).

The group's detection thresholds did not differ ($F_{1, 75} = 2.24, p = .139, \eta_p^2 = .029$) nor did the relation to the administered substance ($F_{1, 75} = 0.40, p = .531, \eta_p^2 = .005$). The interaction substance x group was also non-significant ($F_{1, 75} = 0.28, p = .597, \eta_p^2 = .004$).

No significant effects of group, oxytocin, or their interaction emerged in the control task (all $p > .05$). Oxytocin did not influence mood, wakefulness, or calmness (all $p > .05$). In female subjects, estradiol and progesterone levels did not differ between the two groups at both sessions (all $p > .05$), and were not related to performance on the RMET or the Gradual Emotion Recognition Test. All analyses remained stable after controlling for estradiol and progesterone levels in the female subsample.

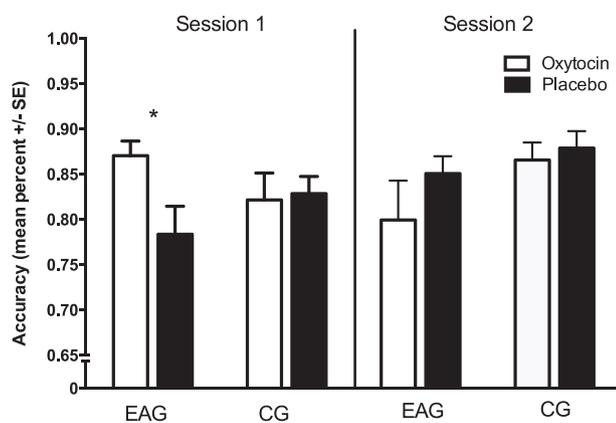


Fig. 2. Accuracy on the emotion recognition test for each group, separated per trial as a function of substance administration. Abbreviations: SE, standard error; EAG, early adversity group; CG, control group. * $p < 0.05$.

4. Discussion

The experience of adversity such as abuse or neglect in childhood has been associated with deficits in emotion processing and other aspects of social cognition. Furthermore, childhood adversity has been linked to altered oxytocin production and/or sensitivity. Here, we assessed two aspects of social cognition, namely the ability to correctly label basal emotions, and the ability to infer mental states from the eye region in adults reporting childhood adversity. Analysis of the RMET showed that both, participants in the early adversity group and the control group, performed significantly better on the RMET following oxytocin administration, compared to those who received placebo, but only in the first of two sessions. There was no oxytocin effect in the second experimental session, possibly due to learning effects. Our data might suggest that the positive effect of oxytocin in the first session was sustained over time and influenced the performance in the second session, even under placebo. This could be indicative of an oxytocin effect on task comprehension (i.e. grasp) and motivation. This possibility of a sustained oxytocin effect should be the subject of further investigation.

In our second task, which involved emotion recognition from dynamically evolving facial expressions, there were no differences between the early adversity group and the control group under placebo. Under oxytocin, however, the early adversity group showed a significant increase in emotion recognition accuracy, scoring 9% higher than the participants who received placebo. Separate analyses per emotion revealed that this effect was mainly due to items depicting fearful or angry faces. Accuracy significantly rose by 16% for fearful and by 12% for angry faces, and (non-significantly) by 6% for sad faces. It is unclear, however, whether this reflects an improvement in emotion recognition limited to negative emotions, as we observed a ceiling effect for happy faces, where accuracy was extremely high both under placebo and oxytocin in both groups. It is also conceivable that the observed pattern of results reflects a general improvement in emotion recognition abilities. For the early stages of facial stimulus processing, i.e. very brief presentation of emotional faces, oxytocin improved detection accuracy for faces regardless of valence (Schulze et al., 2011). On the other hand, in a sample of female patients with borderline personality disorder, valence specific effects were observed, as oxytocin reduced attentional bias toward facial expression of anger and also reduced amygdala activation in response to angry faces compared with happy faces (Bertsch et al., 2013).

The suggested alterations in the oxytocin system in individuals with a history of early adversity could be maintained in different ways. Negative experiences during sensitive periods might lead to altered connectivity between brain regions involved in emotional processing (i.e. limbic structures; Herpertz and Bertsch, 2015). Changes in the oxytocin system induced by early adversity might also occur on the receptor level, including alterations in receptor functioning, density, or affinity (Bakermans-Kranenburg and van IJzendoorn, 2013), possibly brought about by differential methylation of the oxytocin receptor gene (Kumsta et al., 2013; Smearman et al., 2016). Lastly, there could be deficient oxytocin availability due to an inadequate release of oxytocin from hypothalamic neurons (Heim et al., 2009).

An investigation of patients with borderline personality disorder (BPD), where childhood adversity often plays an etiological role provided evidence neural and behavioral patterns in response to a facial emotion recognition test were normalized and comparable to healthy controls after oxytocin administration (Bertsch et al., 2013). Other studies, however, have demonstrated decreased oxytocin sensitivity in individuals with childhood adversity (Meinschmidt and Heim, 2007; van IJzendoorn and Bakermans-Kranenburg, 2012), which might in part be explained by person- and task-dependent oxytocin effects (Bartz et al., 2011).

An improvement in reading social signals could enable individuals to interact socially more successfully, thereby strengthening stress-

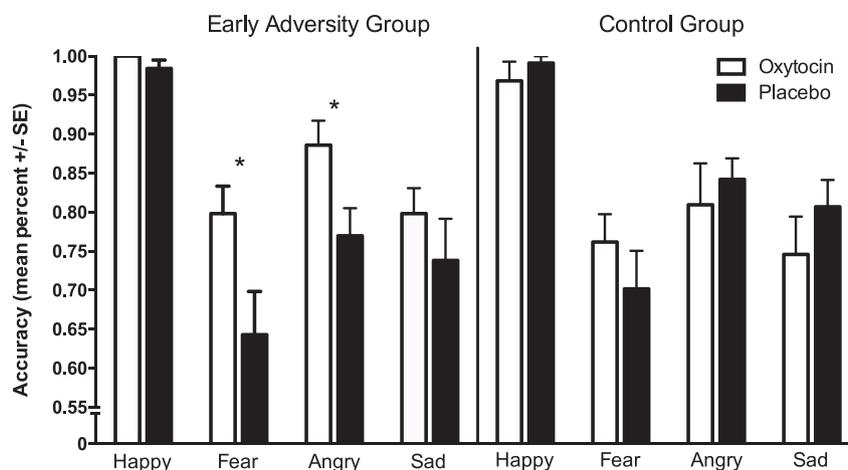


Fig. 3. Accuracy on the emotion recognition test in session 1 separate for emotions in both groups as a function of substance administration. Abbreviations: SE, standard error; EAG, early adversity group; CG, control group. * $p < 0.05$.

protective resources such as social support (Ditzen and Heinrichs, 2014). The possibility of using oxytocin administration in combination with psychotherapy has been discussed to establish trust and to facilitate social interaction (Meyer-Lindenberg et al., 2011). On the other hand, given that oxytocin likely increase sensitivity to and salience of social cues regardless of valence (Domes et al., 2007; Schulze et al., 2011) – although valence specific effects have also been observed (Bertsch et al., 2013) – increased oxytocin availability might also have an effect on the processing of negative emotions, which should be taken into consideration when using oxytocin in intervention contexts.

Our modest sample size precluded the analysis of genetic factors. For instance, inter-individual variability in oxytocin sensitivity is known to be influenced by genetic variability at the *OXTR* locus (Chen et al., 2015; Kumsta and Heinrichs, 2013). Furthermore, genetic variability might moderate the association between early adversity and long-term deficits in social cognition. Future studies with sufficient power to detect gene-environment interaction effects might include genotyping of candidates involved in oxytocin production, release, or the metabolism of oxytocin (such as *OXT*, *LNPEP*, as well as *CD38* (Feldman et al., 2016)). Additionally, epigenetic processes such as alterations in DNA methylation at the *OXTR* locus might be mechanistically involved in the association between childhood adversity and long-term outcomes (Kumsta et al., 2013; Smearman et al., 2016).

The following limitations should be noted. First, we relied on self-reported childhood adversity, and the credibility of retrospective self-reports has been discussed. However, a meta-analysis revealed that false positive reports of childhood adversity are rare (Hardt and Rutter, 2004). Additionally, we validated group assignment with the ETI, a structured trauma interview, in order to further improve credibility.

Furthermore, the long time span between exposure to adversity and investigation of emotion recognition has to be considered, as the investigated participants were aged between 40 and 60 years. Presumed effects of early adversity cannot be disentangled from potential other effects such as ongoing adversity, adult trauma, or other factors that could not be assessed in the present investigation. Conversely, it is well possible that adversity-associated deficits have been compensated for across the life-span. In general, models addressing the question of how the long-lasting health consequences of early adverse environments are sustained – or biologically embedded – assume stable alterations in structure and function of several target systems, including emotion processing or stress-responsive biological regulatory systems. It is unclear, however, how stable these alterations actually are, and the degree of stability and change following a change to positive environments is likely to be domain specific. For instance, deficits associated with early institutional rearing, such as inattention/overactivity, disinhibited

social engagement and autistic features show remarkable stability into young adulthood despite the positive rearing environment following adoption in early childhood, whereas for cognitive abilities almost complete recovery was observed (Sonuga-Barke et al., 2017). Individuals tested in the present study were also investigated with regard to regulation of the HPA axis and stress-induced transcription responses. Following exposure to the Trier Social Stress Test (TSST), the early adversity group showed significantly reduced cortisol responses. Differences between groups in stress-induced regulation of gene transcription were observed for genes involved in steroid binding, hormone activity, and G-protein coupled receptor binding, in part explained by an increased activity of pro-inflammatory upstream signaling in the early adversity group (Schwaiger et al., 2016). These results suggest high stability of physiological alterations, at least for HPA axis function.

In conclusion, the data reported here provide further support for the notion that the long-term effects of adverse childhood experiences on deficits in social behavior and cognition might be mediated via oxytocin functioning. The current study found an improvement in social processing abilities in a sample of participants reporting childhood adversity after the application of a single dose of oxytocin.

Conflict of interests

Oxytocin administration and emotion recognition abilities in adults with a history of childhood trauma. All authors report no biomedical financial interests or potential conflicts of interest.

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