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The effect of oxytocin administration on empathy and emotion recognition in residential youth: A randomized, within-subjects trial

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A B S T R A C T

Previous research has revealed a positive effect of oxytocin administration on several social behaviors especially in individuals with social-affective deficits. However, it is still unknown whether intranasal oxytocin administration (OT-IN) can be beneficial to residential youth who exhibit severe social-affective impairments. We conducted a randomized, double-blind, placebo-controlled, within-subjects, sequential study to examine the effect of OT-IN on empathy and emotion recognition in 100 male adolescents living in residential youth care facilities. We also explored the moderating role of callous-unemotional traits, trauma, and dissociation in the oxytocin effect. Participants self-administered one dose of 24 IU of oxytocin or placebo and performed experimental tasks on empathy and emotion recognition before and after the administration. The same procedure was performed one week later with the other substance. We found that empathy was increased after oxytocin administration compared to placebo and this effect was specific to individuals with high callous-unemotional traits. There was no effect of OT-IN on the overall emotion recognition, but there was a positive effect on accuracy of fear recognition. Trauma and dissociation did not moderate the oxytocin effect on empathy or emotion recognition. Our findings provided evidence of a beneficial effect of OT-IN on empathy and fear recognition in residential youth. We propose that a combination of OT-IN and psychological interventions merits further exploration, as it might be a novel promising direction for more tailored approaches and better treatment outcomes.

1. Introduction

Extensive research on oxytocin has revealed its involvement in several social-affective behaviors, such as social affiliation, social cognition, pair bonding, attachment, and prosocial behavior (Campbell, 2008, 2010; De Dreu and Kret, 2016; Lee et al., 2009). Experimental studies on the effect of intranasal oxytocin administration (OT-IN) have demonstrated a positive effect on empathy, trust, emotion recognition, cooperation, and generosity in humans (Bartz et al., 2011a; De Dreu and Kret, 2016; Leppanen et al., 2017; Shahrestani et al., 2013). However, this effect is not ubiquitous, but depends on the context and the perception of the stimuli (Bartz et al., 2011a). It also varies based on individual differences and is more pronounced in subjects with social-affective deficits (Bartz et al., 2010, 2019; De Dreu and Kret, 2016; Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016; Zik and Roberts, 2015).

Specifically, OT-IN promotes bonding, empathy, trust, and cooperation in in-group but not out-group contexts (De Dreu and Kret, 2016). When the out-group is perceived as threatening, OT-IN elicits competitive behavior and defensive aggression. Additionally, a meta-analysis on the effect of OT-IN on emotion recognition found that a single dose of oxytocin enhanced the recognition of basic emotions and especially fear recognition in healthy populations (Leppanen et al., 2017). Relatedly, a review showed that OT-IN affected several brain areas and more consistently reduced amygdala activity in response to fearful faces in males, suggesting that the anxiolytic effect of oxytocin might facilitate fear recognition (Tully et al., 2018). The authors also suggested a potential therapeutic role of oxytocin in regulation of facial emotion processing in anxiety and antisocial personality disorder that are characterized by impaired fear recognition.

The specific effects of oxytocin are also supported by meta-analytic evidence demonstrating the differential effects of OT-IN on amygdala activity (Wang et al., 2017). OT-IN increased amygdala activity in response to positive social-affective processes, but decreased amygdala activity in response to negative social-affective processes (Wang et al., 2017). The authors argued that OT-IN might promote social functioning by enhancing positive social processes and mitigating the response to negative social stimuli. Lastly, individual characteristics considerably affect the oxytocin effect. In particular, OT-IN has been more beneficial to individuals with social-affective deficits (eg., low empathic ability; Feeser et al., 2015), individuals with autism spectrum disorders or social anxiety (e.g., Bartz et al., 2010, 2019; Domes et al., 2014), and individuals with avoidant attachment style (Bartz et al., 2015). Empirical evidence showed that OT-IN had distinct behavioural and neural effects on different psychiatric patients (e.g., individuals with social anxiety disorder or autism spectrum disorder), highlighting that OT-IN might follow different pathways targeting specific deficits in order to ameliorate abnormal behavior and promote engagement in social

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interactions (see for a review Ma et al., 2016). In contrast, attenuated effects of oxytocin have been observed in individuals with borderline personality disorder (e.g., Bartz et al., 2011b) or trauma history (e.g., Ebert et al., 2013; Riem et al., 2013).

Several approaches have been posited to understand the underlying mechanisms of oxytocin in social-affective behaviors. The social salience hypothesis suggested that OT-IN modulates the salience of all social stimuli by interacting with dopamine's signal on salience coding and attention orientation (Shamay-Tsoory and Abu-Akel, 2016). Particularly, OT-IN enhances prosocial behavior when the stimuli are positive, but leads to competitive and negative responses when the stimuli are perceived as negative (Bartz et al., 2011b; Shamay-Tsoory and Abu-Akel, 2016). The social approach/withdrawal hypothesis proposed that OT-IN enhances the salience of cues, but its effects extend beyond social cues and include all stimuli that have personal relevance or provoke emotional responses (Harari-Dahan and Bernstein, 2018). Another approach argued that oxytocin is related to self-referential processing and interoception that might contribute to the development of empathy and promote in-group survival (Hurlemann and Scheele, 2016). A recent unified framework posited that the aforementioned approaches are not mutually exclusive, but rather suggested that oxytocin is involved in multiple stages of the decision-making process (Piva and Chang, 2018). Moreover, it has been suggested that oxytocin might play a role in the development of the social brain due to its involvement in the processing of social sensory input in the neocortex during the first postnatal years, which is implicated in more complex social and cognitive processing (Vaidyanathan and Hammock, 2016). Lastly, the social adaptation model argued that oxytocin promotes social adaptation, based on evidence supporting the effect of OT-IN on down-regulation of stress and intrinsic reward that promote social interactions (Ma et al., 2016). This model proposes that OT-IN might be able to adapt hyper- or hypo-activity of brain networks in subjects with social impairments in order to regulate social-affective processes and achieve successful social relationships.

Based on this evidence, we argue that OT-IN might also be beneficial to individuals with antisocial behavior who exhibit social-affective deficits. There are two different approaches to address this question. The first approach is to investigate whether OT-IN can have an effect on the primary symptom, in this case antisocial or aggressive behavior. A limited number of studies examined the effect of oxytocin on aggressive behavior in humans yielding conflicting evidence. One study found that oxytocin increased aggressive responses to aggression provocation tasks in healthy adults (Ne'eman et al., 2016). The authors suggested that their findings were in line with the social salience hypothesis, as after oxytocin the participants might have perceived their opponent as more aggressive and thus responded more aggressively to their opponent's provocation (Ne'eman et al., 2016). In contrast, a recent study in healthy males found that oxytocin administration decreased aggressive responses to an aggression provocation task (Berends et al., 2019). Two other studies with a similar design did not find an effect of oxytocin on aggressive responses after aggression provocation in two small samples of healthy adults and individuals with antisocial personality disorder (ASPD) (Alcorn et al., 2015a, b). However, healthy individuals with high levels of interpersonal manipulation and anger exhibited more aggressive responding after OT-IN compared to placebo (Alcorn et al., 2015a). Another study showed that oxytocin increased intimate partner violence inclinations only in individuals with high physical aggression trait in a sample of undergraduate students (DeWall et al., 2014). It is therefore unclear whether OT-IN has an effect on antisocial behavior as the limited evidence revealed the role of contextual and individual characteristics.

The second approach is to explore whether OT-IN can have a positive effect on the social-affective deficits commonly observed in individuals with antisocial behavior, such as impairments in emotion recognition and empathic responding. Given the cumulative evidence on oxytocin's involvement in social behaviors and social adaptation as well as the role of contextual and personal characteristics, it seems more promising to focus on this approach. Oxytocin administration might improve impaired social behaviors that can further contribute to better treatment responses in antisocial individuals. Only one study addressed this question and examined the effect of OT-IN on emotion recognition in adults with ASPD and healthy controls and found that OT-IN improved recognition of fear and happiness in adults with ASPD (Timmermann et al., 2017). We argue that this line of research needs further investigation, replication, and extension to antisocial youth.

During adolescence, there is an ongoing development and maturation of brain networks, neuroendocrine systems, cognitive processes, and social cognition (Lenroot and Giedd, 2006; Shirtcliff et al., 2009; Steinberg, 2005). Relatedly, social-affective behaviors, such as emotion recognition and empathy, continue to develop and improve from adolescence to adulthood (Allemand et al., 2015; Eisenberg et al., 2005). However, youth with antisocial behavior already exhibit severe social-affective deficits from early adolescence (Marsh and Blair, 2008). Examining the effect of OT-IN on social-affective behaviors during this period is imperative to determine whether OT-IN can improve these behaviors in antisocial youth. Importantly, adolescents with severe antisocial and delinquent behavior are frequently admitted to residential youth care institutions and a wide range of comorbid disorders, such as depression, anxiety, and substance use disorders, has been documented in residential youth (Fazel et al., 2008).

Lastly, given the role of individual differences in the effect of OT-IN, we argue that the potentially moderating effect of callous-unemotional (CU) traits, dissociation, and trauma should be taken into account. First, CU traits are highly prevalent in antisocial youth and can lead to the development of psychopathy in adulthood (Frick and White, 2008). Previous studies have also found lower salivary oxytocin levels in adolescents with CU traits (Levy et al., 2015) and a specific association between low salivary oxytocin and primary psychopathic traits was observed in adolescents living in residential youth care facilities (Fragkaki et al., 2019a). Importantly, adolescents with high CU traits exhibit deficits in social-affective behaviors, such as affective empathy and emotion recognition (Frick et al., 2014). These deficits might be a key target for oxytocin administration.

Second, high levels of dissociation have also been found in antisocial individuals and approximately one quarter of offenders exhibit pathological dissociation (Fragkaki et al., 2019b; Frick and White, 2008; Moskowitz, 2004). In addition, dissociation is associated with social-affective deficits, such as impairments in empathy (Schimmenti, 2016) and emotion recognition (Renard et al., 2012). Preliminary evidence has also shown lower plasma oxytocin in relation to dissociation in depressive patients (Bizik et al., 2012) and salivary oxytocin was lower in response to stress in undergraduate students with high dissociation (Monde et al., 2014).

Third, trauma is also commonly observed in antisocial youth and predicts persistent aggression and offending (Dierkhising et al., 2013; Fox et al., 2015). It has been proposed that trauma can modify oxytocin synthesis and oxytocin receptor binding and these changes may mediate the relationship between early negative experiences and social behaviors (Veenema, 2012). Lower peripheral oxytocin levels have been observed in healthy populations with history of trauma (Heim et al., 2009; Opacka-Juffry and Mohiyeddini, 2012), in women with borderline personality disorder (Bertsch et al., 2013), revictimized individuals (Chatzittofis et al., 2014), and traumatized adolescents with conduct disorder (Levy et al., 2015). Most importantly, previous studies have shown that the positive effect of OT-IN in social behaviors is attenuated in individuals with history of trauma, such as emotional neglect and harsh parenting (see for reviews Fragkaki et al., 2018; Donadon et al., 2018). It has been posited that oxytocin administration might not be beneficial to individuals with early negative experiences because they may be negatively biased in the interpretation of social stimuli (Bartz et al., 2011b). Overall, these factors contribute to several different profiles of antisocial youth that need to be taken into consideration.

Taken together, this study applied a randomized, double-blind, placebo-controlled, within-subjects, sequential design to examine the effect of OT-IN on empathy and emotion recognition as well as the moderating role of CU traits, trauma, and dissociation in male adolescents living in residential youth care institutions. We expected a positive effect of OT-IN on empathy and emotion recognition that would be more pronounced in subjects high CU traits, who exhibit severe social-affective deficits, but attenuated in subjects with high levels of childhood trauma. Secondly, due to lack of previous evidence, we also explored the moderating role of dissociation. Thirdly, as a secondary research question we examined whether OT-IN was especially beneficial for fear recognition based on the specific effect of OT-IN on fear recognition and the salient deficits in fear recognition in antisocial youth.

2. Method

2.1. Participants

The study included 100 male adolescents (*M*age = 16.51, *SD*age = 0.96) recruited from residential youth care facilities in the Netherlands from March 2017 to July 2018. The participants were admitted to residential care for externalizing problems and delinquency, and/or adverse family environment. Male adolescents aged 15 to 18 living in groups for youth with typical intelligence were approached for participation. Exclusion criteria were low level of intelligence (measured previously by the psychiatrists of the institutions), severe medical illness, medication for severe medical illness (specific to severe medical conditions and not psychiatric conditions such as ADHD), severe nasal surgery, and schizophrenia (n = 1). The majority of the participants were of Dutch origin (n = 83) and 96 participants followed a vocational-oriented stream in school. Eighty-seven participants exhibited conduct disorder (CD), oppositional-defiant disorder (ODD), attention-deficit hyperactivity disorder (ADHD), or resided in a closed group due to severe delinquent behavior. High rates of alcohol/substance abuse/dependence (n = 71), depression (n = 33), anxiety (n = 35), and manic/hypomanic symptoms (n = 40) were also reported, and 81 subjects had two or more comorbid disorders. Eight participants dropped out after the screening and were excluded from the analyses. Four participants dropped out after the second session, but they were included in the analyses. The total sample size included in the analyses was 91 (*M*age = 16.50, *SD*age = 0.93).

2.2. Instruments

2.2.1. Clinical diagnosis

The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID; Sheehan et al., 1998) was administered to assess the presence of psychiatric disorders. MINI-KID is a fully structured and widely used screening interview for youth aged 6 to 17 years with very good psychometric properties (Sheehan et al., 2010).

2.2.2. Callous-unemotional (CU) traits

CU traits were assessed with the Inventory of Callous-Unemotional traits – Youth version (ICU; Frick, 2003). It consists of 24 items rated on 4-point scale (*0 = not at all true*, *3 = definitely true*) and it has three subscales: callousness, uncaring, and unemotional. The total sum score is computed and higher scores indicate higher CU traits. The ICU is widely used in healthy and clinical samples and has very good psychometric properties in antisocial youth (Feilhauer et al., 2012; Kimonis et al., 2008). The Cronbach's α in this study was 0.83.

2.2.3. Childhood trauma

Childhood traumatic experiences were assessed with the Childhood Trauma Questionnaire – Short Form (CTQ; Bernstein et al., 2003). It consists of 25 items and has five subscales: physical/sexual/emotional abuse and physical/emotional neglect. The items are rated on a 5-point scale indicating the frequency of the traumatic experiences (*1 = never true*, *5 = very often true*). The sum score of all the items was calculated in this study and higher scores indicated higher frequency of childhood trauma. CTQ has very good psychometric properties in community, psychiatric, and forensic populations (Cima et al., 2008; Thombs et al., 2009). The Cronbach's α in this study was 0.93.

2.2.4. Dissociation

The Adolescent Dissociative Experiences Scale (A-DES; Armstrong et al., 1997) was administered to assess dissociative symptoms. It includes 30 items rated on an 11-point scale (*0 = never*, *10 = always*). The mean score is calculated and higher scores indicate higher dissociation. A-DES has been used in healthy and clinical adolescent samples and has very good psychometric properties (Armstrong et al., 1997; Farrington et al., 2001). The Cronbach's α in this study was 0.94.

2.2.5. Empathy

Participants watched eight emotional film clips that evoke empathic reactions. Six of the clips have been used in previous studies (De Wied et al., 2005; De Wied et al., 2012) and two more clips were added. The stories in the film clips are part of documentaries or real-life scenes from television and include real-life people and not actors. The prominent emotion of the new clips was validated in a small sample of graduate students (N = 10). Participants watched two films at each time point (before/after placebo/oxytocin). The clips displayed short stories (123–179 s) with the prominent emotion of happiness, sadness, or anger. We used a simplified version of the Empathy Continuum scoring system to assess empathic responses that combined the similar and same emotional responses (Strayer and Rossberg-Gempton, 1992). Participants were asked “What did [protagonist's name] feel in the film and why?” and then “What did you feel while watching the film and why?” This system jointly assesses cognitive and affective empathy taking into account the intensity and emotional attributions in response to the clips. This scoring system has been used in several studies to code for empathic responding (e.g., De Wied et al., 2005, 2012). The score ranged between 0 (wrong identification of protagonist's emotion and neutral emotional response) to 14 (correct identification of protagonist's emotion, experience of the same/similar emotion to the same intensity, and emotional attribution that indicates explicit role taking). The responses were coded by the first author with the help of two graduate students. The detailed description of the scoring system can be found in the supplementary material.

2.2.6. Emotion recognition

Emotion recognition was assessed with the Dynamic Affect Recognition and Evaluation v2.3 (DARE; Porges et al., 2007, 2016), which includes video sequences of facial expressions that slowly progress from neutral to emotional expressions (happiness, sadness, anger, fear, disgust, surprise). The DARE stimuli are derived from the Cohn-Kanade Action Unit-Coded Facial Expression Database (Cohn et al., 1999; Kanade et al., 2000) and they are considered a more naturalistic and ecologically valid measurement of emotion recognition. The participants are asked to determine the emotion of each stimulus as fast as possible. The correct answers (accuracy) and reaction time (latency) were calculated as indicators of emotion recognition. The task includes six practice videos and 42 trial videos. The length of the videos varied from 15 to 31 s. Latency was calculated only for the accurate responses as a percentage score of the reaction time divided by the total length of each video. The trial videos were divided into 4 sets of 10 or 11 videos to be used before/after placebo/oxytocin. All trial sets contained at least one video for every emotion and the videos were randomly divided into the four trial sets.

2.2.7. Oxytocin administration

Participants self-administered intranasally a single dose of 24 IU of oxytocin (Syntocinon; Sigma Tau Pharmaceuticals) or placebo (sodium

chloride) in accordance with the guidelines by Guastella et al. (2013). The bottles were identical to ensure double-blinding. The dose of 24 IU is the most frequently used dose in previous experimental studies (MacDonald et al., 2011) and OT-IN has no adverse side effects when delivered in doses 18–40 IU in research settings (MacDonald et al., 2011). The experimental tasks were performed before and 30 min after administration as OT-IN induces changes in resting regional cerebral flow 25–78 min after administration (Paloyelis et al., 2014).

2.2.8. Mood state

Mood state before and after oxytocin/placebo administration was measured with the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) to check for mood effects. PANAS includes 20 items that assess positive and negative affect on a 5-point scale (*1 = very slightly or not at all*, *5 = extremely*). In this study, the Cronbach's alpha was 0.86 for positive affect and 0.90 for negative affect.

2.2.9. Intelligence

Typical level of intelligence had been measured previously at the institutions and we only approached adolescents with typical level of intelligence who lived in separate groups from those with low intelligence. Typical level of intelligence was confirmed with the short version of the Raven Progressive Matrices (RPM; Bilker et al., 2012). RPM is a test of nonverbal visual-spatial processing, inductive reasoning, relational reasoning, and problem solving. Raven is a widely used, reliable, easy to administer, and time efficient measurement of general intelligence (Carpenter et al., 1990). The abbreviated version includes 9 items and predicts the total score of the initial 60 items with good accuracy and saves a significant amount of time (Bilker et al., 2012).

2.3. Procedure

The study had a randomized, double-blind, placebo-controlled, within-subjects, sequential design with three sessions (approximately 75 min each). Written informed consent was obtained from all the participants. Additional parental written informed consent was obtained for participants below the age of 16 according to the Dutch law. During the first session (screening), the MINI-KID, ICU, CTQ, and ADES were administered. Typical level of intelligence was confirmed with the short version of the RPM and exclusion criteria were assessed with relevant questions (e.g., history of nasal disease/surgery). Participants were instructed to abstain from caffeine and nicotine 2 h prior to the next sessions. During the second session, participants completed the mood questionnaire, performed the experimental tasks on empathy and emotion recognition, and then self-administered oxytocin or placebo. The order of the substance allocation was randomized with block randomization (blocks of 10). The order of the films and videos at each condition was randomized with computer randomization. The clinical research coordinator generated the randomization codes and directly communicated to the experimenters the group to which the participant was assigned at each session and the order of the stimuli. Only the clinical research coordinator had access to the assignment schedule to ensure allocation concealment. Thirty minutes later, the participants repeated the experimental tasks with different stimuli. Upon completion of the tasks, the participants completed again the mood questionnaire and were asked which condition they thought they were allocated to. Similarly, the experimenters also reported which condition they thought the participant was allocated to. In the third session (one week later), participants underwent the same procedure but the other substance was administered. Participants received financial compensation for their participation. The study was granted medical ethical approval by the Central Committee on Research Involving Human Subjects and the Dutch Ministry of Health. The study has been registered to the EU Clinical Trials Registry (EudraCT: 2016-000367-16).

2.4. Analytic strategy

Mixed effects models were performed using R (R Core Team, 2017). Latency scores ($n = 3746$) were examined to ensure validity of responses and reaction time below 2 s ($n = 29$) or > 2 s after the end of the video ($n = 28$) were excluded as invalid. The random effects of participants, films/videos, and emotion were also included. Random effects of time and condition were examined, but not included, as they did not significantly improve the models. CU traits, trauma, and dissociation were centered and added as moderators and age was centered and added as a control variable. Optimizers with increased number of iterations were applied, when necessary, to achieve convergence of the models. Due to the high number of score 1 in empathy (60.3%), a log distribution was better fitted to the data and generalized mixed models were performed. Standardized values above 3 were treated as outliers and the analyses were rerun without them. The results remained similar and we thus reported the results including the outliers. We also examined whether the results changed when the participants who dropped out after the first experimental session were excluded. The results remained the same and we thus reported the results including these participants. Secondary analyses examined the two-way interaction on emotion recognition separately for fear. R^2 was used as an index of effect size with the method proposed by Nakagawa and Schielzeth (2013). Finally, we examined whether the order of substance administration affected the findings as previous studies have found carry-over effects in repeated measurements (e.g., Wallen and Rupp, 2010). We added a variable indicating which substance was administered in the first session in the models and examined the potential moderating effects.

3. Results

3.1. Manipulation checks

Table 1 presents the descriptive statistics of all the variables. Manipulation checks showed no significant differences at baseline for empathy, $t(83) = -0.98$, $p = .33$, accuracy, $t(83) = 0.05$, $p = .96$, or latency, $t(69) = -1.29$, $p = .20$. Mood state did not differ significantly at baseline for positive, $t(85) = 0.09$, $p = .93$, or negative affect, $t(85) = 0.47$, $p = .64$. The condition allocation was presumed correctly at 52.3% of both sessions by the participants and at 39.8% by the experimenters. Table 2 presents the side effects reported after administration. Oxytocin administration did not increase positive affect, $F(84) = 0.03$, $p = .87$, but it decreased negative effect, $F(84) = 5.35$, $p = .02$, compared to placebo.

3.2. Empathy

Generalized mixed models revealed a trend of significance for the Time x Condition interaction, $b = -0.15$, $SE = 0.09$, $t(693) = -1.70$, $p = .09$. When CU traits were added, the Time x Condition interaction was significant, $b = -0.20$, $SE = 0.09$, $t(689) = -2.28$, $p = .02$. Additionally, a three-way CU traits x Time x Condition interaction was observed, $b = -0.02$, $SE = 0.01$, $t(689) = -2.54$, $p = .01$, and the full model explained 16% of the variance, $R^2 = 0.16$. A simple slope analysis was performed using values corresponding to +1 *SD* above the mean and − 1 *SD* below the mean of CU traits. The slope in oxytocin condition and high CU traits was significant, $b = 0.27$, $p = .006$, demonstrating that subjects with high CU traits showed increased empathy after oxytocin administration (Fig. 1). Trauma and dissociation were added in the model and the 3-way interaction remained significant, $b = -0.02$, $SE = 0.01$, $t(687) = -2.54$, $p = .01$. Separate models showed no significant Trauma x Time x Condition interaction, $b = 0.01$, $SE = 0$, $t(689) = 1.58$, $p = .11$, or Dissociation x Time x Condition interaction, $b = 0.04$, $SE = 0.06$, $t(689) = 0.68$, $p = .50$.

Table 1
Descriptive statistics before and after oxytocin and placebo administration.

	Total	Placebo		Oxytocin	
	M(SD)	Before	After	Before	After
Age	16.50 (0.93)				
CU traits	29.33 (10.28)				
Trauma	46.50 (18.62)				
Dissociation	1.95 (1.63)				
RAVEN score	5.95 (1.40)				
Empathy (*M*, *SD*)		2.60 (2.97)	2.47 (2.65)	2.33 (2.59)	2.78 (2.97)
Emotion Recognition:					
Accuracy (*% of* correct responses)					
Total		73.80	74.44	73.40	75.45
Fear		46.88	41.18	39.29	50.67
Latency (*M*, *SD*)					
Total		47.12(18.20)	43.66(17.27)	45.14(16.56)	44.28(17.20)
Fear		56.09(15.05)	56.17(15.93)	51.93(12.96)	53.99(17.53)

Table 2
Side effects after oxytocin/placebo administration.

	Oxytocin (*n*)	Placebo (*n*)
Better mood	9	5
Sleepiness	1	1
Feeling energetic	2	0
Light-headedness/headache	5	7
Difficulty to concentrate	1	1
Tiredness	2	1
Nausea	1	2
Dry/irritated nose	1	3
Irritated eyes	0	1
Feeling warm	0	2

3.3. Emotion recognition

3.3.1. Accuracy

There was no significant Time x Condition interaction on accuracy, $b = -0.10$, $SE = 0.17$, $z = -0.57$, $p = .57$. There was also no moderating effects of CU traits, $b = 0.01$, $SE = 0.02$, $z = 0.69$, $p = .49$, trauma, $b = 0$, $SE = 0.01$, $z = 0.24$, $p = .81$, or dissociation, $b = 0.12$, $SE = 0.11$, $z = 1.06$, $p = .29$. Examining fear separately, a significant Time x Condition interaction was observed, $b = -0.78$, $SE = 0.37$, $z = -2.09$, $p = .04$, indicating that subjects recognized fear more accurately after oxytocin administration compared to placebo (Fig. 2). This model explained 22% of the variance, $R^2 = 0.22$. A simple slope analysis showed that fear accuracy was marginally significantly improved after oxytocin, $b = 0.50$, $p = .06$, but not after placebo, $b = -0.28$, $p = .28$. When CU traits, trauma, and dissociation were included in this model, the Time x Condition interaction remained significant, $b = -0.75$, $SE = 0.36$, $z = -2.09$, $p = .04$.

3.3.2. Latency

There was a significant Time x Condition interaction for latency toward the opposite direction, $b = -2.44$, $SE = 0.98$, $t(2278.61) = -2.49$, $p = .01$, suggesting that participants responded faster after both placebo and oxytocin, but the difference from pre-administration was higher in the placebo condition. There was no moderating effect of CU traits, $b = 0.12$, $SE = 0.10$, $t(2281.31) = 1.23$, $p = .22$, trauma, $b = 0.04$, $SE = 0.05$, $t(2275.01) = 0.83$, $p = .41$, or dissociation, $b = 0.68$, $SE = 0.58$, $t(2274.95) = 1.19$, $p = .24$, on latency. Examining fear separately, we found no significant Time x Condition interaction, $b = -0.78$, $SE = 0.74$, $t(181.65) = -1.05$, $p = .30$.

3.4. Carry-over effects

As a last step, we examined whether the order of substance influenced the results. The "order" variable was included in the interactions for empathy, overall accuracy, overall latency, accuracy of fear, latency of fear, and with all the moderators. The 3-way and 4-way interactions were not significant in all the analyses ($ps > 0.05$), indicating that the order of substance at the first experimental session did not have any carry-over effects on the participants' responses in the second experimental session. A detailed report of these analyses can be found in the supplementary material.

The flowchart and the CONSORT checklist are provided as supplemental material.

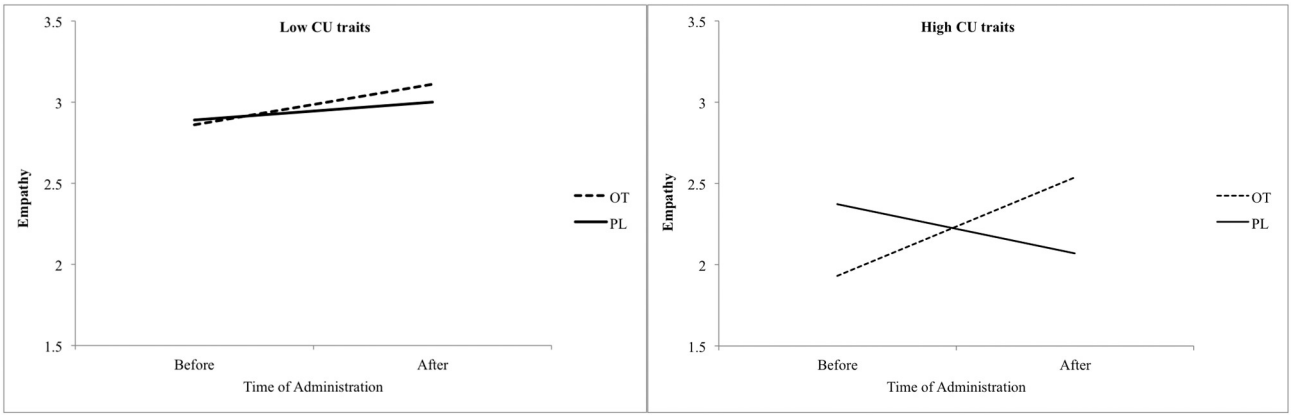

Fig. 1. The 3-way interaction on empathy before and after oxytocin (OT) and placebo (PL) administration for high and low callous-unemotional (CU) traits (median split).

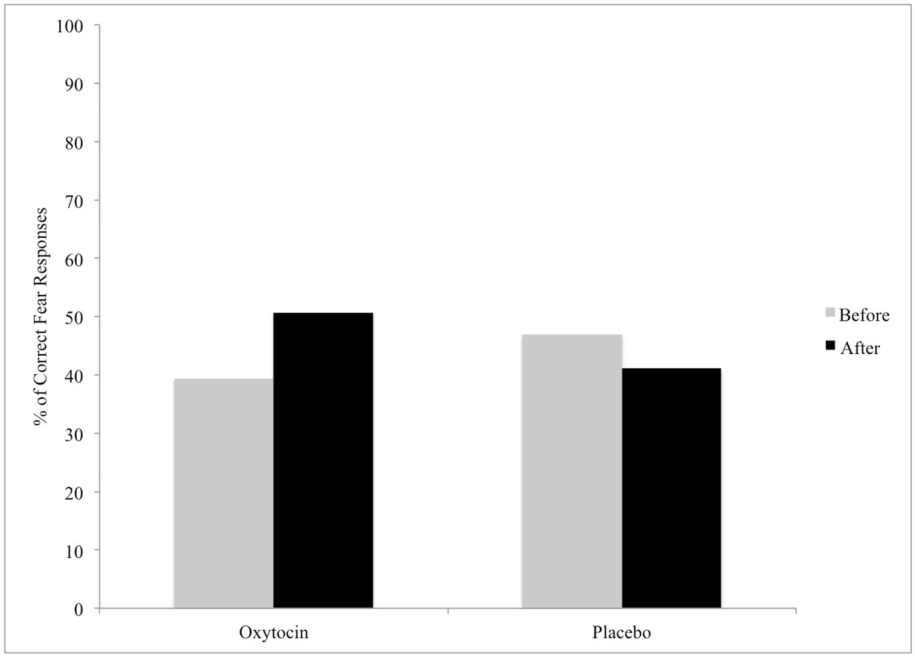

Fig. 2. The 2-way interaction on percentage of correct fear responses before and after oxytocin and placebo administration.

4. Discussion

The present study investigated the effect of OT-IN on empathy and emotion recognition in residential youth and the moderating effect of CU traits, trauma, and dissociation. We found that empathy improved after OT-IN compared to placebo especially in adolescents with high CU traits. Additionally, overall emotion recognition did not improve after OT-IN, but there was a positive effect on accuracy of fear recognition.

These findings are in line with previous research on the effects of OT-IN on social-affective behaviors and especially in individuals with social-affective deficits (Bartz et al., 2010, 2015, 2019; Domes et al., 2014; Feeser et al., 2015). We observed a positive effect of OT-IN on empathy for subjects with high CU traits, who have severe deficits in empathic responding and are at high risk for developing psychopathy in adulthood (Frick and White, 2008). Psychopathy is linked to several brain abnormalities and a model of psychopathy has incorporated the role of oxytocin in differential amygdala activation (Moul et al., 2012). According to this model, central amygdala is overactivated, whereas basolateral amygdala is underactivated in psychopathy and oxytocin modulates amygdala activation due to its inhibitory effect on the medial central amygdala. This inhibitory effect may be reduced when the levels of central oxytocin are low, leading to higher activity of central amygdala and contributing to the development of psychopathy. Future research is urged to examine whether OT-IN alters amygdala activity in response to empathy-evoking stimuli in youth with high CU traits to further contribute to this model. Moreover, our findings are in accordance with the social adaptation model, which suggests that OT-IN targets specific deficits (Ma et al., 2016). OT-IN increased empathy in subjects with high CU traits, possibly by regulating social-affective processes that can contribute to better empathic responding.

The second interesting finding was the improvement of fear recognition after OT-IN. This is in line with meta-analytic evidence on the positive effect of OT-IN on fear recognition specifically (Leppanen et al., 2017). Antisocial adolescents exhibit deficits in fear recognition (Marsh et al., 2005), which was also confirmed in our sample as fear recognition had the lowest accuracy at baseline. In specific, before oxytocin 39% of the stimuli depicting fear were correctly recognized, whereas after oxytocin the percentage of correct responses rose up to 50%, indicating a clinically meaningful change that is also comparable to improvement after emotion recognition training (Hubble et al., 2015). Our findings were also in accordance with the study by Timmermann et al. (2017) in adults with antisocial personality disorder who also showed improvement in fear recognition after oxytocin administration. This further corroborates that OT-IN might be beneficial for targeting specific deficits rather than an overall positive effect. Fear recognition is highly relevant in antisocial behavior, as distress cues, and especially fear, elicit empathy and inhibit aggression (Marsh and Blair, 2008), emphasizing the importance of targeting the recognition and understanding of fear in treatment.

A surprising opposite interaction on latency was found, indicating that participants responded faster after placebo compared to oxytocin. However, baseline differences at latency might have driven this effect, as latency was higher before placebo ($M = 47.12$) than before oxytocin ($M = 45.14$), whereas after administration latency scores were very close (placebo: $M = 43.66$; oxytocin: $M = 44.28$). These effects should thus be interpreted with caution, as statistical significance in this case is not clinically meaningful.

Finally, trauma and dissociation did not moderate the oxytocin effect. Previous evidence found that trauma attenuated the effect of OT-IN possibly due to its effect on the oxytocin system (Veenema, 2012). However, previous studies included adults and different types and levels of trauma (e.g., Ebert et al., 2013) that may not be comparable to our sample that reported low to moderate levels of trauma. Dissociative symptoms were also low in our sample. There is no previous evidence on the potential moderating role of dissociation and our findings suggest that low levels of dissociation did not attenuate the oxytocin effect. Given the high prevalence of trauma and dissociation in antisocial youth, it is critical to know that these factors do not seem to attenuate the effects of OT-IN on empathy and fear recognition in our sample. Therefore, OT-IN can be beneficial to this population, although further research with higher levels of trauma and dissociation is required to draw solid conclusions.

Several limitations of this study should be acknowledged. First, our sample included adolescents with antisocial behavior but high rates of comorbidity were also observed. Consequently, the effects of OT-IN cannot be perceived as specific effects on antisocial youth, but rather as distinct effects on specific social-affective deficits in this population. An important aspect of residential youth and juvenile delinquents that was

not included in this study was the role of intelligence. Lower levels of intelligence have been found in juvenile delinquents (e.g., Haysom et al., 2014) and could potentially influence the oxytocin effect. We recruited adolescents with typical level of intelligence in order to ensure that the tasks and questionnaires were understandable and simple for them. It is thus crucial to emphasize that these results cannot be generalized to residential youth with lower levels of intelligence. Second, our study was limited to males and thus no conclusions or generalization to females can be applied. Third, we used a limited number of video clips to measure empathy. This decision was made to limit the time of the sessions and not overwhelm the participants. Given that empathic responses can be evoked under various different circumstances, future studies are encouraged to include a higher number of diverse stimuli. Relatedly, we combined cognitive and affective empathy as the majority of the participants could identify correctly the emotion of the protagonist in the film and understand the situation that evoked each particular emotional response. There was thus not enough variability to examine cognitive and affective empathy separately. Fourth, we focused on overall emotion recognition and fear recognition but our findings do not provide information on whether oxytocin improved fear recognition because it was the most difficult emotion to recognize (the most errors at baseline) or because oxytocin influences specific fear recognition via its proposed effects on amygdala. In this sample, the other emotions had higher accuracy at baseline; for happiness > 90% of the responses were correct, for anger, sadness, and surprise around 70–85% of the responses were correct, and for disgust around 60% of the responses were correct. Thus, some ceiling effects could have driven the non-significant finding on overall emotion recognition. We checked the effect of oxytocin on accuracy of disgust and we found that oxytocin did not have a significant effect ($b = 0.01$, $p = .98$). It would be interesting to examine the oxytocin effect in subjects with more pronounced deficits in recognition of several emotions to determine the specificity of the effect. Lastly, we focused on CU traits, trauma, and dissociation, but there are several other individual characteristics that might moderate the effect of OT-IN and warrant future investigation. In particular, comorbidity was highly prevalent in this sample, but we decided not to focus on comorbidity as it was outside of the scope of the current study. As mentioned in the introduction, there is evidence on positive effects of oxytocin administration on several psychiatric disorders and the investigation of potential effects on comorbid disorders is the next step in this line of research. For instance, evidence from a recent animal study supported that oxytocin administration could block the increased motivation for alcohol drinking via effects on GABA transmission (Tunstall et al., 2019) and a randomized trial in heroin-dependent males found that oxytocin reduced craving and withdrawal symptoms (Moeini et al., 2019). Relatedly, oxytocin administration reduced amygdala hyperactivity to fearful faces in patients with generalized social anxiety disorder (Labuschagne et al., 2010). It would be beneficial for future research to further explore the oxytocin effect in individuals with comorbid psychopathology and other social-affective deficits, such as emotion dysregulation, fearlessness, or anger to elucidate which behaviors are susceptible to the oxytocin effect in residential youth.

The current study revealed a positive effect on social-affective behaviors in residential youth, suggesting that this line of research might be a promising approach. Previous evidence on the oxytocin effect on antisocial behavior have been mixed (Alcorn et al., 2015a; Berends et al., 2019; DeWall et al., 2014; Ne'eman et al., 2016) and one study showed that oxytocin could even increase aggression in negative contexts (Ne'eman et al., 2016). These conflicting findings as well as the manifestation of antisocial behavior in diverse contexts suggest that oxytocin should be administered with caution when trying to reduce aggression and the personal and contextual characteristics should be taken into consideration in the study design. On the other hand, targeting social-affective behaviors that are impaired in antisocial individuals seems a safer and more promising line of research, as it might improve social skills that can further promote successful social interactions and better treatment responses.

Crucially, these findings provide an insight into novel approaches for the treatment of residential youth and CU traits. It is well established that adolescents with high CU traits exhibit more severe antisocial behavior, have adverse long-term outcomes, and a poor treatment response (Frick et al., 2014). Based on our findings, OT-IN might be beneficial for improving empathy, which constitutes one of the treatment goals of current psychological interventions. We argue that it would be meaningful to test whether OT-IN is useful in addition to cognitive-behavioural training or empathy training for adolescents with high CU traits in order to improve their effectiveness. Moreover, emotion recognition trainings may benefit from combined OT-IN, which might boost their effectiveness in improving fear recognition. Therefore, we propose that a combination of OT-IN and existing psychological interventions warrants further investigation as it may lead to better treatment outcomes.

Conclusively, we provided evidence of a positive effect of OT-IN on empathy and fear recognition in residential youth. We found that OT-IN improved empathy in adolescents with high CU traits compared to placebo and also enhanced fear recognition in the total sample. Our study gave an insight into the beneficial effect of OT-IN on social-affective behaviors in residential youth and we suggest that OT-IN may be a useful addition to existing psychological interventions as a novel combined approach aiming at better treatment outcomes.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yhbeh.2019.104561.

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