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Dose-response effects of exogenous oxytocin on social cognition: A systematic review

Simon Barton [a,*], Annika Pruin [a,1], Janna Schulze [a,1], Maximilian Kiebs [a,b], Dirk Scheele [c,d], René Hurlemann [a]

[a] Department of Psychiatry & Psychotherapy, School of Medicine & Health Sciences, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany
[b] Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany
[c] Department of Social Neuroscience, Faculty of Medicine, Ruhr University Bochum, Bochum, Germany
[d] Research Center One Health Ruhr of the University Alliance Ruhr, Ruhr University Bochum, Bochum, Germany

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ABSTRACT

Oxytocin, a neuropeptide known for its role in social bonding, has garnered considerable attention for its potential to enhance social cognition in humans. Intranasal administration of oxytocin is the standard method in exogenous oxytocin research. This systematic review critically examines the effects of exogenously administered oxytocin on three core components of social cognition: emotion recognition, empathy, and interpersonal trust. By comparing findings across studies using intranasal oxytocin doses ranging from 1 IU to 48 IU in healthy adult humans, we evaluate evidence for a potential dose-response relationship. The majority of studies administered a standard dose of 24 IU and generally reported significant improvements in emotion recognition, empathy, and trust. However, divergent findings at this dose have also been observed. Evidence for both lower and higher doses remains mixed. Much of the support for the Inverted-U Curve hypothesis - suggesting that oxytocin's effects follow a nonlinear trajectory with optimal outcomes at moderate doses - comes from studies lacking direct dose comparisons. Furthermore, the effects of oxytocin on social cognition appear to be strongly moderated by individual and contextual factors, raising questions about the generalizability of the Inverted-U model. Additional research is necessary to clarify the conditions under which dose-dependent effects occur.

1. Introduction

Oxytocin is a neuropeptide produced primarily in the paraventricular and supraoptic nuclei of the hypothalamus. Although it is traditionally associated with physiological functions such as childbirth and lactation, there is a growing body of evidence highlighting its critical role in modulating social cognition and behavior, particularly in forming and maintaining social bonds (Carter, 2014). Centrally, oxytocin functions as a neuromodulator and influences brain networks involved in emotional salience, social memory, and affiliative behavior. When administered intranasally, oxytocin is believed to reach the brain via perineural and perivascular pathways, bypassing the blood-brain barrier (Quintana et al., 2021a; Striepens et al., 2013b). Neuroimaging studies have shown that exogenous oxytocin modulates activity in key regions of the "social brain," including the amygdala, ventromedial prefrontal cortex, and striatum—areas associated with emotion recognition, reward, empathy, and trust-related processes (Bethlehem et al., 2013; Striepens et al., 2013b). These central effects are thought to underlie oxytocin's ability to enhance these crucial aspects of social cognition.

Since early proof-of-concept studies (Kosfeld et al., 2005), oxytocin research has evolved toward investigating moderators (Bartz et al., 2011), neural mechanisms (Meyer-Lindenberg et al., 2011), and addressing replication challenges (Nave et al., 2015). Competing models - such as oxytocin as a social salience enhancer versus a social approach modulator (Shamay-Tsoory and Abu-Akel, 2016; Bartz et al., 2011) - highlight its complex role. Dose-response studies, especially on the Inverted-U hypothesis (Cardoso et al., 2013; Spengler et al., 2017), help clarify these mechanisms by linking dosage with neural and behavioral effects. Neuroimaging findings involving the amygdala and striatum (Bethlehem et al., 2013) provide insights but require further integration with behavior. To improve replicability and advance the field,

* Corresponding author.
E-mail address: simon.barton@uol.de (S. Barton).
[1] These authors contributed equally to this work.

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pre-registration, data sharing, and harmonized reporting are crucial (Nosek et al., 2015).

This systematic review focuses on the impact of administered oxytocin on the following social cognitive functions: Emotion recognition refers to the ability to accurately identify and interpret others' emotional expressions (Adolphs, 2002). Empathy involves understanding and sharing the emotional states of others (Decety and Jackson, 2004). Trust is the willingness to be vulnerable to another's actions based on expectations of their behavior (Kosfeld et al., 2005). These three areas were selected for investigation due to their central role in interpersonal interaction and the substantial empirical evidence indicating that oxytocin modulates these processes. Oxytocin has been shown to enhance the recognition of emotional expressions, particularly from subtle facial cues such as the eye region (Domes et al., 2007; Shahrestani et al., 2013a). It has also been associated with increased emotional sensitivity and empathic responding (Hurlemann et al., 2010). Regarding trust, studies indicate that oxytocin promotes greater interpersonal trust and cooperative behavior, as seen in improved social decision-making and increased willingness to engage in trusting interactions (Baumgartner et al., 2008). The three constructs of emotion recognition, empathy and trust thus represent central facets of social cognition that are closely linked, both theoretically and empirically, to the function of the oxytocinergic system.

Intranasal administration of oxytocin (IN-OT) is the standard method in exogenous human oxytocin research, primarily due to its relative ease, logistic benefits, non-invasiveness, and presumed ability to bypass the blood-brain barrier and exert effects on the central nervous system relatively quickly (Born et al., 2002). However, this route remains controversial, and the mechanisms by which oxytocin may reach central targets are not fully understood (Churchland and Winkielman, 2012; Leng and Ludwig, 2016). The extent to which intranasally administered oxytocin reaches the human brain remains uncertain. While intranasal delivery is widely used to bypass the blood-brain barrier, direct evidence of central uptake in humans is limited. Current methods do not allow precise quantification of how much oxytocin reaches central targets, and estimates vary depending on delivery technique, dose, and timing (Quintana et al., 2021b; Martins et al., 2020b). As such, it is unclear whether observed behavioral or neural effects are due to direct central action, peripheral mechanisms, or indirect pathways. This uncertainty should be considered when interpreting dose-dependent effects.

Understanding dose-response relationships is essential to interpreting the effects of exogenously administered oxytocin on social cognition. This knowledge helps identify the minimum effective dose, avoiding under- or overdosing, which could lead to inconsistent or adverse outcomes. Furthermore, clarifying these relationships informs personalized treatment approaches and improves the reliability and reproducibility of research findings. Although many studies have explored the influence of oxytocin on social cognition, relatively few have systematically examined how dosage and administration parameters modulate these outcomes. The 24 IU intranasal dose is used as the standard (potentially moderate) dose in human oxytocin research, largely due to its early use in influential studies (e.g., Kosfeld et al., 2005), and has since been widely adopted as the default in experimental research on social cognition. Differential dosages may yield different behavioral and neural effects. This review aims to provide a comprehensive overview of experimental studies investigating the impact of administered oxytocin on the high-level social cognitive processes of emotion recognition, empathy, and trust. Specifically, the review focuses on how oxytocin dosage influences specific components of social cognition and intends to answer the research question of whether social-cognitive responses to oxytocin follow the *Inverted U-Curve Hypothesis*. This hypothesis posits that oxytocin's effects on social cognition may follow a non-linear trajectory, where moderate doses produce optimal effects, but both lower and higher doses may be less effective or even counterproductive (Cardoso et al., 2013; Heinrichs et al., 2009). The review evaluates whether this hypothesis is supported by consistent evidence.

A clearer understanding of oxytocin's dose-response relationship is crucial for translating experimental findings into clinical applications, such as the treatment of affective dysregulation, social anxiety or loneliness. By focusing explicitly on dose-dependent effects across different domains of social cognition and including both behavioral and neural outcomes, the present review addresses a key gap left by previous broader syntheses (e.g., Ellenbogen, 2017; Barchi-Ferreira and Osório, 2021). This targeted approach contributes to resolving inconsistencies in the literature and sheds light on potential sources of heterogeneity, including contextual and individual moderators. These insights are essential for guiding future trials, improving the design of social neuroscience studies, and advancing toward more personalized, mechanism-based interventions. Such inverted U-shaped dose-response relationships are common in neuropharmacology and reflect the complex modulation of neural systems, where both insufficient and excessive stimulation can impair function.

2. Methods

2.1. Review design

This systematic review was designed to comprehensively evaluate the existing literature on the effects of oxytocin on social cognition. It followed a predefined protocol outlining the objectives, methodology and inclusion/exclusion criteria, adhering to best practices in systematic reviewing. Conducted using a systematic approach, this review examines the dose-response effects of oxytocin on social cognition, with a specific focus on empathy, trust, and emotion recognition. The review was conducted in accordance with the PRISMA 2020 guidelines (Page et al., 2021). A structured protocol was developed to define the scope, inclusion criteria, data extraction process and synthesis methods. The review aimed to provide a comprehensive overview of the dose-response effects of oxytocin on these areas of social cognition in healthy adult populations.

2.2. Information sources and search strategy

A systematic literature search of the PubMed (accessed via Ovid) and Web of Science databases was performed for articles published between 01/01/2005 and 31/03/2025. The following search string was used: ("oxytocin" AND "social cognition" OR "emotion recognition" OR "empathy" OR "trust" OR "theory of mind"). In addition, the reference lists of the included articles and relevant systematic reviews / meta-analyses were manually searched for potentially eligible studies.

2.3. Eligibility criteria

Eligible studies were randomized controlled trials (RCTs) examining the effects of exogenously administered oxytocin on social cognition in humans, with a focus on emotion recognition, empathy, and trust. The inclusion criteria required participants to be healthy adults aged 18–65. This age range was chosen to reduce developmental and age-related variability in oxytocin responsiveness. The outcome focused on effects on social behavior. There were no restrictions to the type of outcome measures except that the tests are standardized and psychometrically validated. Studies had to be original research and published in English in peer-reviewed journals between January 2000 and March 2025. To organize the exclusion process systematically, we applied a cascade of exclusion criteria based on relevance and methodological rigor. The primary criterion was publication type; we excluded secondary literature such as reviews, meta-analyses, and commentaries. We also excluded descriptive or conceptual articles that did not present original experimental data. Next, we excluded studies involving non-target populations, including clinical populations, pregnant women, and participants outside the defined age range, as well as all animal studies. In the third step, we removed studies with unsuitable designs - specifically,

lack of a control group, those focusing on substances other than oxytocin (e.g., LSD or MDMA), exploring genetic mechanisms of oxytocin (e.g., oxytocin receptor gene), analyzing only baseline oxytocin levels, or focusing solely on the neurological or neurophysiological effects of oxytocin without addressing social cognition outcomes. Finally, we excluded studies with a misaligned study focus - such as those investigating forms of social cognition not directly relevant to our research question.

2.4. Selection and data collection process

Two independent reviewers (AP and JS) screened the titles and abstracts of the identified studies using the Rayyan automation platform (Ouzzani et al., 2016). Studies that appeared to meet the inclusion criteria were retrieved for a full-text review. Any discrepancies between the reviewers were resolved through discussion or by consulting a third reviewer (SB). Both independent reviewers extracted the data using a standardized data extraction form. Any disagreements were resolved by consensus. Fig. 1 displays the selection process for this review. The following information was recorded for data collection: study design and methodology (e.g. sample size, population characteristics, research design); intervention (e.g. oxytocin administration method, dosage, timing); outcome measures (e.g. psychometric tools used); and key findings and conclusions.

2.5. Synthesis methods and assessments

The influence of oxytocin on emotion recognition, empathy and trust were assessed. Common outcome measures included behavioral, self-reported and neuroimaging-based measures. This systematic review synthesizes the findings in accordance with the PRISMA guidelines. The synthesis approach included quantitative and, where applicable, qualitative methods. A narrative qualitative synthesis was conducted to summarize and integrate the findings of the included studies. The results were categorized based on empathy, trust and emotion recognition. Findings based on oxytocin administration methods were systematically compared. Contradictory findings were discussed in relation to study quality, methodological differences and potential moderators, such as sex, individual differences and social context. The findings were summarized in structured tables reporting the key characteristics of the studies, the outcome measures, and the main results.

The risk of bias for each study was assessed using the Cochrane Risk of Bias (RoB) tool categorized as "low", "some concerns" or "high". To evaluate the reliability and applicability of the evidence to the research question, we employed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2008). With regard to study design, all of the included studies were randomized controlled trials (RCTs), which increases confidence in the findings.

3. Results

3.1. Emotion recognition

Thirty studies investigating the effect of exogenous oxytocin on emotion recognition met the eligibility criteria. Studies in this domain primarily used facial expression recognition tasks, such as the Ekman or Karolinska face sets, where participants identify basic emotions from static or dynamic facial stimuli. Oxytocin was always administered intranasally, except in the study of Quintana et al. (2015), which used IN-OT as well as a very low dose of intravenously administered oxytocin (IV-OT). Seventeen of the studies comprised exclusively male participants, ten comprised mixed samples, and three comprised exclusively female participants. Twenty-four studies administered the standard dose of 24 IU. Only two studies applied a different dose (16 IU and 40 IU, respectively) and four studies compared multiple doses (ranging from 6 IU to 48 IU). The methodological quality was rated as moderate (RoB) due to lack of variability in dosage, route of administration and gender of participants. Table 1 summarizes the main results regarding the impact of exogenous oxytocin on emotion recognition. The recognition tasks examined across studies are heterogeneous in emotional valence and design, which should be considered when reviewing the results.

3.1.1. Emotion recognition studies comparing different doses

Several studies have directly compared multiple IN-OT doses on emotion recognition, but the findings are inconsistent regarding the presence of an Inverted U-shaped dose-response relationship. Lieberz et al. (2020) compared 6 IU, 12 IU, 24 IU, and placebo using an Emotional Face Recognition Task combined with fMRI. They found no effects on recognition accuracy or reaction times (RTs). However, right putamen activation to low-intensity happy faces increased significantly at the higher doses (12 IU and 24 IU) in women ($d = 0.16$). Quintana et al. (2015) compared 8 IU and 24 IU IN-OT (via breath-powered device), 1 IU IV-OT, and placebo. Only the 8 IU dose significantly decreased anger ratings in ambiguous facial expressions ($d = 1.76$), while 24 IU and 1 IU showed no effect. Spengler et al. (2017) tested doses of 12 IU, 24 IU, and 48 IU at various time intervals (15–40 min, 45–70 min or 75–100 min) before exposure to emotional facial expressions. Their results indicated that only 24 IU administered 45–70 min prior significantly increased recognition of ambiguous faces as neutral ($d = 0.59$) and decreased amygdala activity to fearful faces ($d = 0.80$). Shin et al. (2018) compared 32 IU and 40 IU IN-OT doses to placebo and found that only the 40 IU dose significantly affected the recognition of happy faces ($\eta^2 = 0.64$). Overall, these studies show no consistent dose-response pattern, with significant effects occurring at lower (8 IU), standard (24 IU), and higher (40 IU) doses, thus contradicting a simple Inverted-U hypothesis.

3.1.2. Emotion recognition studies applying a non-standard dose

Two studies examined the effects of single non-standard IN-OT doses. Voorthuis et al. (2014) compared 16 IU IN-OT with placebo during recognition of infants' facial expressions, reporting increased activation in brain areas including the inferior frontal gyrus and superior temporal gyrus ($d = 0.41$), but a decrease in recognition accuracy ($d = 0.29$). Maier et al. (2019) administered 40 IU IN-OT versus placebo and observed a significant reduction in the impact of stress odors on ambiguous fearful face recognition in women ($d = 0.29$). They also found significantly decreased stress-associated neural activity in the right amygdala across both genders, with sex-specific reductions in the anterior cingulate cortex and hippocampal activation ($d = 0.41$). These findings highlight that both lower and larger doses than the standard 24 IU can produce meaningful behavioral and neural effects, though effects may vary depending on sex and context.

3.1.3. Emotion recognition studies applying a standard dose

Studies using the standard 24 IU IN-OT present a mixed picture. Six studies (Dam et al., 2019; Daughters et al., 2022; Domes et al., 2013; Guastella et al., 2009; Hubble et al., 2017a; Kis et al., 2013) reported no significant effects on the recognition accuracy of emotional facial expressions. One study (Macchia et al., 2022) found a negative effect of IN-OT on recognition accuracy. Conversely, eighteen studies reported selective significant effects, with some showing increased recognition of negative emotions such as fear or disgust (Feeser et al., 2014; Fischer-Shofty et al., 2010; Lischke, 2012; Perry et al., 2013), and others reporting enhanced recognition of positive emotions (Marsh et al., 2010; Schulze et al., 2011). Some studies reported general improvements in emotion recognition accuracy, regardless of valence, including from faces (Daughters et al., 2021; Schwaiger et al., 2019) or body language (Bernaerts et al., 2016). Evidence regarding effects on eye gaze and RTs was inconsistent (e.g., Domes et al., 2013; Fischer-Shofty et al., 2010; Lischke et al., 2012; Wang et al., 2020).

Notably, several studies identified subgroup-specific effects. Yue et al. (2018) found significantly increased recognition accuracy for

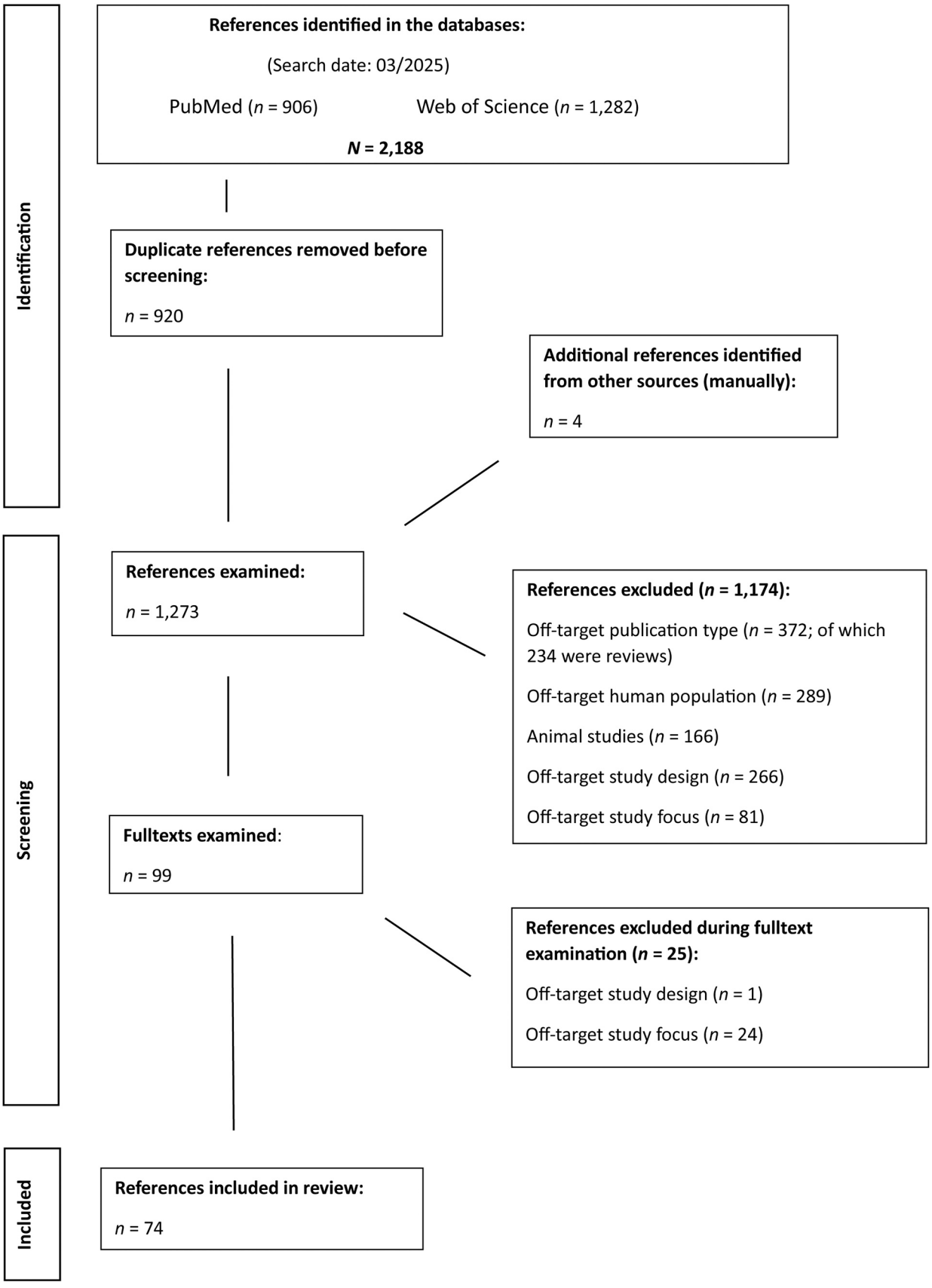

Fig. 1. PRISMA flowchart.

Table 1
Studies examining the influence of exogenous oxytocin on emotion recognition.

Reference	Objective	Sample	Method	OT effects	Moderators
Guastella et al. (2009)	Whether IN-OT affects early perceptual detection of emotional facial expressions	$n = 104$ (71 M/ 33 F; age range: 18–25, $\bar{x} = 19.14$)	IN-OT (24 IU) or PLC. Timing: 45 min Visual search task to detect angry or happy faces among neutral distractors. Accuracy, RTs, eye-tracking	No sig. effect on accuracy, RTs or eye gaze toward emotional faces	Gender: no sig. effect
Fischer-Shofty et al. (2010)	Whether IN-OT enhances recognition of fear in facial expressions	$n = 27$ (M; age: $\bar{x} = 26.93$)	IN-OT (24 IU) and PLC in separate sessions. Timing: 45 min Dynamic facial expression task.	↑ recognition accuracy only for fearful expressions ($p < .05$). No sig. effect on RTs.	Mood: no sig. effect
Marsh et al. (2010)	Whether IN-OT enhances recognition of positive facial affect	$n = 50$ (29 M/ 21 F; age: $\bar{x} =$ 26.41, age range 20–40)	IN-OT (24 IU) or PLC. Timing: 35 min Identification of various emotional facial expressions at different intensities.	↑ recognition accuracy for positive expressions ($p < .10$), esp. subtle ones ($p < .05$). No sig. effect on recognition of negative emotions or RTs	Gender: no sig. effect
Schulze et al. (2011)	Whether IN-OT enhances recognition of briefly presented masked emotional faces	$n = 56$ (M; age: $\bar{x} = 24.18$)	IN-OT (24 IU) or PLC in separate sessions. Timing: 45 min Facial expressions briefly presented and masked to prevent conscious recognition. Identifying emotion of masked faces.	↑ recognition of masked emotional faces ($p = .007$, $\eta^2_p = .128$), esp. happy faces ($p = .005$, $\eta^2_p = .134$)	
Lischke et al. (2012)	Whether IN-OT enhances emotion recognition from dynamic facial expressions	$n = 47$ (M; age: $\bar{x} = 26.09$)	IN-OT (24 IU) or PLC. Timing: 45 min Dynamic facial emotion recognition task	↑ recognition of emotional expressions at lower intensities ($p = .03$, $f = 0.32$), specifically angry ($p < .01$) and fearful ($p = .05$). ↑ recognition accuracy for fearful expressions ($p = .02$). No sig. effect on eye-gaze	Mood: no sig. effect
Domes et al. (2013)	Whether IN-OT selectively affects eye gaze toward happy and angry expressions	$n = 62$ (M; age: $\bar{x} = 24.0$)	IN-OT (24 IU) or PLC. Timing: 40 min Video sequences of faces transitioning from neutral to either happy or angry expression	No sig. effect on emotion recognition accuracy. ↑ eye gaze towards happy faces ($p = .070$), ↓ eye gaze towards angry faces ($p = .23$). ↑ RTs to happy faces ($p = .013$)	
Kis et al. (2013)	Whether IN-OT and short-term social interaction similarly influence recognition of negative facial expressions	$n = 52$ (M; age range: 18–30, $\bar{x} =$ 23.03)	IN-OT (24 IU), PLC, social interaction (Soc) or no social interaction (NSoc). Timing: 40 min break Learning: Images of faces varied in valence, subjects rated emotion. Testing: Ratings of neutral faces (some previously emotional)	No sig. effect on recognition accuracy. For ratings of negative expressions, ↑ perceived emotion ($p = .011$)	
Leknes et al. (2013)	Whether IN-OT modulates pupil dilation and sensitivity to subtle emotional facial expressions	$n = 39$ (19 M/ 20 F; age range: 20–39, $\bar{x} = 26$)	IN-OT (24 IU) or PLC. Timing: 40 min break Morphed emotional faces, blending neutral with happy, fearful, or angry expressions (low intensity emotional cues). Eye-tracking to measure pupil dilation. Ratings of emotional valence or intensity of faces.	↑ pupil dilation in response to emotionally ambiguous faces ($p < .05$). ↑ detection of low-intensity emotional expressions, esp. for fearful and happy expressions ($p < .05$)	Emotional sensitivity: sig. higher effect of OT on lower e.s. participants (as they found the tasks more demanding in the beginning) ($p = .014$)
Perry et al. (2013)	Whether IN-OT influences recognition of facial emotions despite incongruent body language	$n = 30$ (19 M/ 11 F; age range: 21–59, $\bar{x} = 38.9$)	IN-OT (24 IU) and PLC in separate sessions. Timing: 45 min Images of facial expressions paired with incongruent body postures, asked to identify facial emotion.	↑ recognition accuracy for facial expressions of disgust in body context of anger ($p = .026$). No sig. effect to recognize disgust in disgust context. No sig. effect for sadness or fear context. No sig. effect for RTs.	Gender: no sig. effect
Prehn et al. (2013)	How IN-OT influences physiological responses during the processing of facial emotions	$n = 47$ (M; age: $\bar{x} = 26.08$)	IN-OT (24 IU) or PLC. Timing: 45 min break Dynamic facial emotion recognition task (happy, sad, fearful, angry). Pupil dilation (indicator of attentional allocation)	↑ recognition of faces at lower intensity levels ($p = .031$, $\eta^2_p = .010$), ↑ pupil diameter for happy expressions ($p = .020$, $\eta^2_p = 0.11$), ↓ recognition threshold for angry expressions ($p = .010$, $\eta^2_p = .014$)	Gender of the face in the task: no sig. effect in OT group
Cardoso et al. (2014)	Whether IN-OT enhances emotional intelligence (emotion perception, emotion understanding)	$n = 82$ (41 M/ 41 F; age range: 18–30)	IN-OT (24 IU) or PLC. Timing: 35 min (relaxation) Perceiving emotion (recognizing emotions in faces, pictures) and understanding emotion (reasoning about emotional transitions)	↑ on the emotion perception subscale ($p < .05$, $d \approx 0.6$). No sig. effect on emotion understanding	Gender: no sig. effect Oral contraceptive use: no sig. effect

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Table 1 (*continued*)

Reference	Objective	Sample	Method	OT effects	Moderators
Feeser et al. (2014)	Whether IN-OT enhances recognition of avoidance-related facial emotions (fear, disgust), influenced by early life stress (ELS)	$n = 71$ (M; age range: 21–4, $\bar{x} = 28.1$, SD = 4.8)	IN-OT (24 IU) or PLC. Timing: 45 min break Emotion recognition task using facial expressions of various emotions.	↑ recognition accuracy of fear ($p = .042$) and disgust ($p = .077$). ↑ recognition accuracy only in subjects with low ELS ($p = .001$). No sig. effect on recognition of approach-related emotions (happiness, anger)	Early life stress: sig. effect on emotion recognition ($p < .05$) Ability to empathize: sig. difference under OT for those with low score ($p < .05$)
Voorthuis et al. (2014)	How IN-OT influences neural behavioral activity during recognition of infant emotional faces	$n = 50$ (F; age range: 18–27, $\bar{x} = 19.66$, SD = 1.45)	IN-OT (**16 IU**) or PLC. Timing: 50–60 min break Infant Facial Expressions of Emotions from Looking at Pictures (IFEEL) task, fMRI	↑ activation primarily in left hemisphere during the emotion recognition task ($p < .05$), ↓ recognition accuracy for infants' facial expressions ($p = .046$)	Early Life Stress: sig. differences in recognition accuracy ($p < .05$)
Hirosawa et al. (2015)	Whether IN-OT enhances attentional-inhibitory control and positive interpretation of neutral or ambiguous faces	$n = 20$ (M; age range: 20–46, $\bar{x} = 31.4$)	IN-OT (24 IU) and PLC in separate sessions. Timing: 45 min break Hostility ratings of happy, angry, neutral and ambiguous faces (hostility detection ratio). RTs to congruent and incongruent stimuli (conflict duration).	No sig. effects on hostility detection ratio and conflict duration. Positive correlation between changes in attentional control and in interpretation of ambiguous and neutral expressions ($\rho = .52$, $p = .027$)	
Quintana et al. (2015)	To investigate effects of low doses of IN-OT delivered via Breath Powered device on social-cognitive behavior	n = 57 (M; age range: 18–35, $\bar{x} = 23.81$, SD = 3.33)	IN-OT via Breath Powered advice (**8 IU** or 24 IU), IV-OT (1 IU) or PLC. Timing: 40 min break Ratings of emotional intensity (e.g., anger, happiness) for ambiguous facial expressions, MRI	8 IU IN-OT ↓ anger ratings for ambiguous facial expressions ($p < .05$, $d \approx 0.65$). Larger nasal cavity dimensions associated with stronger sig. effects at 8 IU. No sig. effect of 1 IU and 24 IU	Nasal valve dimensions affect face ratings ($p < .05$) after 8 IU OT
Bernaerts et al. (2016)	Whether IN-OT enhances recognition of emotions conveyed through body language	$n = 46$ (M; age: OT group $\bar{x} = 21.5$, SD = 2.02; PLC group $\bar{x} = 21.78$, SD = 2.11)	IN-OT (24 IU) or PLC. Timing: 30 min break Bodily emotion recognition task, i.e. identifying emotions from point-light displays (human motion without facial features)	↑ in recognizing emotions from body language from baseline to post session ($p < .05$, $\eta^2 = 0.12$). No sig. effect on RTs	Stimulus orientation: sig. effect on RTs ($p < .05$)
Korb et al. (2016)	Whether IN-OT enhances spontaneous facial mimicry	$n = 60$ (M; age range: 19–35, $\bar{x} = 24.85$, SD = 4.75)	IN-OT (24 IU) or PLC. Timing: mean 56 min (range 40–70) break Video clips depicting dynamic facial expressions of adults and infants.	↑ facial mimicry to angry infant faces ($p = .003$, $d = 0.23$, 0.39, and 0.46 for three-time windows). ↓ RTs to AngryToHappy infant faces ($p = .02$, $d = 0.07$), ↑ RTs to HappyToAngry infant faces ($p = .02$, $d = 0.11$). No sig. effect for adult faces	Age of stimulus faces: sig. differences in RTs ($p < .05$)
Hubble et al. (2017a)	Whether IN-OT influences the speed and accuracy of facial emotion recognition	$n = 40$ (M; age: $\bar{x} = 20.98$, SD = 4.55)	IN-OT (24 IU) and PLC in two separate sessions. Timing: 30 min break Facial emotion recognition task, eye-tracking	↓ RTs in face processing across various emotions ($p = .06$, $\eta^2_p = 0.11$). No sig. effect on emotion recognition accuracy and eye-gaze	Intensity of emotion: sig. difference between intensities ($p < .05$) Visual attention: no sig. difference in recognition accuracy
Spengler et al. (2017)	To determine optimal dose and timing of IN-OT for modulating amygdala reactivity	$n = 116$ (M; age: $\bar{x} = 24.7$, SD = 4.4)	IN-OT at doses of **12 IU, 24 IU, 48 IU** or PLC Timing: 15/45/75 min break Emotional face recognition task during fMRI at three intervals (15–40 min, 45–70 min, and 75–100 min)	24 IU after 45 min: ↓ amygdala activity to fearful faces ($p = .01$, $d = 0.80$), most in subjects high on autistic traits ($p = .041$, $d = 1.12$). ↑ perception of ambiguous faces as neutral ($p = .03$, $\eta^2_p = .08$). No sig. effect after 15 or 75 min	Autism Quotient: sig. differences ($p < .05$)
Shin et al. (2018)	To investigate dose-dependent effects of IN-OT on emotion recognition accuracy	$n = 60$ (M; age: 32 IU group $\bar{x} = 22.8$, SD=3.2; 40 IU group $\bar{x} = 23.1$, SD=2.8)	IN-OT at doses of **32 IU**, **40 IU** or PLC. Timing: 45 min break Facial Emotion Recognition Test (anger, disgust, fear, happiness, sadness, surprise). Accuracy and RTs	No sig. effect of 32 IU on recognition or RTs. For 40 IU, ↑ recognition of happy faces ($p = .005$; $\eta^2 = 0.64$), but no sig. effect on RTs	Attachment style: no sig. effect Empathic ability: no sig. effect
Yue et al. (2018)	Whether IN-OT influences working memory for facial expressions (sex differences)	$n = 91$ (45 M/ 46 F, age: $\bar{x} = 21.2$, SD = 1.76)	IN-OT (24 IU) or PLC. Timing: 45 min break EMO Task (recognizing emotional expressions) and ID Task (recognizing facial identities, irrespective of emotional expression). Accuracy, RT	In F, ↑ accuracy in recognizing angry ($p < .05$, $\eta^2_p = 0.05$) and happy faces ($p < .05$, $\eta^2_p = 0.06$); ↓ RTs to sad ($p < .01$, $\eta^2_p = 0.08$), fearful ($p < .05$, $\eta^2_p = 0.07$) and angry faces ($p < .05$, $\eta^2_p = 0.05$). In M, no sig. effects	Gender: sig. differences in recognizing faces under OT ($p < .05$)
Dam et al. (2019)	Whether IN-OT influences hot cognition in women and modulation by serotonin 4 receptor	$n = 35$ (F, age range: 20–39)	IN-OT (24 IU) and PLC in separate sessions. Timing: 40 min break Emotion recognition of facial expressions, PET scans to measure serotonin 4 receptor binding in the brain	No sig. effect on emotion recognition and of serotonin 4 receptor binding on cognitive performance	

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Table 1 (*continued*)

Reference	Objective	Sample	Method	OT effects	Moderators
Schwaiger et al. (2019)	Whether IN-OT enhances emotion recognition in adults with childhood adversity	$n = 80$ (54 M/ 26 F; age: adversity group $\bar{x} = 52$, SD = 6.01; control group $\bar{x} = 49.98$, SD=5.11)	IN-OT (24 IU) and PLC in separate sessions in adversity group and control group. Timing: 45 min movie break RMET, Emotion Recognition Task	In RMET, ↑ accuracy for both groups ($p = .049$, $\eta^2_p = .051$). In Emotion Recognition Task, ↑ accuracy for only Adversity ($p = .035$, $\eta^2_p = .058$), esp. for angry and fearful expressions.	Gender: no sig. effect
Wang et al. (2020)	Whether IN-OT influences gaze toward facial features and variation based on attachment anxiety	$n = 73$ (41 M/ 32 F; age range: 18–25, $\bar{x} = 19.64$, SD = 1.55)	IN-OT (24 IU) and PLC in separate sessions. Timing: 45 min break Emotion recognition task while tracking their eye movements to measure visual attention to different facial regions (eyes and mouth).	↑ in gaze toward the eye region of facial expressions, regardless of emotional valence of the expressions ($p < .05$). Only subjects with high attachment anxiety: ↑ gaze toward eyes ($p < .001$), ↓ gaze toward mouth ($p < .05$)	Gender: no effects reported Mood: no sig. effect
Maier et al. (2019)	whether IN-OT modulates behavioral and neural responses to stress-related body odors	$n = 58$ (30 M/ 28 F; age range: 19–31, $\bar{x} = 24.9$, SD = 0.41)	IN-OT (**40 IU**) or PLC. Timing: 30 min break fMRI, emotion recognition task (faces with varying intensities of fear) while being exposed to stress-related sweat or non-social control odor.	↓ bias in recognition of fearful faces by stress- sweat donors ($p < .05$). ↓ activation in amygdala (both sexes), anterior cingulate cortex (F), and hippocampus (M) ($p < .05$). ↑ functional connectivity between anterior cingulate cortex & fusiform face area ($p < .05$)	Gender: no sig. effect Childhood maltreatment: sig. influence of CM in oxytocin condition ($p < .05$)
Daughters et al. (2021)	Whether IN-OT enhances emotion recognition through facial synchrony and eye gaze	$n = 104$ (M; age: $\bar{x} = 19.90$, s.e.m. = 2.26)	IN-OT (24 IU) and PLC in separate sessions. Timing: 30 min filler task Emotion Recognition Task (dynamic facial expressions), facial EMG and Eye-Tracking	↑ accuracy in recognizing emotions from facial expressions ($p < .001$, $\eta^2_p = 0.700$). No sig. effect on facial synchrony and on gaze toward eye region	
Boyle et al. (2022)	Whether IN-OT affects visual attention to emotional faces	$n = 61$ (29 M/ 32 F; age range 18–35, $\bar{x} = 24.44$, SD = 4.27)	IN-OT (24 IU) and PLC in separate sessions. Timing: 30 min break Images of emotional facial expressions. Eye tracking, BDI scores	↑ fixations on the mouth region of happy and surprised faces ($p = .034$, $\eta^2_p = .05$), esp. in M with high depressive scores	BDI Scores: higher scores under oxytocin sig. moderate fixation times, percentages and attentional focus location (all $p < .05$)
Daughters et al. (2022)	To compare effects of IN-OT and emotion training on emotion recognition abilities	$n = 104$ (M; age: $\bar{x} = 19.90$, s.e.m. = 2.26)	IN-OT (24 IU) Timing: 30 min filler task Emotion training or combined group. Cardiff Emotion Recognition Training	No sig. effect on recognition, no additive benefit combined with emotion training. ↑ identification of low-intensity happy expressions ($p = .051$, $\eta^2_p = .037$)	
Macchia et al. (2022)	Whether IN-OT influences performance on RMET	$n = 20$ (M; age: $\bar{x} = 22.85$, SD = 3.5)	IN-OT (24 IU) or PLC in separate sessions. Timing: 45 min break RMET, mood questionnaires and serum OT levels	↓ lower accuracy on RMET ($p = .023$, $d = 0.55$), consistent across valence and intensity of items	Trait empathy: OT impaired mind reading in subjects with high perspective taking skill ($p < .05$)

Notes: Studies marked in bold applying at least one non-standard dose (other than 24 IU). esp: especially, ↑: Increased, ↓: Decreased, M: males, F: females, OT: oxytocin, IN-OT: intranasal oxytocin, IV-OT: intravenous oxytocin, PLC: PLC, RTs: reaction times, (f)MRI: (Functional) Magnetic Resonance Imaging, PET: Positron Emission Tomography, EMG: electromyography, RMET: Reading the Mind in the Eyes Test, sig: significant.

angry and happy faces only in females. Schwaiger et al. (2019) and Feeser et al. (2014) reported that IN-OT enhanced recognition of certain negative expressions specifically in individuals with specific adverse childhood experiences. Boyle et al. (2022) observed effects on visual attention limited to men with high depressive scores, while Wang et al. (2020) noted effects of eye gaze confined to individuals with high attachment anxiety. Spengler et al. (2017) reported the strongest amygdala modulation in individuals with higher autistic-like traits.

Additionally, several studies showed that IN-OT improved recognition of facial expressions at a lower intensity thresholds (Daughters et al., 2022; Marsh et al., 2010; Schulze et al., 2011; Lischke et al., 2012; Prehn et al., 2013). Three fMRI studies documented significant OT-induced changes in task-related brain activity (Maier et al., 2019; Spengler et al., 2017; Voorthuis et al., 2014).

3.2. Empathy

Twenty-eight studies measuring the effect of exogenous oxytocin on empathy met the eligibility criteria. Empathy was assessed using a range of tasks, including the Multifaceted Empathy Test (MET), self-report questionnaires (e.g., Interpersonal Reactivity Index), and behavioral paradigms involving emotional perspective-taking or affective resonance. In all of these studies, oxytocin was administered intranasally. Sixteen studies comprised exclusively male participants and the remaining twelve studies comprised mixed samples. Twenty-one studies administered a dose of 24 IU. Seven studies applied a different dose of IN-OT (20 IU in one study, 30 IU in one study, 32 IU in one study and 40 IU in four studies), but none compared multiple doses. The methodological quality was rated as moderate (RoB) for the same reasons as above, i.e., lack of methodological variability. Table 2 summarizes the main results regarding the impact of exogenous oxytocin on empathy.

3.2.1. Empathy studies comparing different doses

Only one study examining directly compared different doses of IN-OT in empathy tasks. Geng et al. (2018a) administered 24 IU and 40 IU in two separate experiments. Both doses significantly increased self-reported emotional empathy ($\eta^2 = 0.06, 0.12$). fMRI was utilized only in the 40 IU condition, revealing enhanced functional connectivity between regions associated with empathy, such as the insula ($\eta^2 = 0.09$). Additionally, a larger P200 amplitude and faster RTs were observed in response to in-group facial expressions of pain. While both doses produced significant effects, the absence of a lower-dose condition (< 24 IU) limits conclusions regarding the Inverted U-shaped dose-response.

Table 2
Studies examining influence of exogenous oxytocin on empathy.

Reference	Objective	Sample	Method	OT effects	Moderators
Singer et al. (2008)	Whether IN-OT enhances empathy by modulating brain responses to pain (to self and others)	$n = 21$ (M; age range: 20–31, $\bar{x} = 24.60$)	IN-OT (24 IU) or PLC. Timing: 45 min break fMRI, painful stimuli to self and another person. Standardized questionnaires assessing prosocial behavior.	No sig. effect on behavioral empathy ($p = .41$) ↓ in amygdala activation during self-experienced pain ($p < .05$), esp. in subjects low on prosocial behavior. No sig. effect in empathy-related brain regions during observation of others in pain	Personality: OT reduced amygdala activation in selfish participants — suggesting oxytocin made them less emotionally reactive to their own pain. ($p < .05$)
Hurlemann et al. (2010)	Effects of IN-OT on socially reinforced learning and emotional empathy	$n = 48$ (M; age: PLC group $\bar{x} = 25.20$, SD = 2.5; OT group $\bar{x} = 26.7$, SD = 2.2)	IN-OT (24 IU) or PLC. Timing: 45 min break Learning from social feedback (positive or negative reinforcement), followed by emotional empathy task fMRI	No main effect on cognitive empathy (p = .80). ↑ direct ($p = .0001$ −.011) and indirect ($p = .003$ −.007) emotional empathy effect size d = 1.32.	Gender: men receiving OT reach similar empathy levels as women without OT ($p < .05$)
Bartz et al. (2010)	Whether IN-OT enhances empathic accuracy, and dependence on baseline social proficiency	$n = 27$ (M; age: $\bar{x} = 26.8$)	IN-OT (24 IU) or PLC. Timing: 45 min break Videos of subjects (targets) discussing emotional events, ratings how the target was feeling. Empathic Accuracy, Autism Questionnaire (AQ) scores	No sig. main effect ↑ empathic accuracy only for subjects with high AQ scores ($p < .05$)	AQ scores: participants with high AQ scores scored sig. higher in the empathic accuracy in the OT condition ($p < .05$)
Sheng et al. (2013)	Whether IN-OT influences the racial bias in empathic neural responses	$n = 16$ (M; age range: 18–26, $\bar{x} = 21.88$)	IN-OT (**32 IU**) or PLC. Timing:45 min break Race judgment task involving in-group and out-group faces displaying either painful or neutral expressions. ERPs, IAT	↑ P200 amplitude in response to in-group pain expressions, but not of racial out-group members ($p < .026$). ↓ RTs toward racial in-group members ($p < .05$)	Ethnicity of the faces rated: Asian faces were associated with a sig. positive rather than negative attitude after OT treatment ($p < .05$).
Theodoridou et al. (2013)	Effects of IN-OT on affective empathy and perspective-taking abilities	Study 1: $n = 96$ (48 M/ 48 F; age range: 18–40, $\bar{x} = 21.4$) Study 2: $n = 120$ (60 M/ 60 F; age range: 18–44, $\bar{x} = 22.40$)	Study 1: IN-OT (24 IU) or PLC. Timing: 35 or 55 min Self-reports (empathic concern) in response to empathy-inducing scenarios. Study 2: IN-OT (24 IU) or PLC. Timing: 35 or 60 min 3PP task, RTs	No sig. effect on self-reported empathic concern ($p = .69$) or perspective-taking performance ($p = .18$)	Gender: in the PCB group, men were faster than women at perspective taking, but not in OT condition ($p = 0.02$)
Krueger et al. (2013)	Whether IN-OT modulates perceptions of harm on victims and desire to punish offenders	$n = 54$ (M; age: $\bar{x} = 24.2$)	IN-OT (**40 IU**) or PLC. Timing: 45 min Vignettes depicting criminal offenses, subjects rated harm on the victim and extent to which the offender deserved punishment. IRI	↑ main effect empathic concerns (harm ratings, $p = .011$, d = 0.74). No sig. effect on subjects' desire to punish offenders or on trait empathy.	Severity of the offense: no sig. effect
Shamay-Tsoory et al. (2013)	Whether IN-OT reduces in-group empathy bias by enhancing empathy towards an adversarial out-group	$n = 55$ (37 M/ 18 F; age range: 19–46)	IN-OT (24 IU) or PLC. Timing: 45 min Images depicting individuals from three groups experiencing pain (in-group, neutral out-group, adversary out-group). Ratings of level of empathy for each image.	No main effect on empathy ratings ($p = .52$) ↑empathy ratings for members of an adversarial out-group, reducing the typical in-group empathy bias ($p = 0.018$ for treatment × target interaction; $p = 0.048$ for treatment × target × pain interaction).	Ethnicity: OT eliminated ingroup-bias ($p = 0.018$); sig. under PCB, nor under OT Pain condition: empathy bias between groups sig. reduced for painful stimuli under OT ($p = .048$)
Tabak et al. (2015)	Whether IN-OT or IN-AVP influences empathic concern and moderation by parental warmth	$n = 125$ (35 M/ 90 F; age range: 18–31, $\bar{x} = 20.88$)	IN-OT (24 IU), IN-AVP (20 IU) or PLC. Timing: 40 min PANAS, PBI. Empathic concern ratings for distressing and uplifting videos.	No sig. effects for IN-OT on empathic concern (in contrast to AVP) or in relation to maternal warmth.	Gender: no sig. effect Paternal warmth: no sig. effect (in contrast to AVP) Maternal warmth: no sig. effect
Perry et al. (2015)	Whether IN-OT affects preferred interpersonal distance and moderation by individual empathy	$n = 54$ (M; age range: 19–32, $\bar{x} = 25.29$)	IN-OT (24 IU) or PLC. Timing: 45 min Interpersonal distance task (preferred distance from an approaching experimenter). Measures: PID, IRI	↓ PID among subjects with high trait empathy ($p = .005$). No sig. effect on PID among subjects with low trait empathy ($p = 0.18$)	Non-social distances: no sig. effect
Abu-Akel et al. (2015)	Whether IN-OT increases empathy for others' pain when subjects adopt another person's perspective	$n = 29$ (19 M/ 10 F; age: $\bar{x} = 39.14$)	IN-OT (24 IU) or PLC. Timing: 45 min Images depicting painful and non-painful situations. Self-perspective, other-perspective. Empathic response rated.	↑ empathy ratings when adopting other-perspective compared to the self-perspective ($p = .011$, $\eta^2_p = 0.211$)	Gender: no sig. effect Pain-condition: no sig. effect Perspective-taking: OT enhancing empathy only when participants imagined others in pain, not themselves ($p = .017$)

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Table 2 (*continued*)

Reference	Objective	Sample	Method	OT effects	Moderators
Palgi et al. (2015)	Whether IN-OT enhances compassion toward women compared to men	$n = 30$ (19 M/ 11 F; age: $\bar{x} =$ 39.2)	IN-OT (24 IU) or PLC. Timing:45 min Audio recordings of M and F individuals describing distressing emotional situations. Subjects provided compassionate advice, evaluated by two psychologists blinded to the treatment condition	↑ compassion toward F, but no sig. effect on compassion toward M ($p = .029$, d = 0.426). This effect was consistent across both M and F subjects.	Treatment order: no sig. effect Compassion-subscales: no sig. effect
Feeser et al. (2015)	Whether effects of IN-OT on mentalizing depend on an individual's baseline empathy levels	$n = 71$ (M; age range 21–42: $\bar{x} =$ 28.10, SD = 4.90)	IN-OT (24 IU) or PLC. Timing: 45 min break RMET, Empathy Quotient (EQ)	↑ mentalizing accuracy (p = .012), particularly for difficult RMET ($p = .002$) items but not for easy items. ↑ mentalizing accuracy in low empathy group ($p = .006$). No sig. effect in high empathy group.	
Bos et al. (2015)	Whether IN-OT enhances neural responses associated with empathy for pain	$n = 24$ (M; age range 19–27, $\bar{x} =$ 23.10)	IN-OT (24 IU) and PLC in separate sessions. Timing: mean 55 min break (range 47–60 min, SD = 4.6 min) fMRI while shown images depicting others in painful situations.	↓ activation in the brain's pain circuitry when observing others in pain, including insula and sensorimotor regions ($p < .05$)	Hand color: sig. difference in rFG activation ($p < .05$ (FWE))
Gallup & Church (2015)	Whether IN-OT influences contagious yawning	$n = 60$ (M; age range: 18–30, $\bar{x} =$ 19.20, SD = 1.65)	IN-OT (**30 IU**) or PLC. Timing: 45 min break alone or in pairs, with added confederate Video stimulus designed to elicit yawning (linked to empathy)	No sig. effect on frequency of yawning ($p = .226$). ↑ yawning latency ($p = .038$) ↑ social awareness (more likely to conceal yawns; $p = .044$)	Pairing participants during waiting period: no effects reported
Strang et al. (2017)	How IN-OT influences generosity across social distances and moderation by individual empathy	$n = 132$ (M; age: $\bar{x} = 24.4$, SD = 3.2)	IN-OT (24 IU) or PLC. Timing: 45 min break Willingness to forgo money to benefit others at different social distances (friends vs. strangers). IRI	↑ generosity toward socially close others among subjects with high trait empathy ($p = .024$). No sig. effect of OT among subjects with low trait empathy	
Hubble et al. (2017b)	Whether IN-OT increases attention to the eye region of emotional faces and affective empathy	$n = 40$ (M; age $\bar{x} = 20.98$, SD = 4.55)	IN-OT (24 IU) or PLC. Timing: 30 min break Pictures of facial expressions (fear, happiness, sadness, anger, neutral), eye-tracking. Ratings for affective empathy	Only for fearful faces, ↑ in gaze duration on the eye region ($p = .018$, $d = 0.77$) and in affective empathy ($p = .007$, $d =$ 0.88). No sig. effect for other emotions (happy, sad, angry, neutral)	
Geng et al. (2018a)	Whether IN-OT enhances emotional empathy across different cultures and sexes	Study 1: $n = 60$ (M; age $\bar{x} =$ 22.42, SD = 2.23) Study 2: $n = 72$ (38 M/ 34 F; female age $\bar{x} =$ 21.18, SD = 1.95; male age $\bar{x} =$ 22.61, SD = 2.01)	Study 1: IN-OT (24 IU) or PLC. Timing: 45 min break Multifaceted Empathy Test. Study 2: IN-OT (40 IU) or PLC Timing: 45 min break Emotional empathy (EE), fMRI and SCR	↑ EE across both studies and sexes, ↑ SCR ($p = .04$, $\eta^2 = 0.06$). ↓ bilateral amygdala activity (left: $p = .01$, $\eta^2 = 0.09$; right: $p = .03$, $\eta^2 = 0.08$). ↑ functional connectivity for positive stimuli	Gender: no sig. effect Autism scores: trends towards sig. effect on processing
Geng et al. (2018b)	Whether IN-OT influences embarrassment for self and others	$n = 70$ (38 M/ 32 F; age: OT group $\bar{x} = 22.03$, SD = 2.15; PLC group $\bar{x} = 21.86$, SD = 1.97)	IN-OT (**40 IU**) or PLC. Timing: 45 min break Images of subjects in embarrassing situations. Rated their levels of empathic embarrassment for self and others. fMRI, SCR	Both types of embarrassment: ↑ SCR ($p = .04$, $\eta^2 = 0.06$), ↓ SCR ($p = .009$, $\eta^2 = 0.12$)). ↑ in right amygdala SCR ($p(FDR) = .01$, $\eta^2 = 0.10$) and right dorsal anterior insula ($p(FDR) = .03$, $\eta^2 = 0.08$).	Gender: no sig. effect Mood: no sig. effect Trait anxiety: sig. different ($p < .05$)
Xu et al. (2019)	Whether IN-OT promotes altruistic or self-serving behavior in competitive social interactions	$n = 82$ (M; age range: 18–27 years, $\bar{x} = 21.36$, SD = 0.24)	IN-OT (24 IU) or PLC. Timing: 45 min break Modified version of the Cyberball game (virtual ball-tossing task designed to simulate social inclusion/exclusion). fMRI. Trait altruism questionnaires	↑ to throw ball to players who had previously excluded them ($p = 0.016$, Cohen's d = 0.543). fMRI: ↑ activation in left medial orbitofrontal cortex ($p < .047$), correlated negatively with trait altruism scores ($p < .047$)	
Tabak et al. (2019)	Effects of IN-OT and IN-AVP on various social cognitive and behavioral tasks	$n = 125$ (35 M/ 90 F; age range: 18–31, $\bar{x} = 20.88$, SD = 2.71)	IN-OT (**20 IU**), IN-AVP (20 IU) or PLC. Timing: 40 min reading newspapers Behavioral tasks designed to assess social cognition and behavior.	No sig. main effects of IN-OT or IN-AVP across the various social cognitive and behavioral tasks.	Gender: no sig. effect
Le et al. (2020)	Whether IN-OT enhances emotional empathy and association with visual attention to emotional faces	$n = 40$ (M; age: $\bar{x} =$ 20.80, SD = 0.38)	IN-OT (24 IU) or PLC. Timing: 45 min break Multifaceted Empathy Task (images of subjects expressing emotions). Emotional empathy (ratings of how much subjects felt the same as depicted person), eye gaze	↑ emotional empathy ratings for both negative ($p = .008$, $d =$ 0.486.) and positive ($p = .010$, $d =$ 0.469.) stimuli. Eye gaze: ↑ time spent viewing the face region ($p = .012$, $d = 0.525$).	Autism Scores: no sig. effect Empathy Scores: no sig. effect

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Table 2 (*continued*)

Reference	Objective	Sample	Method	OT effects	Moderators
Baettig et al. (2020)	How IN-OT affects brain activity when threats directed at self (fear condition) vs. others (empathy condition)	$n = 27$ (M; age: OT group $\bar{x} = 33.50$, SD = 9.8; PLC group $\bar{x} = 31.00$, SD = 7.00; age range 20–45)	IN-OT (24 IU) and PLC in separate sessions. Timing: 45 min break Images depicting themselves or others in threatening situations. fMRI, IRI, Empathy Quotient (EQ)	↑ activation in the anterior cingulate cortex (ACC) during the fear condition ($p = .023$, $d = 0.9$). No sig. effect on activation in anterior insula (AI) in empathy condition and in amygdala activation across conditions.	Depression scores - not investigated Anxiety scores: higher insular activity in less anxious subjects ($p < .05$) Empathy scores: differences in amygdala activity in more empathetic subjects ($p < .05$)
Cui et al. (2022)	Whether IN-OT influences subjects' willingness to share resources	$n = 77$ (M; age: $\bar{x} = 21.13$, SD = 1.93)	IN-OT (**40 IU**) or PLC. Timing: 35 min break Scenarios of resource scarcity. Cognitive empathy (CE) levels, fMRI	Interaction between treatment and cognitive empathy ($p = .043$, $\eta^2_p = 0.054$). ↑ resource sharing and ↑ activation in brain regions associated with perspective-taking among subjects with high CE	
Yue et al. (2020)	Whether IN-OT modulates self-other distinction during empathic responses to sadness	$n = 39$ (M; age: $\bar{x} = 20.65$, SD = 1.85)	IN-OT (24 IU) or PLC. Timing: 45 min break Self-task (evaluation of own emotional responses to sad and neutral facial expressions), Other-task (evaluation of emotional state of other person), ERPs	During self-task for difference between sad and neutral faces, ↓ P200 amplitudes ($p < .05$, $\eta^2_p = 0.10$) and ↓ LPC amplitudes ($p < .05$, $\eta^2_p = 0.17$). During other-task, ↑ P200 amplitudes to sad faces ($p < .05$, $\eta^2_p = 0.10$).	
Straccia et al. (2023)	Whether IN-OT or IN-AVP influences mentalizing abilities	$n = 186$ (67 M/ 119 F; age range: 18–28, $\bar{x} = 20.30$, SD = 1.72)	IN-OT (24 IU), PLC or IN-AVP (20 IU). Timing: 40 min break fMRI during Why/How task. Accuracy, RTs, neural activity	No sig. effects on self-reported empathy, task accuracy, RTs and neural activation	Gender: no sig. effect Autism Quotient: sig. effect in mirror network ($p < .05$ uncorrected)
Lin et al. (2023)	Whether effect of IN-OT on empathy for others' pain is mediated by first-hand pain sensitivity	$n = 120$ (60 M/ 60 F, age: $\bar{x} = 19.29$, SD = 0.15)	IN-OT (24 IU) or PLC. Timing: 45 min break Assessments of first-hand pain sensitivity (pressure pain thresholds) and empathy for others' pain (ratings of others' pain experiences)	↓ in first-hand pain sensitivity, evidenced by higher pressure pain thresholds ($p < 0.001$, η^2_p =0.46). No direct effect on empathy ratings for others' pain ($p > .05$), but indirectly through first-hand pain sensitivity ($p = 0.047$, $\beta = -0.04$)	Gender: no differences of OT on pain sensitivity

Notes: Studies marked in bold applying at least one non-standard dose (other than 24 IU). esp: especially, ↑: Increased, ↓: Decreased, M: males, F: females, OT: oxytocin, IN-OT: intranasal oxytocin, PLC: PLC, RTs: reaction times, fMRI: Functional Magnetic Resonance Imaging, IRI: Interpersonal Reactivity Index, IN-AVP: intranasally administered vasopressin, 3PP task: third-person perspective-taking task, PANAS: Positive and Negative Affect Schedule, SCR: skin conductance responses, PBI: Parental Bonding Instrument, ERPs: event-related potentials, LPC: late positive complex, IAT: Implicit Association Test, AQ: Autism Spectrum Quotient, sig: significant.

3.2.2. *Empathy studies applying a non-standard dose*

Several studies used doses either below or above the standard 24 IU to investigate effects on empathy-related processes.

At the lower end, Tabak et al. (2019) administered 20 IU and found no significant behavioral effects across a range of social and cognitive empathy tasks. Gallup and Church . (2015) administered 30 IU to examine yawning as a measure of empathy and likewise reported no significant effects on behavioral measures of empathy, though they observed increased self-reported social awareness. Sheng et al. (2013) administered 32 IU and found a significantly enhanced P200 amplitude ($d = 0.62$) and decreased RTs ($d = 0.59$) for in-group pain expressions, suggesting selective neural effects without corresponding behavioral improvements.

By contrast, three other studies using 40 IU reported significant positive effects. Krueger et al. (2013) found increased perceptions of harm directed at victims of depicted criminal offenses ($d = 0.74$). Geng et al. (2018b) observed increased self-reported embarrassment for oneself and others ($d = 0.67, 0.74$) as well as increased activation in associated brain regions. Cui et al. (2022) demonstrated an increase in resource sharing and activation in brain regions involved in perspective-taking ($\eta_p^2 = 0.054$). Together, these studies suggest that 40 IU may induce selective improvements in empathy, although these effects are domain-specific.

3.2.3. *Empathy studies applying a standard dose*

Most studies administered the standard 24 IU dose. Findings in this group are mixed.

Several studies reported no significant effects on empathy (Straccia et al., 2023; Tabak et al., 2015; Theodoridou et al., 2013). Lin et al. (2023) found only indirect effects on empathy for others' pain, mediated through other factors. In contrast, multiple studies reported enhanced empathy-related ratings or neural activity: Abu-Akel et al. (2015), Hubble et al. (2017b), Hurlemann et al. (2010), Le et al. (2020), and Shamay-Tsoory et al. (2013) found significant increases in self-reported empathy. fMRI studies revealed significant changes in empathy-related brain regions, including both increased activation (Baettig et al., 2020; Xu et al., 2019) and decreased activation in response to pain (Bos et al., 2015; Singer et al., 2008). Yue et al. (2020) found a significant effect in the P200 component in response to sad faces.

Moderation by participant characteristics or stimulus type was also observed. Bartz et al. (2010) found a significant increase in empathic concern only in healthy subjects high in autism spectrum traits. Feeser et al. (2015) found an increase in mentalizing accuracy only in subjects with low trait empathy, while Strang et al. (2017) and Perry et al. (2015) observed increased generosity and reduced interpersonal distance only among subjects with high trait empathy. Palgi et al. (2015) reported increased compassion specifically towards women only.

Replication studies also showed inconsistency. Bartz et al. (2019) found a significant increase in empathic accuracy only in men with higher autism spectrum quotient (AQ) scores, i.e. with lower social proficiency. Radke and de Bruijn (2015) found no main effect on performance in the Reading the Mind in the Eyes Test (RMET), though subjects with lower trait emotional empathy improved slighty.

3.3. *Trust*

Seventeen studies measuring the effect of exogenous oxytocin on trust met the eligibility criteria. Kis et al. (2013) measures emotion

recognition as well as trust, therefore the study is repeated in this section with only the respective results. Trust was commonly measured through economic exchange paradigms like the Trust Game, in which participants decide how much money to invest with a partner, or through self-report trust scales. As in the previously discussed domains, oxytocin was administered intranasally in all these studies. Twelve studies comprised exclusively male participants and the remaining five comprised mixed samples. Ten studies administered a single dose of 24 IU, while seven applied a different dose (32 IU in four studies; 40 IU in the other three studies) and none compared multiple doses. The methodological quality was rated as moderate (RoB), again due to lack of variability. Table 3 summarizes the main results regarding the impact of exogenous oxytocin on trust.

3.3.1. Trust studies applying a non-standard dose

Several studies administered non-standard doses of IN-OT (i.e., doses other than 24 IU) to investigate its effects on trust-related behavior and perception, with varying results depending on dose and context.

At the 32 IU dose, Mikolajczak (2010a; 2010b) conducted two separate studies using a trust game and found significant increase in trust relative to placebo (d = 0.55, 0.50). In contrast, Berends et al. (2021), also using 32 IU, reported a significant decrease in trust following a breach of trust (d = 0.38), indicating that the direction of the effect may depend on contextual factors such as trust violation. Lane et al. (2015) administered 32 IU in a different paradigm (the Envelope Task), which measured behavioral trust toward the experimenter through the degree of envelope sealing. This study did not find any significant effects on trust behavior at this dose.

Studies using 40 IU also yielded mixed results. Merolla et al. (2013) assessed self-reported interpersonal trust via questionnaire, while Human et al. (2016) used a sequential monetary trust game; both found significant increases in trust (d = 0.31, 0.69). However, Ide et al. (2018), also administering 40 IU, observed no significant effect on trust.

Thus, while several studies with non-standard doses reported significant effects, the direction and strength of these effects appear to be context-dependent, and no consistent pattern emerges regarding dose-response. Notably, 32 IU produced both positive and negative outcomes, and the evidence for 40 IU remains inconclusive.

3.3.2. Trust studies applying a standard dose

The majority of studies used the standard 24 IU dose of IN-OT to assess its effect on trust, again with inconsistent findings.

Some studies found significant positive effects of IN-OT on trust-related behavior. For example, Kosfeld et al. (2005) and Baumgartner et al. (2008) both reported increased trust following IN-OT administration. Notably, Baumgartner et al. (2008) also found changes in brain activity associated with trust, suggesting neurophysiological correlates of oxytocin's behavioral effects. However, other studies using the same dose failed to replicate these findings. Declerck et al. (2020), Klackl et al. (2013), Luo et al. (2017), and Yao et al. (2014) all found no significant effect of IN-OT on trust-related measures.

Several studies reported context-dependent or task-specific effects. Kis et al. (2013) found that the direction of the effect on trust depended on valence of facial expressions and whether the task was during the learning or retrieval phase. Kret and De Dreu (2017) observed a significant decrease in trust in an investment game.

Subgroup-specific effects were also reported. De Dreu (2012) found a significant increase in trust only among subjects with high attachment avoidance. Luo et al. (2017) reported a significant increase in acceptance of advice (indicator of trust), but only when the advice came from female psychologists. Schiller et al. (2023) found a gender-specific and cue-specific effect, where trust (measured via P100 and behavioral responses) increased for male subjects in response to low-attractiveness and low-threat cues, but showed opposite effects for females.

3.4. Comparison of the effects of non-standard doses

The following section compares findings on emotion recognition, empathy and trust that involved non-standard doses of IN-OT (i.e., doses other than the standard 24 IU). Eight studies found non-standard doses to be ineffective: Emotion recognition was not significantly affected at 1 IU (Quintana et al., 2015), 6 IU and 12 IU (Lieberz et al., 2020; Spengler et al., 2017), 32 IU (Shin et al., 2018), and 48 IU (Spengler et al., 2017). Empathy was not significantly affected at 20 IU (Tabak et al., 2019) and 30 IU (Gallup and Church, 2015). Trust was not significantly affected at 32 IU (Lane et al., 2015) and 40 IU (Ide et al., 2018). Fig. 2 illustrates the studies that found significant effects of non-standard doses ranging from 1 to 48 IU. These effects were divided into two categories: psychological measures (behavioral tasks and self-reports) and neural measures (fMRI and ERPs). For each category, the highest effect size is shown. Most studies have used doses ranging from 32 to 40 IU, which have moderate to large effect sizes. Effect sizes for lower doses tend to be smaller. The effect size of d = 1.76 from Quintana et al. (2015) is an outlier. Overall, there is more evidence for the effects of higher doses than lower doses on psychological and neural measures.

4. Discussion

4.1. Summary and integration of findings

This systematic literature review examined the effects of exogenous oxytocin on social cognition in the domains of emotion recognition, empathy, and trust, and included a total of 75 studies. Twenty of these studies administered at least one non-standard dose (i.e. other than 24 IU), ranging from 1 IU to 48 IU. As only five of these studies directly compared several doses (Geng et al., 2018a; Lieberz et al., 2020; Quintana et al., 2015; Spengler et al., 2017; Shin et al., 2018), and the others compared with a placebo, conclusions regarding dose-response effects must primarily be drawn by comparing different studies. This underscores the need for additional research that directly compares several doses, as different methodologies make comparisons challenging. For the purposes of the following discussion, it is assumed that 24 IU represents the midpoint of the Inverted-U curve, primarily because it is the most frequently used dose in the literature. However, this midpoint is not empirically established and may differ depending on the behavioral measure, timing, individual characteristics, or delivery method. This assumption should therefore be interpreted as a practical convention rather than a validated pharmacodynamic anchor.

For emotion recognition, the four studies directly comparing different IN-OT doses do not provide consistent evidence for an Inverted-U-shaped dose-response relationship. The studies of Quintana et al. (2015) and Shin et al. (2018) contradict the Inverted-U Curve hypothesis, as only the lowest (8 IU versus 24 IU) and highest doses (40 IU versus 32 IU) yielded significant effects on emotion recognition. However, the results of Spengler et al. (2017) found that 24 IU (compared to 12 and 48 IU) was the most efficient dose to modulate behavioral and neural variables of emotion recognition. Lieberz et al. (2020) found no significant effect on emotion recognition in behavioral measures (6, 12 and 24 IU). Two other studies comparing a single dose of IN-OT with a placebo (Maier et al., 2019; Voorthuis et al., 2014) indicate that both lower (16 IU) and higher (40 IU) doses have a significant effect on brain activity, as measured by fMRI. However, recognition accuracy decreased significantly after 16 IU, indicating an adverse effect of a lower dose. In contrast, the significant effect of 40 IU on recognition was related to a bias induced by stress odor. Overall, the behavioral evidence for the Inverted-U Curve hypothesis is mixed (two studies support it and two others refute it), while the two fMRI studies reject the premise of the hypothesis that only 24 IU leads to significant prosocial effects. Domain-specific variability in task valence and underlying processing pathways may partly explain the inconsistent effects of IN-OT observed across studies.

Table 3
Studies examining influence of exogenous oxytocin on trust.

Reference	Objective	Sample	Method	OT effects	Moderators
Kosfeld et al. (2005)	Effect of IN-OT on trusting behavior	$n = 58$ (M; age: $\bar{x} = 22.0$ SD = 3.40)	IN-OT (24 IU) or PLC. Timing: 50 min break Trust game (investment) Average investment (Monetary Units) measured.	↑ trusting behavior, 17 % higher average monetary transfer ($p = .029$)	
Baumgart-ner al. (2008)	IN-OT effect on trusting behavior after betrayal	$n = 49$ (M; age: $\bar{x} = 21.7$, SD = 2.50)	IN-OT (24 IU) or PLC. Timing: 50 min break Trust game (investment) Measures: average investment, fMRT, RTs	No sig. change in trusting behavior after trust had been breached (PLC: ↓ trust, $p = .05$, $\eta^2 = 0.11$.) ↓ RTs ($p < .01$) during postfeedback, but no sig. differences between groups during pre-feedback. ↓ activation in amygdala, midbrain regions, and dorsal striatum	Trait trust, sensation seeking, Mood: all sig. effect in left caudatus (all $p < .05$)
Mikolajczak et al. (2010a)	Whether IN-OT's effects on trust are context dependent	$n = 60$ (M; age: $\bar{x} = 21.2$, SD = 2.4)	IN-OT **(32 IU)** or PLC. Timing: 45 min Trust game. Investment measured.	↑ trust, larger transfers than PLC group ($p < .018$). No sig. trust-enhancing effect when the partner was untrustworthy ($p = .038$)	Trustee human or computer: possibly influential on trust behavior (no p-values reported) Individual differences: no sig. effect
Mikolajczak et al. (2010b)	How IN-OT influences trust behavior in the context of confidential information	$n = 60$ (M; age: $\bar{x} = 21.2$, SD = 2.40)	IN-OT **(32 IU)** or PLC. Timing: 45 min break Tasks: Trust game (confidential information). Measures: observable behavior (leaving envelope open, seal it or seal and tape it)	↑ trust. 44 times more trusting that privacy would not be violated than under PLC ($p \leq .001$, $d = 2.41$)	Sexual practices and fantasies: no sig. effect Movie watched: possible influence (no p-values reported)
De Dreu (2012)	IN-OT modulation of relationship between individual differences in social attachment and cooperation	$n = 77$ (M; age: $\bar{x} = 20.81$)	IN-OT (24 IU) or PLC. Timing: 35 min filler task Social dilemma task. Measures: Investment, AAS (18-items)	No sig. effect on trust, no sig. effect for attachment avoidance when M received OT. ↑ trust in subjects with high attachment avoidance when given OT ($p < .001$)	Attachment anxiety: no sig. effects Betrayal aversion: sig. modified attachment avoidance x treatment interaction ($p < .05$)
Kis et al. (2013)	Whether IN-OT and social interaction similarly influence trustworthiness of negative facial expressions	$n = 52$ (M; age: $\bar{x} = 23.02$, SD = 3.32, age range: 18–30)	IN-OT (24 IU), PLC, social interaction (Soc) or no social interaction (NoSoc). Timing: 40 min break Learning: Images of faces varied in valence, subjects rated trustworthiness. Testing: Ratings of neutral faces (some previously emotional)	No main effect of pretreatment. Learning phase: ↑ trust, higher rating of trust in negative emotional faces in OT group ($p = .032$) Testing phase: ↓ trustworthiness rating of neutral faces that were previously negative ($p = .005$)	Experimental design: learning and testing phase at different timepoints relative to OT admin - possibly influential (no p-values reported)
Klackl et al. (2013)	Whether IN-OT changes attribution processes in favor of non-personalistic ones and thereby boosts subsequent trust	$n = 40$ (M; age: $\bar{x} = 23.67$, SD = 6.08)	IN-OT (24 IU) or PLC Timing: 40 min break Trust game. Measures: investments	No sig. effect on trust and on how much people invested. ↑ relationship between angry rumination and non-personalistic attribution of opponents' behavior ($p < .05$). ↓ link between angry rumination and personalistic attribution ($p < .05$).	Personalistic attributions: no sig. effects on trust
Merolla et al. (2013)	Whether IN-OT affects interpersonal trust as well as political trust	$n = 88$ (M; age: $\bar{x} = 20.5$)	IN-OT (**40 IU**) or PLC Timing: 60 min filling out questionnaire Tasks: Questionnaires on interpersonal trust, political attitudes, trust in government. Scores of questionnaires	↑ trust ($p < .05$), ↑ interpersonal and governmental trust ($p = .038$).	Pretreatment trust: sig. more effect of OT in those with lower trust ($p < .05$) Partisanship: larger effect of OT in Democrats ($p < .05$)
Yao et al. (2014)	Whether IN-OT modulates effects on restoring damaged trust	$n = 104$ (57 M/ 47 F; age: $\bar{x} = 21.20$, SD = 1.76)	IN-OT (24 IU) or PLC Timing: 45 min break Trust investment game with betrayal and repair attempts	No sig effect on trust or trait forgiveness. Trust could be partially repaired across genders. F receiving OT showed worse trust repair, esp. in high trait forgiveness ($p < .05$)	Gender: females less forgiving (all $p < .05$), no sig. differences in questionnaire scores Repair strategies: sig. differences between strategies (all $p < .05$)
Human et al. (2016)	Whether IN-OT interacts with trait extraversion in predicting prosocial behavior and interpersonal trust	Study 1: $n = 121$ (57 M/ 64 F; age: $\bar{x} = 25.01$, SD = 4.01) Study 2: $n = 112$ (45 M/ 67 F; age: $\bar{x} = 24.27$, SD = 3.62)	Study 1: IN-OT (**40 IU**) or PLC. Timing: 40 min video watching Task: Ratings of social organizations Measure: Positive behavioral responses to help and interpersonal trust, prosocial decision making Study 2: IN-OT (**40 IU**) or PLC. Timing: 40 min video watching	↑ trust ($p < .05$), ↓ extraversion subjects under IN-OT: ↑ social connection, prosocial tendencies, positive behavioral responses to help ($p = .02$) and interpersonal trust ($p = .009$)	Gender: not reported Study 1:m Extraversion: greater social connection ($p < .05$)

(*continued on next page*)

Table 3 (*continued*)

Reference	Objective	Sample	Method	OT effects	Moderators
			Task: Receiving help, sharing money in trust setting. Measure: Positive behavioral responses to help and interpersonal trust, prosocial decision making		
Kret and De Dreu (2017)	Whether IN-OT and sex modulate the link between pupil mimicry and trust	$n = 59$ (28 M/ 31 F; age: $\bar{x} =$ 22.00)	IN-OT (24 IU) or PLC Timing: 30 min break Tasks: investment game Measures: pupil dilation, investment decisions	↓ trust (less investment) in partners with constricting pupils ($p = .001$), this effect only shown in M ($p = .005$). ↓ trust in F with partners with dilating pupils ($p = .031$). ↑ preference for dilating pupil partners in M ($p = .01$), but ↓ in F ($p = .031$); ↓ dilation mimicry; ↑ pupil constriction (both $p < .005$)	Gender: see results Ethnicity of stimulus faces: ingroup more trusted than outgroup ($p < .05$), independent of sex (partner or participant) and treatment
Luo et al. (2017)	Whether IN-OT influences acceptance of advice of individuals independently of trustworthiness or likeability	$n = 150$ (75 M/ 75 F; age: $\bar{x} =$ 22.13, SD = 2.34)	IN-OT (24 IU) or PLC Timing: 45 min break Tasks: solve social problems and rank solutions, accept/ reject advice, Measures: trustworthiness rating, likeability ratings, problem solutions	No sig. effect on trust (advisors' trustworthiness). ↑ acceptance of advice trust) from F, but not a M psychologist ($p = .025$, d = 0.369). This effect was not maintained after 7 days. Transiently (7 days): ↑ acceptance of and conforming to advice from most trusted advisors ($p = .025$, $d = 0.45$).	Gender: see results Advice type: better advice accepted more ($p < .05$) likeability: No sig. effect of OT on likeability
Ide et al. (2018)	Whether IN-OT modulates expectation updating and reinforcement learning within a social context	$n = 17$ (M; age: $\bar{x}$ = 25.40, SD = 3.70)	IN-OT (**40 IU**) or PLC Timing: 60 min break Tasks: Iterative trust Game Measures: fMRI, Investments made, money gained	No sig. effect on trust; no difference in investment between OT and PLC. ↓ feedback learning via reward circuit ($p < .05$) compared to PLC, ↓ activation of salience circuit during decision making ($p < .05$), ↓ amygdala response to prediction error ($p < .01$), which is a reduced ability to modulate beliefs rather than trust.	
Berends et al. (2021)	Whether IN-OT moderates association between testosterone-cortisol ratio and trustworthiness after trust violation	$n = 53$ (M; age: PLC group $\bar{x} =$ 21.60, SD = 2.90; OT group $\bar{x} =$ 22.00, SD = 1.90)	IN-OT (**32 IU**) or PLC. Timing: 45 min break, activity of choice Tasks: Trust game. Measures: Game scores, trust repair scores	↓ trust after trust violation ($p = .039$). Trust repair for high testosterone-cortisol ratio subjects ($p = .07$)	
Schiller et al. (2023)	Whether there are sex differences in IN-OT's effect on trust	$n = 144$ (71 M/ 73 F; age range: 18–35, $\bar{x} =$ 23.49, SD = 3.59)	IN-OT (24 IU) or PLC. Timing: 40–50 min break while EEG is fitted Tasks: Trust game with trustees of varying attractiveness and threat. Measures: EEG, trust decisions	No sig. effect on trust. For low-attractiveness and low-threat trustees: ↑ trust and P100 in M ($p = .047$), ↓ trust and P100 in F ($p = .038$)	Gender: males more trusting ($p < .05$) Risk-taking: no sig. effect Charity donations: no sig. effect

Notes: Studies marked in bold applying at least one non-standard dose (other than 24 IU). esp: especially, ↑: Increased, ↓: Decreased, M: males, F: females, OT: oxytocin, IN-OT: intranasal oxytocin, PLC: PLC, RTs: reaction times, fMRI: Functional Magnetic Resonance Imaging, AAS: Adult Attachment Style questionnaire, EEG: electroencephalography, sig: significant.

In terms of empathy, doses of 20 IU (Tabak et al., 2019) and 30 IU (Gallup and Church, 2015) had no significant effect. These two studies support the Inverted-U hypothesis, as neither lower nor higher doses were effective. However, four other studies administered 40 IU and observed significant positive effects on behavioral measures of empathy (Cui et al., 2022; Krueger et al., 2013; Geng et al., 2018a, 2018b), thus contradicting the Inverted-U hypothesis. Geng et al. (2018a), (2018b) also observed significant effects of these higher doses on brain activity and skin conductance levels. Overall, most of this evidence contradicts the hypothesis that 40 IU is not effective.

Regarding trust, Mikolajczak (2010a; 2020b) found a significant increase in trust following 32 IU in a trust game, whereas Berends et al. (2021) found a significant decrease in trust after a breach of trust in response to 32 IU. These conflicting results may be due to methodological differences, as the latter study specifically implemented a trust violation. However, evidence regarding the Inverted-U hypothesis is contradictory. Regarding 40 IU, two studies (Human et al., 2016; Merolla et al., 2013) found a positive effect on trust, while Ide et al. (2018) found no effect. Overall, the results of the four studies contradict the Inverted-U hypothesis, suggesting efficacy at higher doses, while the results of two studies support the hypothesis of a negative or null effect.

For emotion recognition several studies showed an improvement after 24 IU of IN-OT, particularly for subtle facial expressions or when social cues are difficult to interpret (e.g., Marsh et al., 2010; Prehn et al., 2013). These results fit the meta-analysis of Shahrestani et al. (2013b) showing that IN-OT led to a modest overall improvement in the recognition of emotional faces, particularly happy and fearful expressions. Several studies showed 24 IU of IN-OT to promote measures of empathy (Abu-Akel et al., 2015; Hurlemann et al., 2010), though the effects are context-dependent by influencing the brain's reward circuitry (e.g., the striatum and the ventromedial prefrontal cortex) in social situations. Also, the effects of oxytocin are moderated by individual characteristics such as attachment style and social proficiency (Bartz et al., 2011). The enhancing effect of oxytocin on trust was first demonstrated by Kosfeld et al. (2005) in an economic decision-making game in which the medium dose significantly increased trust. However, this effect is context-dependent, and not all studies applying 24 IU of IN-OT have replicated these results (e.g., Declerck et al., 2020; Klackl et al., 2013; Schiller et al., 2023; Yao et al., 2014), particularly in situations involving ambiguous or threatening social cues. Oxytocin may enhance the salience of social cues such as emotional facial expressions by modulating amygdala activity and prefrontal cortex processing (Shamay-Tsoory and Abu-Akel, 2016). However, there were also studies founding no significant effect for the medium dose of 24 IU (e.g.,

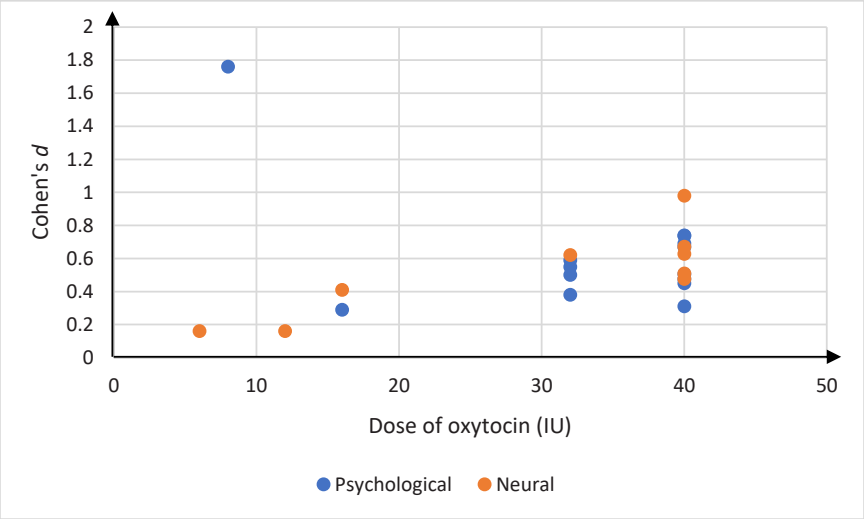

Fig. 2. Significant effects of non-standard (other than 24 IU) doses of oxytocin. *Notes*: The X-axis shows the intranasally administered dose of oxytocin. The y-axis shows effect size (Cohen's *d*). Psychological measures include behavioral tasks and self-reports, while neural measures include fMRI tasks. Sixteen studies have been included in this graphic. The 24 IU dose is excluded to maintain the figure's exploratory focus on non-standard doses and avoid interpretational complexity from its high volume and heterogeneity.

Guastella et al., 2009; Schiller et al., 2023; Theodoridou et al., 2013). The evidence discussed regarding the effect of lower and higher doses of IN-OT on social cognition is mixed. Most studies using the standard dose of 24 IU do not compare it with lower or higher doses; they only use a placebo for comparison. Consequently, they cannot provide definitive evidence either for or against the inverted-U hypothesis. Thus, there is a lack of studies that provide direct dose comparisons. Understanding the dose-dependent nature of oxytocin's effects is crucial, but it also highlights why consistent replication across studies has been challenging.

In general, the effects of oxytocin on social cognition are not easily replicated (Nave et al., 2015). A previous review (Barchi-Ferreira and Osório, 2021) emphasizes that oxytocin's effects on emotional processing and social behavior are modulated by multiple factors, such as individual differences (e.g., gender and attachment style) and context (e.g., type of emotional stimulus). The authors conclude that findings across studies are inconsistent: sometimes, oxytocin improves social cognition and emotion recognition; in other cases, it shows null or even adverse effects. Likewise, Ellenbogen (2017) highlights that oxytocin's role in social cognition does not follow a universal pattern. Rather, it interacts with individual history (e.g., childhood maltreatment), social context, and genetic factors, resulting in inconsistent outcomes.

A closer specification of not only dosage but also timing could clarify the exact dynamics between oxytocin and social behavior. Spengler et al. (2017) indicates that the optimal testing window lies 45 min post-administration to maximize the likelihood of detecting oxytocin's social cognitive benefits. Martins et al. (2020a) argue that time intervals in the early (15–32 min) and late (87–95 min) stages are important for observing faster or delayed effects of intranasal oxytocin (IN-OT) on brain perfusion. Behavioral and neural effects typically emerge 30–45 min after administration, which coincides with peak oxytocinconcentrations in the cerebrospinal fluid and brain regions involved in social processing (Striepens et al., 2013a; Paloyelis et al., 2016). Testing too early may miss the onset of oxytocin's effects, while testing too late may result in observing diminished or waning effects due to metabolism and clearance.

4.2. Neural pathways of dose-dependent OT effects

Understanding how exogenously administered oxytocin affects social cognition requires clarifying its influence on underlying neural systems. While many of the studies included in this review assessed neural readouts (such as amygdala reactivity, eye gaze, pupil dilation, and ERPs) these mechanisms have not been systematically integrated into a coherent model of oxytocin's dose-dependent effects. Here, we propose a provisional framework to relate neural outcomes to behavioral effects, while acknowledging the inconsistency of dose-response findings across the literature.

Amygdala activity is among the most frequently studied neural targets. Standard doses of oxytocin (typically 24 IU) are often associated with reduced amygdala reactivity to threatening or ambiguous social stimuli (e.g., Spengler et al., 2017), an effect particularly pronounced in individuals with high levels of autistic traits. This dampened threat processing has been interpreted as a possible mechanism for oxytocin's enhancement of interpersonal trust and social approach behavior. However, other studies have reported no significant effects or greater amygdala activation at both lower and higher doses, suggesting that this effect is not uniform and may depend on factors such as timing, sex, or individual traits (Lieberz et al., 2020; Maier et al., 2019).

Visual attention to social cues, such as increased gaze toward the eye region, has also been observed following 24 IU administration, particularly in individuals with elevated attachment anxiety (Wang et al., 2020). Similarly, pupil dilation increases in response to emotionally ambiguous faces have been interpreted as signs of enhanced attentional engagement (Leknes et al., 2013). These effects may underlie improvements in emotion recognition, especially for subtle or low-intensity expressions. However, studies using different doses or varying paradigms have yielded divergent results, and the dose-dependence of these attentional shifts remains unclear.

ERP studies offer additional insights into early-stage processing of social stimuli. Dose of 24–32 IU have been found to modulate components such as P200 and LPC, reflecting changes in attentional allocation and emotional salience (Sheng et al., 2013; Yue et al., 2020). While these findings support the idea that oxytocin can modulate neural responses to socially relevant cues, they do not consistently follow a linear or nonlinear dose trajectory.

Taken together, the available evidence does not support a consistent Inverted-U-shaped dose-response curve across neural systems. While some effects appear strongest at standard doses, others are seen at lower / higher doses or only in specific subgroups. Therefore, rather than endorsing a singular dose-response model, we emphasize the need for mechanistically informed, dose-ranging studies that account for individual differences, contextual moderators, and timing of effects.

4.3. Limitations of the current review

The current body of research on exogenously administered oxytocin and its effects on social cognition has several key limitations that should be addressed by future studies.

First is the lack of variability in dosage. The vast majority of studies used a standardized dose of 24 IU; therefore, conclusions about dose-response effects must be drawn cautiously, particularly given the Inverted-U Curve Hypothesis. The prevalence of the 24 IU standard across studies severely limits the ability to empirically evaluate this model. Without examining a range of doses systematically, it is unclear whether the commonly used 24 IU dose lies on the ascending, peak, or descending portion of the curve.

Second, there is a lack of variability in the route of administration. Although our inclusion criteria were not limited to this route of administration, all of the included studies administered oxytocin intranasally and only one study (Quintana et al., 2015) also administered a very low dose of 1 IU intravenously. This likely reflects the broader field's shift toward intranasal delivery over the past decades. Reliance on intranasal delivery limits our understanding of how oxytocin's effects may differ when administered via other methods, such as intravenously or orally, as these methods may affect social cognition differently. For example, while IN-OT has been shown to decrease amygdala activation in response to emotional faces, oral administration of the same dose increased neural activity in the amygdala (Yao and Kendrick, 2022). The narrow methodological focus on IN-OT constrains the generalizability of the findings.

Third, there has been a predominant inclusion of male participants. Most studies have recruited only males to control for potential hormonal variations associated with the menstrual cycle. However, this gender imbalance limits the generalizability of the findings because the oxytocin system has been found to interact with sex hormones, such as estrogen (Coenjaerts et al., 2022; 2023). There is evidence that oxytocin may influence social cognition differently in males and females. Therefore, conclusions drawn from male-only samples may not accurately reflect oxytocin's effects in females. Borland et al. (2019) provide evidence of a sex-dependent, Inverted-U Curve association between oxytocin levels and social reward. This suggests that females may reach the optimal point at lower doses than males. Importantly, dose-dependent effects may vary between brain regions as significantly reduced amygdala responses to fearful faces were evident across a dose range of 6, 12, and 24 IU IN-OT, while increased striatal responses to happy faces in the striatum were more pronounced for 24 compared to 6 IU in healthy women (Lieberz et al., 2020). In addition to gender, most studies were conducted in European or North American contexts, which limits generalizability across cultures.

Fourth, the effects of oxytocin are not present in all participants, but rather, they often emerge only within specific subpopulations. Some of the included studies, for example, report significant effects only in subjects with specific traits or conditions. These include negative childhood experiences (Feeser et al., 2014; Schwaiger et al., 2019), attachment anxiety (Wang et al., 2020), and autism spectrum traits (Bartz et al., 2010; Spengler et al., 2017). Although only studies involving healthy subjects were included, these subpopulations exhibit mild clinical symptoms. This suggests that individual differences may moderate the behavioral effects of oxytocin. Consequently, findings from such studies cannot easily be generalized to the broader population. Importantly, individual variation may not only moderate the presence or absence of oxytocin effects, but also shift the shape or position of the dose-response curve itself. That is, the "peak" of a potential Inverted-U relationship may vary across individuals, depending on factors such as endogenous oxytocin levels, receptor sensitivity, or hormonal baseline states. This possibility is supported by evidence of substantial inter-individual variability in endogenous oxytocin biology (Martins et al., 2020b), which likely influences sensitivity to exogenous administration.

A meta-analysis was not conducted in this systematic review. This decision was due to substantial heterogeneity among the included studies. The studies differed in terms of design, population characteristics, interventions, outcome measures, and reporting formats. These variations limited the comparability of the data and precluded a meaningful quantitative synthesis. As a result, a narrative synthesis was performed to appropriately summarize the findings. The lack of a meta-analysis is acknowledged as a limitation, as it restricts the ability to statistically pool effect estimates. Similarly, a limitation of Fig. 2 is the exclusion of the standard 24 IU dose, which may constrain broader conclusions about dose-response patterns; however, this decision preserves the figure's exploratory focus on non-standard doses and minimizes interpretational complexity.

4.4. Suggestions for future directions

Recent developments in oxytocin research call for more nuanced interpretations of its effects. While early studies emphasized prosocial outcomes, newer frameworks highlight oxytocin's role as a social salience enhancer rather than a universal prosocial modulator (Shamay-Tsoory and Abu-Akel, 2016). This perspective helps explain inconsistent findings across domains like trust and empathy, particularly when contextual factors such as group dynamics, social threat, or cultural norms are involved (Kogan et al., 2011; Geng et al., 2018a). Oxytocin may also increase social conformity or in-group alignment, even in antisocial contexts, suggesting its effects are more about reinforcing social bonds than moral direction. These outcomes likely depend on individual traits and biological variability, including OXTR distribution, sex-specific signaling, and interactions with other neuropeptides like vasopressin and estradiol. The pharmacokinetics of intranasal administration remain controversial. Although widely used, the degree of central penetration is still debated, with recent multimodal studies (e.g., Martins et al., 2020b; Valstad et al., 2017) offering mixed insights. This uncertainty limits confidence in dose-response interpretations. Finally, the field faces replication challenges, with several well-known effects - such as oxytocin's influence on trust - not consistently reproduced. Meta-scientific critiques (e.g., Nave et al., 2015) and existing meta-analyses (e.g., Shahrestani et al., 2013b) underscore the need for larger samples, transparent methods, and systematic comparisons across doses and populations.

The dose-dependent effects of oxytocin may be partly explained by its ability at higher concentrations to cross-react with vasopressin receptors due to structural similarity (Smith et al., 2019). This cross-activation can lead to effects different from those mediated by oxytocin receptors alone, potentially causing non-linear or unexpected dose-response patterns. Addressing this hypothesis helps clarify the complex mechanisms behind oxytocin's varied outcomes.

Future research should systematically explore a range of doses and administration routes to better elucidate oxytocin's mechanisms of action in social cognition. This includes investigating doses beyond the commonly used standard of 24 IU as well as alternative routes of administration besides intranasal delivery. Moreover, studies should aim to balance sex representation and consider hormonal status as a relevant variable to better understand sex-specific responses to oxytocin administration. In particular, investigations of sex-specific effects of intranasal oxytocin need to control for hormonal contraception, as it has been found to contribute to sex differences in oxytocin effects on striatal responses (Scheele et al., 2013; 2016). This heterogeneity indicates the need for future studies to conduct subgroup analyses to better identify moderators of oxytocin functioning and to clarify individual differences in treatment response. Future studies may also benefit from tailoring doses or interpreting effects relative to individual biological profiles.

Although this review does not find consistent support for an Inverted-U-shaped dose-response relationship, this absence of evidence possibly reflects the limited methodological scope of the existing literature. Most studies included in this review administered a single dose

(typically 24 IU) and few systematically compared multiple doses. As such, current findings do not allow firm conclusions about the shape of the dose-response curve. Nonetheless, the Inverted-U hypothesis remains theoretically plausible, based on broader neuropharmacological models and early studies suggesting stronger effects at intermediate doses. Future research using within-subject or between-group dose-ranging designs is needed to determine whether oxytocin's social-cognitive effects follow a nonlinear pattern or are modulated by other contextual and individual factors.

Due to its role in regulating important aspects of social cognition, such as recognizing emotions, empathy, and trust, oxytocin has been suggested as a potential aid in addressing loneliness (Abu Elheja et al., 2021; Barton et al., 2024). Loneliness is increasingly recognized as a significant public health concern associated with physical and mental health issues (Haihambo et al., 2025; Holt-Lunstad et al., 2015; Morr et al., 2022). Preliminary evidence indicates that chronic loneliness is associated with reduced oxytocinergic responses to positive social interactions (Berger et al., 2024). Evidence suggests that intranasal oxytocin can promote affiliative behaviors, as well as increase trust and empathy, particularly in individuals with a low disposition to trust (Declerck et al., 2020) or individuals experiencing social deficits or high levels of loneliness (Norman et al., 2011; Cardoso et al., 2014). However, recent work by Berger et al. (2024) demonstrated that combining oxytocin administration with a modular group intervention did not significantly augment intervention effects on trait-like loneliness in a randomized controlled trial. Nevertheless, IN-OT significantly facilitated the decrease in state loneliness within sessions and significantly improved positive bonding between the group members. Furthermore, oxytocin's effects depend heavily on social context, personality, and cultural influences; thus, it may not be uniformly beneficial. In some cases, oxytocin can exacerbate social sensitivity or heighten awareness of social threats, especially in individuals with specific personality traits or attachment styles (Barton et al., 2024; Bartz et al., 2011). These findings underscore the need for a personalized medicine approach that integrates individual psychological and biological profiles, including genetic markers and baseline social functioning. Future research should clarify the potential of oxytocin to enhance social cognitive functioning in lonely individuals, which would have important practical implications for clinical research.

5. Conclusion

In conclusion, several studies report that a standard dose of intranasal oxytocin (24 IU) can enhance emotion recognition, particularly for negative emotions, promote empathy in a personality-dependent manner, and increase trust in context-sensitive ways. However, other studies have failed to replicate these effects, highlighting that oxytocin's influence on social cognition is neither universal nor robust across settings. Instead, its effects appear selective and are moderated by individual traits such as gender and personality, as well as situational factors and social expectations. The mixed findings at lower and higher challenge the validity of the Inverted-U-shaped dose–response curve. Future research should move beyond single-dose designs and systematically compare multiple doses, account for baseline biological and psychological variables, and consider individual variability in oxytocin sensitivity. Such work is essential to clarify the mechanisms and boundary conditions of oxytocin's social effects and to inform its potential clinical applications.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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