Psychoneuroendocrinology 132 (2021) 105369

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Review

Intranasal oxytocin administration but not peripheral oxytocin regulates behaviors of attachment insecurity: A meta-analysis

Kejin Zhang [a,b,c,d], Yuhe Fan [a], Rongjun Yu [e], Yajie Tian [a], Jinting Liu [f], Pingyuan Gong [a,b,c,d,*]

[a] College of Life Science, Northwest University, Xi'an 710069, China
[b] Shaanxi Key Laboratory for Animal Conservation, Northwest University, Xi'an 710069, China
[c] College of Medicine, Northwest University, Xi'an 710069, China
[d] Key Laboratory of Resource Biology and Biotechnology in Western China, Ministry of Education, Northwest University, Xi'an 710069, China
[e] Department of Management, School of Business, Hong Kong Baptist University, Hong Kong, China
[f] Research Center of Brain Function and Psychological Science, Shenzhen University, Shenzhen 518060, China

ARTICLE INFO

Keywords:
Attachment dimension
Attachment insecurity
Attachment behavior
Peripheral oxytocin
Intranasal oxytocin administration

ABSTRACT

In light of the roles of oxytocin (OT) in social bonding and interpersonal relationship, studies have examined the roles of OT in human attachment, but by and large previous findings are inconsistent. Here, we conducted - meta-analyses to estimate the associations between peripheral OT level (e.g., blood and salivary OT) and attachment (i.e., attachment dimensions and behaviors of attachment insecurity) and examine the effects of intranasal OT administration on behaviors of attachment insecurity. The analyses indicated that: (1) Peripheral OT level was not significantly associated with attachment dimensions (e.g., attachment anxiety and attachment avoidance) and behaviors of attachment insecurity; (2) intranasal OT administration significantly reduced behaviors of attachment insecurity of neutral contexts, particularly behaviors of attachment avoidance. The findings suggest that intranasal OT administration is an available approach for reducing behaviors of attachment insecurity of interpersonal situations with ambiguous social cues, which implicates suggestions for therapeutic treatments of attachment-related dysfunctions.

1. Introduction

Attachment refers to the psychological system of seeking safety and maintaining proximity to others (Bowlby, 1977), which describes the patterns of close relationships, particularly in times of stress. An individual's attachment style (i.e., one's enduring patterns of thoughts and behaviors of interpersonal relationship) is relatively stable from childhood to adulthood (Belsky, 1997; Bowlby, 1977), which benefits the coherences of self-appraisals on close relationship, one's owe availability, and responsiveness of attachment figures (Belsky, 1997; Bowlby, 1977). Secure attachment style greatly regulates one's behavioral characteristics and social functions such as buffering social stress (Smith et al., 2016) and improving quality of interpersonal relationship (Mikulincer and Shaver, 2009; Wilkinson and Mulcahy, 2010). In the past decades, attachment-based therapy practices have been used for treatments in interpersonal dysfunctions and psychiatric disorders (Diamond, Russon, and Levy, 2016; Shpigel, Diamond, and Diamond, 2012).

Attachment behaviors refer to situational actions that an individual responds to attachment figures in times of need or stress (Ravitz et al., 2010). Attachment behaviors are not always on display, but could be activated by specific events (e.g., dangers and isolations). Thus, attachment behaviors are sensitive to personal characters (i.e., emotional state and memory about frustration of proximity-seeking) and social contexts of interpersonal relationships, in which stress activates attachment system, but personal and contextual factors maybe inhibit one's proximity-seeking responses (Mikulincer, Birnbaum, Woddis, and Nachmias, 2000; Mikulincer, Gillath, and Shaver, 2002). The changeability of attachment behaviors of a given person across situations helps an individual well adapt fast-changing interpersonal interactions. Here, we estimated the relationships between the level of peripheral oxytocin (e.g., blood and salivary OT) and attachment dimensions (i.e., attachment anxiety, attachment avoidance) and behaviors of attachment insecurity and examined the effects of intranasal OT administration on behaviors of attachment insecurity.

Hypothalamic peptide OT deeply grounds in the neuroendocrine

* Correspondence to: College of Life Science, Northwest University, Taibai Ave 229, Xi'an 710069, China.
E-mail addresses: gpy1026@163.com, gpy1026@nwu.edu.cn (P. Gong).

https://doi.org/10.1016/j.psyneuen.2021.105369

Available online 24 July 2021

substrate of attachment. OT regulates diverse social cognitions and interpersonal interactions (Harari-Dahan and Bernstein, 2014; Kemp and Guastella, 2011). For instance, peripheral OT level of blood or saliva is related to the formation and maintenance of social relationships (Algoe, Kurtz, and Grewen, 2017; Gordon, Zagoory-Sharon, Leckman, and Feldman, 2010; Grewen, Girdler, Amico, and Light, 2005; Markova and Siposova, 2019); intranasal administration OT is considered a promising treatment in interpersonal dysfunctions and psychiatric disorders (Bernaerts et al., 2020; Koch et al., 2019; Ramseyer et al., 2020). On the whole, the biological functions of OT in human attachment have been investigated in three ways: (1) Genetic-association studies aim to explore the contributions of oxytocin receptor gene (*OXTR*) to attachment dimensions. For instance, some studies have shown significant relationships between the *OXTR* polymorphisms and attachment dimensions (Monin, Goktas, Kershaw, and DeWan, 2019; Pearce, Wlodarski, Machin, and Dunbar, 2019), while a recent study failed in replicating the relationships (Gong et al., 2020). (2) Hormones-association studies have examined the relationships between peripheral OT level and attachment dimensions or attachment behaviors (Eapen et al., 2014; Feldman et al., 2011; Kohlhoff et al., 2017; Plasencia et al., 2019), which aim to elucidate the relationships between natural OT level and individual differences in attachment. (3) Intranasal OT administration studies have examined OT pharmacological effects on attachment behaviors (Ditzen et al., 2009; Marsh et al., 2012; Riem et al., 2012; Waller et al., 2015; Zhao et al., 2018), which provide potential therapeutic practice of OT for attachment-related dysfunctions.

OT is produced in the hypothalamic nuclei and released into cerebral spinal fluid and blood (Aydin et al., 2019). As a lack of non-invasive access to obtain brain OT measure in humans, no research has directly investigated the relationship between brain OT level and attachment, and thus peripheral OT level is used as a biomarker for examining the relationship between endogenous OT and attachment anxiety (i.e. a pervasive uncertainty about the willingness of attachment figures respond to them). Specifically, four studies indicated a negative correlation between peripheral OT level and attachment anxiety (Eapen et al., 2014; Feldman et al., 2011; Kohlhoff et al., 2017; Plasencia et al., 2019), one study showed a positive correlation (Marazziti et al., 2006), and eight studies failed in detecting any statistically significant effects (Alaerts et al., 2019; Aydin et al., 2019; Baskaran et al., 2017; Ebner et al., 2019; Gordon et al., 2008; Kiss et al., 2011; Schneiderman et al., 2012; Strathearn et al., 2012). Moreover, studies have investigated the link between peripheral OT level and attachment avoidance (i.e., discomfort with psychological intimacy and desire to maintain psychological independence): three studies demonstrated a positive correlation (Kiss et al., 2011; Marazziti et al., 2015; Tops et al., 2007); five studies showed a negative correlation (Baskaran et al., 2017; Eapen et al., 2014; Feldman et al., 2011; Feldman et al., 2007; Kohlhoff et al., 2017); six studies did not detect statistically significant effects (Alaerts et al., 2019; Aydin et al., 2019; Ebner et al., 2019; Gordon et al., 2008; Schneiderman et al., 2012; Serati et al., 2019). Given that only half of the studies detected significant effects, which possibly results from the influences of uncontrolled settings on peripheral OT level and relatively smaller sample sizes, we were unable to draw confirm conclusions.

Studies have extensively investigated the relationships between peripheral OT level and attachment behaviors. However, the findings were mixed. Two studies indicated positive correlations between peripheral OT level and behaviors of attachment insecurity (Daigle et al., 2020; Vittner et al., 2019); seven studies showed negative correlations (Algoe et al., 2017; Atzil et al., 2011; Bick and Dozier, 2010; Gordon et al., 2010; Grewen et al., 2005; Markova and Siposova, 2019; Ulmer-Yaniv et al., 2016); one study reported opposite patterns between females and males (Markova, 2018); and ten studies did not detect any significant relationship (Apter-Levi et al., 2014; Bick et al., 2013; Elmadih et al., 2014; Feldman et al., 2010; Gordon et al., 2017; Grebe et al., 2017; Lebowitz et al., 2017; MacKinnon et al., 2014; Miura et al., 2015; Taylor et al., 2010). Such inconsistencies possibly result from smaller sample sizes, methodological shortcomings in obtaining attachment measures, and unspecific confounders of individual differences (e.g., emotion statement, relationship quality, and educational level).

Intranasal OT administration is an noninvasive method for examining pharmacological effects of exogenous OT on social behaviors (Leng and Ludwig, 2016; Quintana et al., 2021). This approach can spark a greater increase in oxytocin level in the central nervous system via a direct nose-to-brain route as compared with intravenous peripheral oxytocin administration because only a small part of peripheral oxytocin can pass the blood-brain barrier through intravenous administration (Born et al., 2002; Martins et al., 2020; Quintana et al., 2021). A growing number of studies have examined the effects of intranasal OT administration on attachment behaviors. Specifically, seven studies indicated that intranasal OT administration could reduce behaviors of attachment insecurity (Buchheim et al., 2009; Ditzen et al., 2009; Kreuder et al., 2017; Hoge et al., 2014; Marsh et al., 2012; Riem et al., 2012; Zhao et al., 2018), three studies indicated an opposite effect (Ditzen et al., 2013; Riem et al., 2014; Hoge et al., 2014), and ten studies showed that this method has no effect at all (Chen et al., 2015; Cohen et al., 2018; Cohen and Shamay-Tsoory, 2018; Bradley et al., 2019; Flanagan et al., 2018; Naber et al., 2010; Perry et al., 2015; Scheele et al., 2014; Verhees et al., 2020; Wittfoth-Schardt et al., 2012). Overall, intranasal OT squirting experiments showed mixed effects of OT on attachment behaviors. Due to the context-dependent effects of OT on social behaviors (Bartz et al., 2011; Peled-Avron et al., 2020), such discrepancies possibly result from the heterogeneous psychometric properties of attachment behaviors and the diversiform situations in which individuals interacted with attachment figures.

In summary, studies have examined the roles of OT in human attachment, but by and large the findings are inconsistent. To reach clear conclusions, we estimated the roles of OT in attachment with three meta-analyses. First, we investigated the relationships between peripheral OT level and attachment dimensions. Second, we examined the relationships between peripheral OT level and behaviors of attachment insecurity. Finally, we estimated whether intranasal OT administration could modulate situational behaviors of attachment insecurity. Meanwhile, considering that the activation of attachment system greatly depends on social salience of interpersonal events (Belsky, 1997; Mikulincer et al., 2002), we further examined whether the relationships between OT level and behaviors of attachment insecurity are modulated by social contexts of interpersonal interactions.

2. Meta-analyses on the relationships between peripheral OT level and attachment dimensions

2.1. Identification eligible studies

The meta-analysis was performed with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA; Moher et al., 2010). The PRISMA checklist is shown in Supplementary materials. By using databases of the ISI Web of Science, PubMed, MEDLINE, Chinese Science Citation Database, BIOSIS, Derwent Innovations Index, InspecR, KCI-Korean Journal Database, and SciELO Citation Index, two authors independently searched literatures published up to June, 2020 with terms of "peripheral oxytocin, blood oxytocin, salivary oxytocin, urinary oxytocin, or plasma oxytocin" and "separation anxiety, attachment avoidance, dismissing attachment, discomfort with closeness, preoccupation with relationship, disorganized attachment, fearful attachment, attachment insecurity, attachment style, attachment dimension, attachment orientation, or attachment disposition". After a three-step literature screening (Fig. S1 in Supplementary materials), we identified 21 studies with the criteria: (1) Empirical studies to evaluate the relationships between peripheral oxytocin and adult attachment dimensions; (2) and containing statistical information for calculating effect size.

2.2. Systematization on measures of attachment dimensions

Attachment dimensions in these studies were measured with several attachment scales. Considering that attachment insecurity is conceptualized as a relative present of attachment anxiety or attachment avoidance (Ravitz et al., 2010), we systematized the measures of attachment anxiety, attachment avoidance, or both of them as attachment insecurity. Among the studies, five provided the measures of attachment security or attachment insecurity (Alaerts et al., 2019; Baskaran et al., 2017; Jobst et al., 2016; Krause et al., 2018; Samuel et al., 2015), and 16 provided the measures of attachment anxiety (Marazziti et al., 2006; Plasencia et al., 2019; Strathearn et al., 2012; Weisman et al., 2013), attachment avoidance (Feldman et al., 2007; Marazziti et al., 2015; Serati et al., 2019; Tops et al., 2007), or both of them (Aydin et al., 2019; Eapen et al., 2014; Ebner et al., 2019; Feldman et al., 2011; Gordon et al., 2008; Kiss et al., 2011; Kohlhoff et al., 2017; Schneiderman et al., 2012). According to the attachment theory (Paetzold et al., 2015; Ravitz et al., 2010), we treated the measures (attachment anxiety, attachment avoidance, unresolved-disorganized attachment = attachment insecurity, and dismissive attachment = attachment avoidance) of these studies as attachment insecurity (Table S1 in Supplementary materials).

2.3. Statistical analysis

We conducted meta-analysis with the Comprehensive Meta-analyses software (Biostat, Englewood, NJ). To pool the reported statistics in meta-analysis, we transformed the mean and standard deviation (Jobst et al., 2016; Samuel et al., 2015), *t* value and sample size of regression analysis (Plasencia et al., 2019; Serati et al., 2019), and *z* value of Fischer's test (Krause et al., 2018) as *r* values (Table S1 in Supplementary materials). Considering a high heterogeneity of attachment measures, we conducted meta-analysis with random effect model (Cuijpers, 2016), in which heterogeneity was assessed with Cochran's *Q*-statistic and I^2 statistics (Higgins and Thompson, 2002) and publication selection bias was estimated with *Begg's* rank method (Begg and Mazumdar, 1994) and *Egger's* regression test (Egger et al., 1997). Here, we firstly investigated the relationship between OT level and attachment insecurity and then examined the relationships between OT level and attachment dimensions of anxiety and avoidance.

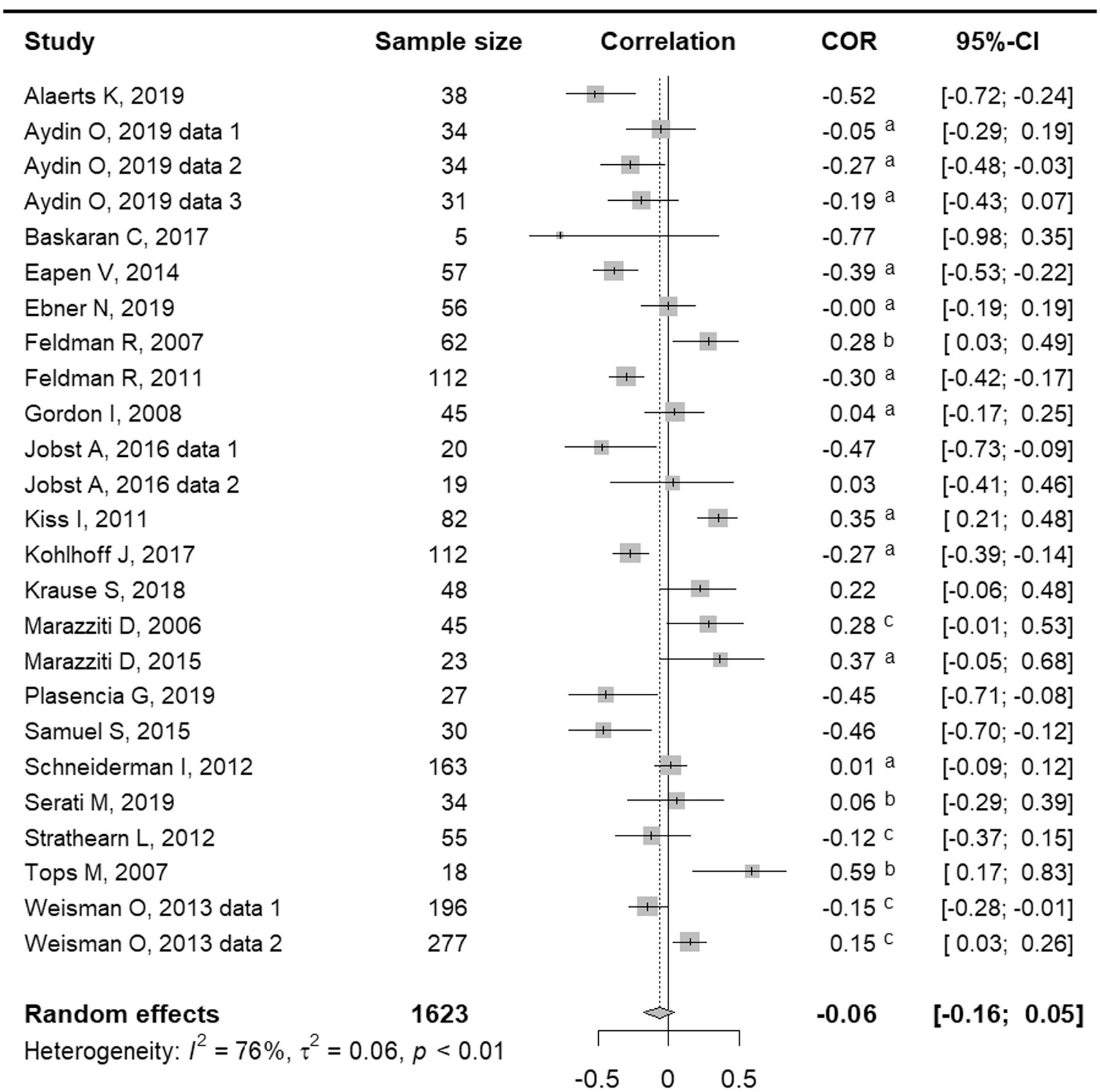

Fig. 1. Relationship between peripheral OT level and attachment insecurity ($r = -0.06$, 95% CI $= -0.16 \sim 0.05$, $z = -1.04$, $p = 0.30$). "a" refferes to attachment insecurity that was calacuted with measures of attachment anxiety and avoidance; "b" refferes to attachment insecurity that was calacuted with measure of attachment avoidance; and "c" refferes to attachment insecurity that was calacuted with measure of attachment anxiety.

2.4. Results

Peripheral OT level was not significantly associated with attachment insecurity ($r = -0.06$, 95% CI $= -0.16 \sim 0.05$, $z = -1.04$, $p = 0.30$; *Begg's* rank test: $tau = 0.08$, $z = 0.56$, $p = 0.58$; *Egger's* regression: $t_{23} = 0.05$, $p = 0.95$; Fig. 1). Sensitivity analysis indicated that the effect sizes after removing any single study ($r = -0.08 \sim -0.04$) did not deviate from the overall 95% CI $= -0.16 \sim 0.05$ (Fig. S2). Furthermore, a meta-analysis indicated that peripheral OT level was not significantly correlated with attachment anxiety ($r = -0.06$, 95% CI $= -0.17 \sim 0.05$, $z = -1.13$, $p = 0.26$; *Begg's* rank test: $tau = -0.07$, $z = 0.37$, $p = 0.71$; *Egger's* regression: $t_{15} = 0.69$, $p = 0.50$; Fig. 2) and attachment avoidance ($r = -0.08$, 95% CI $= -0.23 \sim 0.08$, $z = -0.97$, $p = 0.33$; *Begg's* rank test: $tau = 0.22$, $z = 0.17$, $p = 0.24$; *Egger's* regression: $t_{14} = 0.23$, $p = 0.82$; Fig. 2).

3. Meta-analyses on the relationships between peripheral OT and behaviors of attachment insecurity

3.1. Identification eligible studies

Two authors searched literatures with the terms of "peripheral oxytocin, blood oxytocin, salivary oxytocin, or plasma oxytocin" and "mother-infant bonding, parent-infant contact, parental-infant interaction, parental behavior, affectionate contact, loving touch, parental touch, warm feelings, interpersonal touch, parental responsiveness, maternal affect attunement, interpersonal distance, interpersonal connection, mother-infant synchrony, paternal engagement, infant-mother separation, infant-mother reunion, mother-infant settings, partner interaction, or partners synchrony". Through a three-step literature reviewing (Fig. S3 in Supplementary materials), we identified 20 studies. The PRISMA checklist is shown in Supplementary materials.

3.2. Systematization on behaviors of attachment insecurity

Among the 20 studies, 16 assessed behaviors of mother-infant attachment such as mother-infant interaction and paternal affectionate contact (Apter-Levi et al., 2014; Atzil et al., 2011; Bick and Dozier, 2010; Bick et al., 2013; Daigle et al., 2020; Elmadih et al., 2014; Feldman et al., 2010; Gordon et al., 2017, 2010; Lebowitz et al., 2017; MacKinnon et al., 2014; Markova, 2018; Markova and Siposova, 2019; Miura et al., 2015; Ulmer-Yaniv et al., 2016; Vittner et al., 2019), and four measured behaviors of romantic relationship such as romantic bonding and affectionate contact (Algoe et al., 2017; Grebe et al., 2017; Grewen et al., 2005; Taylor et al., 2010). According to the classic attachment paradigms (Ravitz et al., 2010), including the Strange-situation paradigm (which measures personal distress from separation with caregiver and the signals for resists contact upon caregiver's or immediately calms with contact; Ainsworth et al., 1978), Adult Attachment Interview (which measures parental behaviors of loving, rejecting, neglecting, involving, coherence of discourse, fear of loss, and passive speech; Hesse, 2008), and Current Relationship Interview (which measures partner's behaviors and thinking about attachment-related issues and discourse style; Crowell and Owens, 1996), behaviors of attachment insecurity in these studies were systematized: Negative statement in romantic relationship was directly used as attachment insecurity (Taylor et al., 2010), and positive interpersonal interactions (e.g., parent-infant interaction and constructive communication of romantic couples) of 19 studies were reversely transformed as attachment insecurity (Table S2 in Supplementary materials).

3.3. Statistical analysis

Thirteen studies reported effect sizes as *r* values, and seven studies showed effect sizes as *F* value of repeated-measures ANOVA (Bick and Dozier, 2010; Bick et al., 2013; Lebowitz et al., 2017; Miura et al., 2015), or *t* value of paired *t*-test (Elmadih et al., 2014; Feldman et al., 2010; Grebe et al., 2017). We transformed the effect sizes as *r* values (Table S2 in Supplementary materials). Finally, the effect sizes of 20 studies were pooled in this meta-analysis.

3.4. Results

Peripheral OT level was not significantly associated with behaviors of attachment insecurity ($r = -0.04$, 95% CI $= -0.13 \sim 0.06$, $z = -0.76$, $p = 0.44$; *Begg's* rank test: $tau = 0.20$, $z = 1.53$, $p = 0.12$; *Egger's* regression: $t_{28} = 1.49$, $p = 0.15$; Fig. 3). Sensitivity analysis indicated that the effect sizes after removing any single study ($r = -0.06 \sim -0.02$) did not deviate from overall 95% CI $= -0.13 \sim 0.06$ (Fig. S4). Furthermore, we examined the associations of parental-infant relationship and romantic relationship, respectively. We found that peripheral OT level was not significantly related with behaviors of attachment insecurity of parent-infant ($r = -0.01$, 95% CI $= -0.12 \sim 0.10$, $z = -0.25$, $p = 0.80$) and romantic relationship ($r = -0.11$, 95% CI $= -0.30 \sim 0.09$, $z = -1.05$, $p = 0.29$).

4. Meta-analyses on the effects of intranasal OT administration on behaviors of attachment insecurity

4.1. Identification eligible studies

Two authors searched literatures with the terms of "intranasal oxytocin administration, intranasal oxytocin application, intranasal oxytocin spray, or intranasal oxytocin" and "attachment avoidance, discomfort with closeness, attachment insecurity, avoidant response, warming feeling, warm contact, affectionate contact, interpersonal distance, approachability, interpersonal connection, interpersonal acceptance, parental-infant interaction, or mother-infant synchrony". We further checked registered clinical trials (https://clinicaltrials.gov/ct2/home). One registered trial has been completed (Verhees et al., 2020) and was included in this meta-analysis, and six clinical trials are ongoing or unpublished. We contacted the registers for data, but nobody made response. After a three-step literature screening (Fig. S5 in Supplementary materials), we identified 24 studies. The PRISMA checklist is shown in Supplementary materials.

4.2. Dose of intranasal OT administration

Twenty-two studies were carried out with a single-dose OT administration: 114 administrated 24 unites of OT (Bos et al., 2018; Buchheim et al., 2009; Chen et al., 2015; Cohen et al., 2018; Cohen and Shamay-Tsoory, 2018; Kreuder et al., 2017; Mah et al., 2017; Marsh et al., 2012; Naber et al., 2010; Perry et al., 2015; Riem et al., 2012; Scheele et al., 2014; Waller et al., 2015; Wittfoth-Schardt et al., 2012), five administrated 40 unites of OT (Bradley et al., 2019; Ditzen et al., 2009, 2013; Flanagan et al., 2018; Zhao et al., 2018), and three administrated OT with 30 unites (Hoge et al., 2014), 16 unites (M. M. Riem et al., 2014), or 12 unites (Verhees et al., 2020). Differently, two studies administrated OT with multiple-doses (Bernaerts et al., 2020, 2017). In this meta-analysis, we only included the studies with single-dose OT administration.

4.3. Systematization on behaviors of attachment insecurity

Among the 22 studies, two investigated the changes of attachment behaviors across OT administration with the Adult Attachment Projective Picture System (Buchheim et al., 2009) or the Experience in the Close Relationships questionnaire (Bradley et al., 2019), and 20 measured situational behaviors of attachment insecurity such as maternal responses to infants (Bos et al., 2018; Mah et al., 2017; Marsh et al., 2012; Naber et al., 2010; Riem et al., 2012, 2014; Waller et al., 2015; Wittfoth-Schardt et al., 2012), children's beliefs in maternal

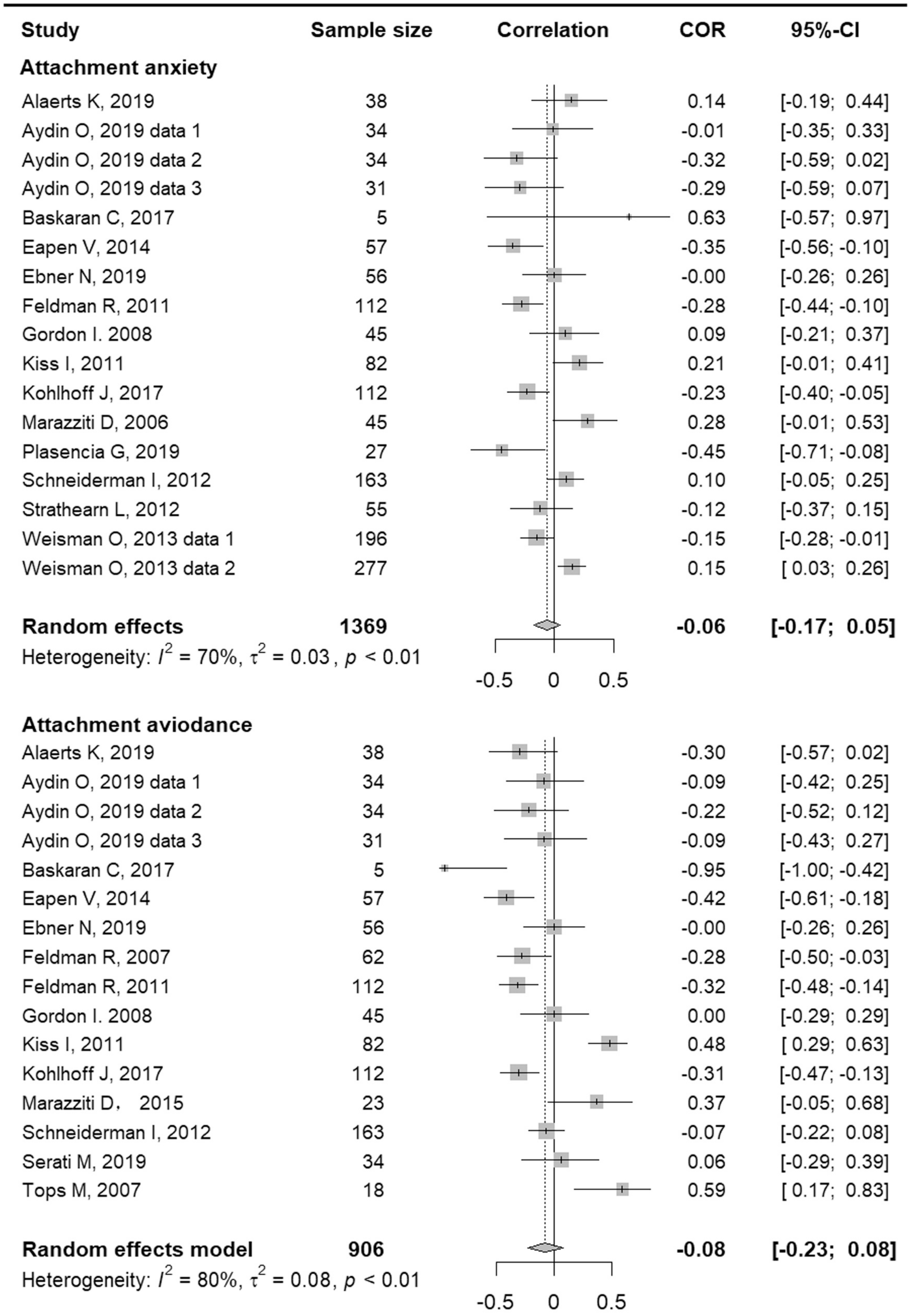

Fig. 2. Relationships between peripheral OT level and attachment anxiety ($r = -0.06$, 95% CI: $-0.17 \sim 0.05$, $z = -1.13$, $p = 0.26$) and attachment avoidance ($r = -0.08$, 95% CI: $-0.23 \sim 0.08$, $z = -0.97$, $p = 0.33$).

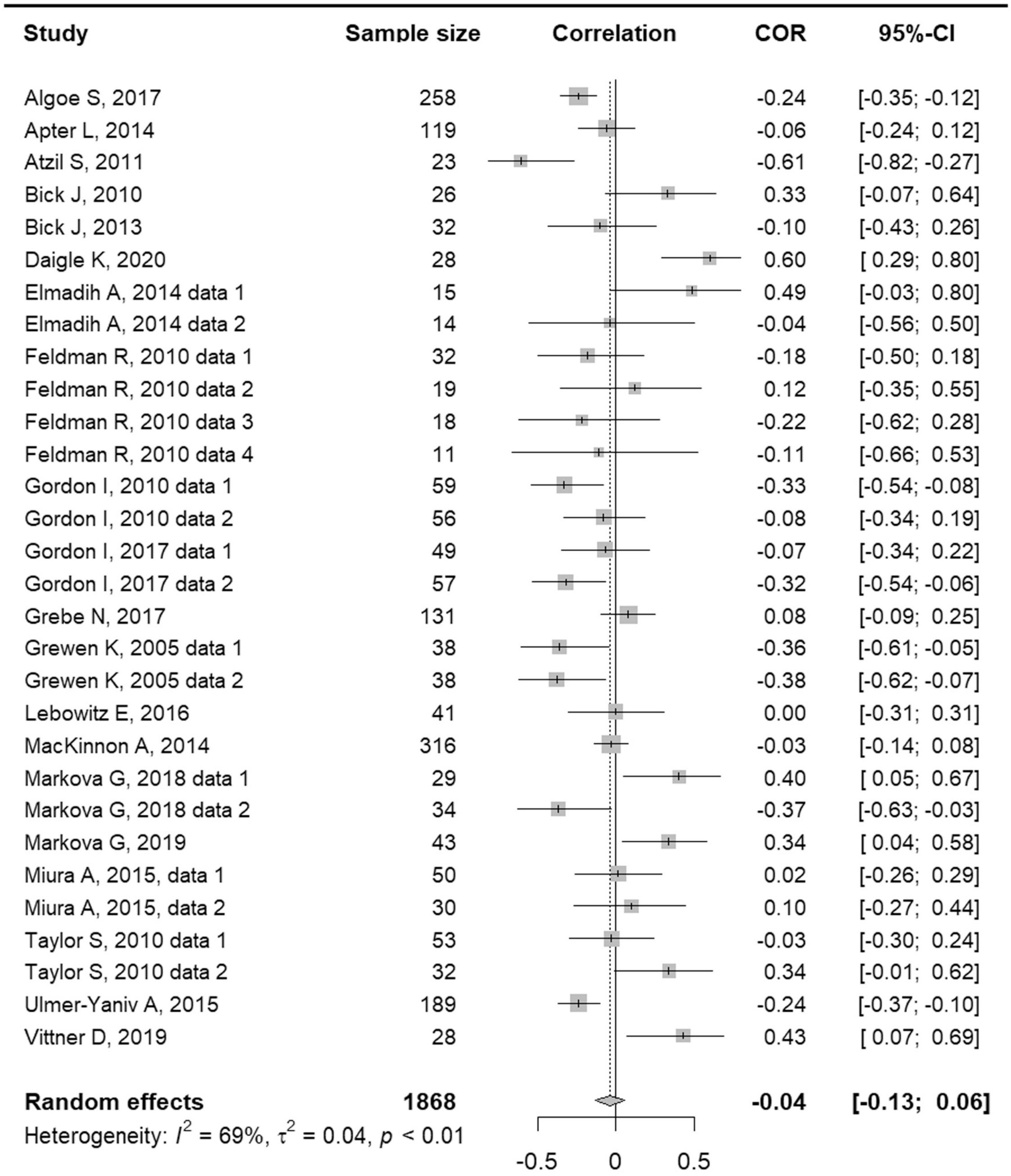

Fig. 3. Relationship between peripheral OT level and behaviors of attachment insecurity ($r = -0.04$, 95% CI $= -0.13 \sim 0.06$, $z = -0.76$, $p = 0.44$).

behaviors (Verhees et al., 2020), adult interpersonal distance (Cohen et al., 2018; Cohen and Shamay-Tsoory, 2018; Hoge et al., 2014; Perry et al., 2015; Zhao et al., 2018), discomfort with other's physical touch (Kreuder et al., 2017; Scheele et al., 2014), likeability for physically formidable men (Chen et al., 2015), and emotional responses of romantic conflicts (Ditzen et al., 2013, 2009; Flanagan et al., 2018). Basing on the attachment measures of the Strange-situation paradigm, Adult Attachment Interview, Adult Attachment Scale, Current Relationship Interview, and Experiences in Close Relationships (Ravitz et al., 2010), the measures of nine studies were directly used as behaviors of attachment insecurity (Bradley et al., 2019; Buchheim et al., 2009; Cohen et al., 2018; Cohen and Shamay-Tsoory, 2018; Ditzen et al., 2013; Flanagan et al., 2018; Perry et al., 2015; Riem et al., 2014; Verhees et al., 2020), and those of 13 studies were inversely scored as behaviors of attachment insecurity (Chen et al., 2015; Ditzen et al., 2009; Hoge et al., 2014; Kreuder et al., 2017; Mah et al., 2017; Marsh et al., 2012; Naber et al., 2010; Riem et al., 2012; Scheele et al., 2014; Waller et al., 2015; Wittfoth-Schardt et al., 2012; Zhao et al., 2018). Similarly, the measures of seven studies were used as behaviors of attachment anxiety (Bradley et al., 2019; Buchheim et al., 2009; Ditzen et al., 2013; Hoge et al., 2014; Riem et al., 2012, 2014; Wittfoth-Schardt et al., 2012; Zhao et al., 2018), those of 11 studies were used as behaviors of attachment avoidance (Bos et al., 2018; Chen et al., 2015; Cohen et al., 2018; Cohen and Shamay-Tsoory, 2018; Ditzen et al., 2009; Kreuder et al., 2017; Marsh et al., 2012; Naber et al., 2010; Perry et al., 2015; Scheele et al., 2014), and two studies provided the both measures (Flanagan et al., 2018; Waller et al., 2015).

4.4. Statistical analysis

Basing on the reported statistics including mean and standard deviation (Chen et al., 2015; Flanagan et al., 2018; Hoge et al., 2014; Verhees et al., 2020), *t* value of regression analysis (Kreuder et al., 2017; Marsh et al., 2012; Riem et al., 2012, 2014; Waller et al., 2015; Zhao et al., 2018), *F* value of ANOVA test (Bos et al., 2018; Cohen et al., 2018; Cohen and Shamay-Tsoory, 2018; Ditzen et al., 2013, 2009; Naber et al., 2010; Perry et al., 2015; Scheele et al., 2014; Wittfoth-Schardt et al., 2012), and *p* value of *t*-test (Bradley et al., 2019; Buchheim et al., 2009; Mah et al., 2017), we transformed such statistics as *r* values (Table S3 in Supplementary materials).

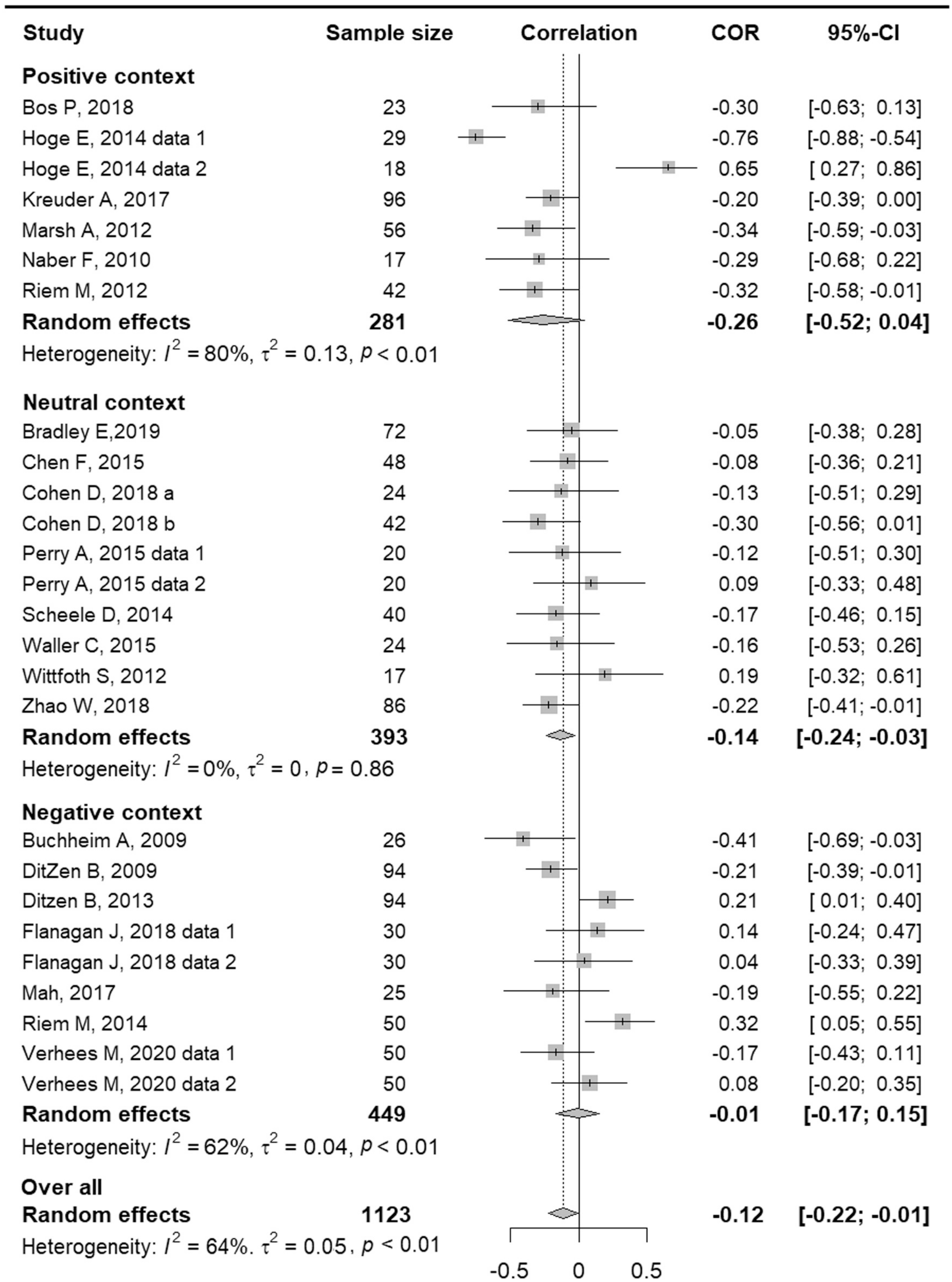

Fig. 4. Effects of intranasal OT adminstration on behaviors of attachment insecurity (Positive context: $r = -0.26$, 95% CI $= -0.52 \sim 0.04$, $z = -1.69$, $p = 0.09$; neutral context: $r = -0.14$, 95% CI $= -0.24 \sim -0.03$, $z = -2.52$, $p = 0.01$; negative context: $r = -0.01$, 95% CI $= -0.17 \sim 0.15$, $z = 0.10$, $p = 0.92$; Overall: $r = -0.12$, 95% CI $= -0.22 \sim -0.01$, $z = -2.12$, $p = 0.03$).

4.5. Results

A meta-analysis showed that OT administration could significantly lessen the behaviors of attachment insecurity ($r = -0.12$, 95% CI $= -0.22 \sim -0.01$, $z = -2.12$, $p = 0.03$; *Begg's* test: *tau* $= 0.07$, $z = 0.51$, $p = 0.61$; *Egger's* regression: $t_{24} = 0.06$, $p = 0.95$; Fig. 4). Sensitivity analysis indicated that the effect sizes after removing any single study ($r = -0.14 \sim -0.09$) did not deviate from the overall 95% CI $= -0.22 \sim -0.01$ (Fig. S6). We further examined whether the effects of OT administration are modulated by social contexts. According to whether the interpersonal situations could elicit strong emotions of individuals or attachment figures, we classified behavioral measures of seven studies into negative context group (e.g., emotional responses to romantic conflicts, emotional responses of listening infant's cry), six studies into positive context group (e.g., pleasantness of partner's touch, cute rating of infants' faces), and nine studies into neutral context group (e.g., calmness of watching infant's faces, likeability rating of friends). A meta-analyses indicated that intranasal OT administration could significantly reduce behaviors of attachment insecurity of neutral context ($r = -0.14$, 95% CI $= -0.24 \sim -0.03$, $z = -2.52$, $p = 0.01$), but not negative context ($r = -0.01$, 95% CI $= -0.17 \sim 0.15$, $z = 0.10$, $p = 0.92$) and positive context ($r = -0.26$, 95% CI $= -0.52 \sim 0.04$, $z = -1.69$, $p = 0.09$). Furthermore, a meta-analysis showed that OT administration significantly reduced behaviors of attachment avoidance

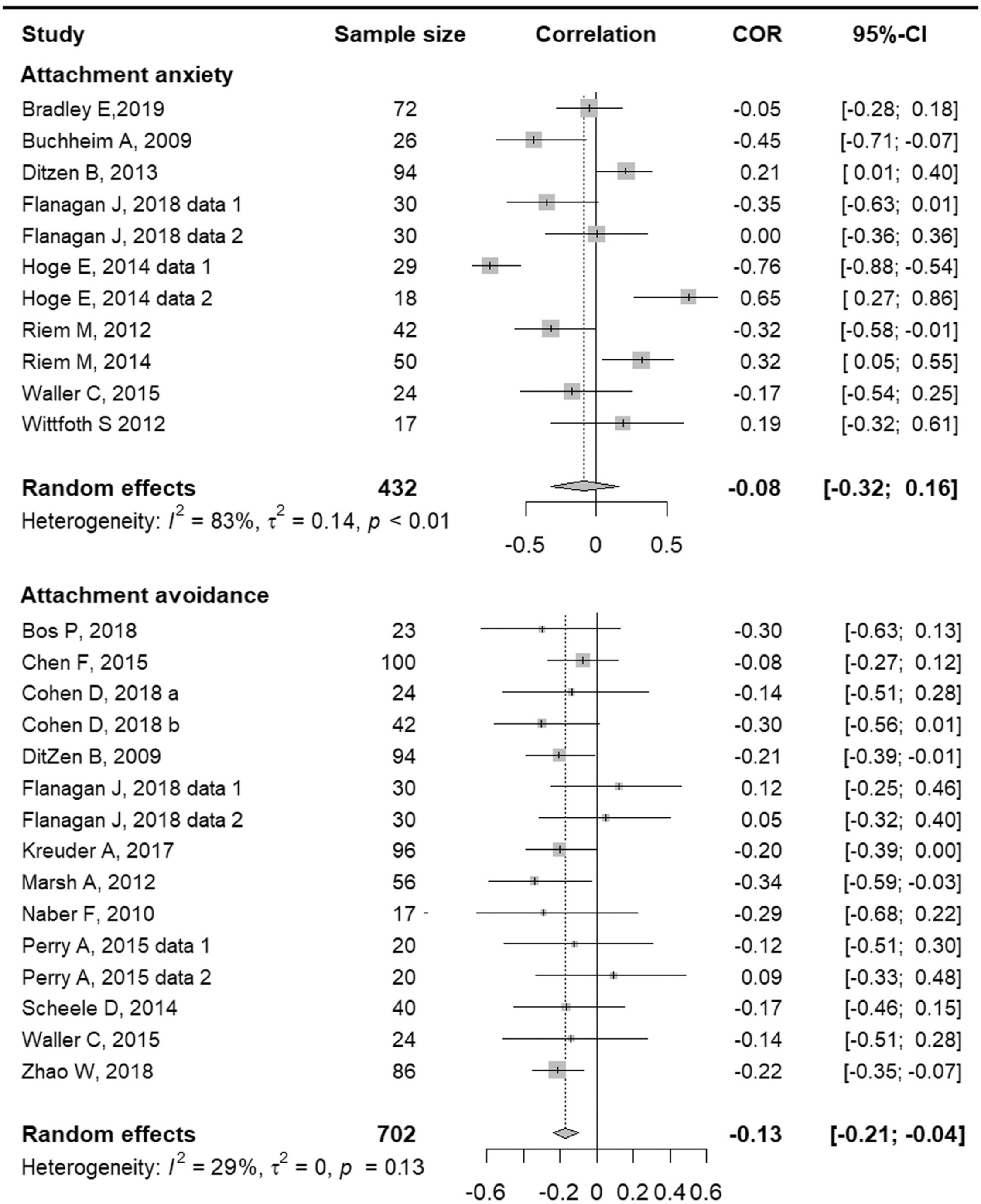

Fig. 5. Effects of intranasal OT administration on behaviors of attachment anxiety ($r = -0.08$, 95% CI $= -0.32 \sim 0.16$, $z = -0.67$, $p = 0.50$) and attachment avoidance ($r = -0.13$, 95% CI $= -0.21 \sim -0.04$, $z = -2.89$, $p < 0.01$).

($r = -0.13$, 95% CI $= -0.21 \sim -0.04$, $z = -2.89$, $p < 0.01$; *Begg's* test: $tau = 0.14$, $z = 0.76$, $p = 0.44$; *Egger's* regression: $t_{14} = 0.12$, $p = 0.91$; Fig. 5), but not behaviors of attachment anxiety ($r = -0.08$, 95% CI $= -0.32 \sim 0.16$, $z = -0.67$, $p = 0.50$; *Begg's* test: $tau = -0.07$, $z = 0.31$, $p = 0.76$, and *Egger's* regression: $t_9 = 0.76$, $p = 0.46$; Fig. 5).

5. Discussion

We estimated the associations between peripheral OT and attachment dimensions and investigated the effects of intranasal OT administration on behaviors of attachment insecurity. The analyses indicated that peripheral OT level is not significantly related to attachment dimensions and situational attachment behaviors, while intranasal OT administration can reduce behaviors of attachment insecurity. The findings suggest that intranasal OT administration but peripheral OT level modulates situational behaviors of attachment insecurity.

Inconsistent with previous studies indicating that peripheral OT level is linked with attachment dimensions (Eapen et al., 2014; Feldman et al., 2011; Kohlhoff et al., 2017; Plasencia et al., 2019; Weisman et al., 2013), our analysis showed that peripheral OT level is not significantly related to attachment dimensions of adults, regardless of the differences in attachment figures. Of note, there are mismatches in the time of OT measuring and attachment experiences, such that peripheral OT measures reflect one's current peripheral OT level, while attachment measures tap one's past attachment experiences (Ravitz et al., 2010). Considering that the peripheral OT measurements could not well reflect one's OT level when individuals are interacting with attachment figures, it may be not an available biomarker. Moreover, OT levels of biological samples (e.g., blood, saliva, and urine) are not significantly correlated (Feldman et al., 2011; McCullough et al., 2013), which possibly results from the differences in the sources of circulating endogenous OT (e.g., blood OT from pituitary gland and salivary OT from salivary glands) and neurobiological significance. The mixture in sample types led to a high heterogeneity in meta-analysis.

Given that peripheral concentration was used as an indirect index for estimating of brain OT concentration, we estimated the associations between OT level and behaviors of attachment insecurity. Against our expectation, peripheral OT is not related to behaviors of attachment insecurity of parental-infant interactions and romantic relationships. In previous studies, situational behaviors such as affectionate contact and warming statement were inversely encoded as behaviors of attachment insecurity (Feldman et al., 2010; Gordon et al., 2010), and peripheral OT level pre or post interpersonal interactions was recorded (Feldman et al., 2010; Gordon et al., 2010). OT level pre interpersonal interaction mainly indexes a baseline of OT level, while OT level post interpersonal interactions is significantly sparked by interpersonal interactions. Given that OT baseline level is influenced by social contextual factors, the level has low power in predicting consequent behaviors. By contrast, the temporary changes of OT levels are more closely related to interpersonal interactions (Grebe et al., 2017; Strathearn et al., 2009), which may be a better index for estimating the relationships between OT functions and attachment behaviors. Of note, only five studies measured the changes of OT level across interpersonal interactions (Daigle et al., 2020; Elmadih et al., 2014; Feldman et al., 2010; Grebe et al., 2017; Lebowitz et al., 2017), but six studies measured OT level of pre-interpersonal interactions (Apter-Levi et al., 2014; Atzil et al., 2011; Bick et al., 2013; Gordon et al., 2010; Grewen et al., 2005; Ulmer-Yaniv et al., 2016), and nine studies measured OT level of post-interpersonal interactions (Algoe et al., 2017; Bick and Dozier, 2010; Gordon et al., 2017; MacKinnon et al., 2014; Markova, 2018; Markova and Siposova, 2019; Miura et al., 2015; Taylor et al., 2019; Vittner, 2019). The mixture in OT level also reduced the analysis power.

Our meta-analysis showed that intranasal OT administration can reduce situational behaviors of attachment insecurity, particularly behaviors of attachment avoidance. As for psychobiological mechanisms, the roles of OT in social motivations possibly contribute to the relief of OT in behaviors of attachment insecurity. According to social approach-avoidance hypothesis, in which OT accounts for social effects through up-regulating approach motivation and down-regulating avoidant motivation (Harari-Dahan and Bernstein, 2014; Kemp and Guastella, 2011), the relief of intranasal OT administration in behaviors of attachment avoidance possibly results from up-regulations of OT on approach motivation and down-regulation of OT on avoidant motivation of individuals in time of stress (Cohen and Shamay-Tsoory, 2018; Harari-Dahan and Bernstein, 2014; Kemp and Guastella, 2011). For neurobiological mechanisms, intranasal OT administration increases OT level in the brain areas (e.g., amygdala, hippocampus, caudate nucleus, ventral striatum, anterior cingulate, inferior frontal gyrus, anterior insula, and superior temporal gyrus) via a direct nose-to-brain route, which in turn acts on central oxytocin receptors to exert its behavioral effects (Born et al., 2002; Martins et al., 2020; Quintana et al., 2021). For instance, studies have indicated that OT administration, on one hand, increases the activities in right posterior superior temporal gyrus in recognizing voice-identity (Borowiak and von Kriegstein, 2020) and the connectivity between hippocampus and bilateral ventral tegmental area in perceiving facial trustworthiness (Teed et al., 2019), on the other hand, reduces the activations in bilateral inferior frontal gyrus in inferring others' emotions (Schmidt et al., 2020) and the activations in amygdala in response to fearful faces (Skvortsova et al., 2020).

The activities of sympathetic nervous system could also mediate the effects of OT administration on social behaviors (Ditzen et al., 2013; Kubzansky et al., 2012; Riem et al., 2020). Intranasal OT administration can lead to a supra-physiologic concentration of OT in peripheral blood (Aydin et al., 2019; Leng and Ludwig, 2016; Neumann et al., 2013), which in turn sparks great reactivity of sympathetic nervous system (Ditzen et al., 2013; Gamer and Buchel, 2012; Norman et al., 2011) and a subsequent functional coupling between paraventricular nucleus and brain regions involving sympathetic branches of the autonomic nervous system (Yee et al., 2016). Accordingly, considering that intranasal administered oxytocin travels both to the brain via the olfactory and to the periphery via highly vascularized nasal cavity, we infer that the regulations of intranasal OT administration on attachment insecurity possibly result from the effects of OT on brain functions and sympathetic nervous system. Of note, the effects of intranasal OT administration greatly depend on the genotypes of oxytocin receptor gene (Feng et al., 2015; Van Cappellen et al., 2016). Considering that the genotypes are fixed characters of an individual, we could control them as variables when investigating the effects of intranasal OT administration on attachment-related behaviors in future study.

Our meta-analysis shows that intranasal OT administration can reduce behaviors of attachment insecurity. Due to the modulations of OT on social behaviors are constrained by social contexts of interpersonal interactions (Bartz et al., 2011), the effects of intranasal OT administration on behaviors of attachment insecurity possibly depend on social salience of interpersonal interactions. Indeed, we found that intranasal OT administration can selectively reduce behaviors of attachment insecurity of neutral contextual interactions. According to the social salience hypothesis (Bartz et al., 2011), we infer that intranasal OT administration possibly makes individuals attend more attachment-related information and better understand other's needs for safety and proximity. In neutral context, due to interpersonal cues are ambiguous, intranasal OT administration maybe amplify one's perception and attention to these cues (Spengler et al., 2017; Wang and Ma, 2020). By contrast, social cues of approach or avoidant behaviors in negative and positive situations are salient. All individuals can well perceive the interpersonal cues and quickly response to others, no matter whether they have received intranasal OT administration. Of note, the emotion valences of such interpersonal situations were not conceptualized as neutral, negative, or positive context by the primary studies themselves. Two of our authors who have over ten years of research experience in field of attachment evaluated the emotion valences, during which we classified interpersonal situations that could not elicit strong emotions into neutral context group. We acknowledged that the neutral context situations did not sound very neutral, and some of them sound more positive. The subjectivity in emotion valence ratings possibly reduced the reliability of our meta-analysis. Overall, these findings implicate a potential therapeutic practice of OT administration for attachment-related dysfunctions (Boris and Renk, 2017; Schroder et al., 2019), in which intranasal OT administration may increase one's attention to ambiguous social cues and differentiates self-appraisals on interpersonal relationship (Bartz et al., 2011). Of note, OT may have divergent effects in psychiatric and healthy populations. Future work should pay more attention to the effects of OT in clinical populations.

Several limitations of the meta-analyses should be noticed. First, considering the effect sizes in several statistic formats, we transformed them as a uniformed format. The statistic differences between original information and transformative values in some studies reduced the reliability of meta-analyses. Second, we treated situational behaviors such as parental behaviors and warm contact as attachment behaviors. Among them, some behaviors (e.g., likeability for physically formidable men) may be not closely related to attachment insecurity. The reliabilities of such behaviors were not well considered in the analysis. Third, primary studies of the meta-analysis did not assess OT level in the brain. Given that only very small amounts of peripherally circulating OT can cross the blood-brain barrier, peripheral OT level has a weak power in indexing brain OT level. Our findings therefore only suggest that peripheral OT level is not associated with human attachment. The roles of brain OT in attachment behaviors should be examined in future work.

6. Conclusions

The meta-analyses reveal that peripheral OT level is not related to attachment insecurity, while intranasal OT administration can reduce behaviors of attachment insecurity of interpersonal interactions with ambiguous social cues.

Acknowledgments

This study was supported by the Ministry of Education of Humanities and Social Science Foundation of China (19YJAZH021) and the National Social Science Fund of China (20BSH165) to Pingyuan Gong.

Declaration of Competing Interests

The authors declare that they have no conflicts of interest with respect to their authorship or the publication of this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105369.

References

Ainsworth, M., Blehar, M.C., Waters, E., Wall, S.N., 1978. Patterns of Attachment: A Psychological Study of the Strange Situation. Lawrence Erlbaum Associates,. https://doi.org/10.4324/9780203758045.

Alaerts, K., Bernaerts, S., Vanaudenaerde, B., Daniels, N., Wenderoth, N., 2019. Amygdala-hippocampal connectivity is associated with endogenous levels of oxytocin and can be altered by exogenously administered oxytocin in adults with autism. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. 4 (7), 655–663. https://doi.org/10.1016/j.bpsc.2019.01.008.

Algoe, S.B., Kurtz, L.E., Grewen, K., 2017. Oxytocin and social bonds: the role of oxytocin in perceptions of romantic partners' bonding behavior. Psychol. Sci. 28 (12), 1763–1772. https://doi.org/10.1177/0956797617716922.

Apter-Levi, Y., Zagoory-Sharon, O., Feldman, R., 2014. Oxytocin and vasopressin support distinct configurations of social synchrony. Brain Res. 1580, 124–132. https://doi.org/10.1016/j.brainres.2013.10.052.

Atzil, S., Hendler, T., Feldman, R., 2011. Specifying the neurobiological basis of human attachment: brain, hormones, and behavior in synchronous and intrusive mothers. Neuropsychopharmacology 36 (13), 2603–2615. https://doi.org/10.1038/npp.2011.172.

Aydin, O., Balikci, K., Tas, C., Unal-Aydin, P., Taneli, F., Esen-Danaci, A., 2019. Assessing the relationship between attachment, parental attitude and plasma oxytocin in schizophrenia patients and their unaffected siblings. Nord. J. Psychiatry 73 (1), 51–57. https://doi.org/10.1080/08039488.2018.1554698.

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. 15 (7), 301–309. https://doi.org/10.1016/j.tics.2011.05.002.

Baskaran, C., Plessow, F., Silva, L., Asanza, E., Marengi, D., Eddy, K.T., Lawson, E.A., 2017. Oxytocin secretion is pulsatile in men and is related to social-emotional functioning. Psychoneuroendocrinology 85, 28–34. https://doi.org/10.1016/j.psyneuen.2017.07.486.

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50 (4), 1088–1101. https://doi.org/10.2307/2533446.

Belsky, J., 1997. Attachment, mating, and parenting: an evolutionary interpretation. Hum. Nat. 8 (4), 361–381. https://doi.org/10.1007/BF02913039.

Bernaerts, S., Boets, B., Bosmans, G., Steyaert, J., Alaerts, K., 2020. Behavioral effects of multiple-dose oxytocin treatment in autism: a randomized, placebo-controlled trial with long-term follow-up. Mol. Autism 11 (1), 6. https://doi.org/10.1186/s13229-020-0313-1.

Bernaerts, S., Prinsen, J., Berra, E., Bosmans, G., Steyaert, J., Alaerts, K., 2017. Long-term oxytocin administration enhances the experience of attachment. Psychoneuroendocrinology 78, 1–9. https://doi.org/10.1016/j.psyneuen.2017.01.010.

Bick, J., Dozier, M., 2010. Mothers' and children's concentrations of oxytocin following close, physical interactions with biological and non-biological children. Dev. Psychobiol. 52 (1), 100–107. https://doi.org/10.1002/dev.20411.

Bick, J., Dozier, M., Bernard, K., Grasso, D., Simons, R., 2013. Foster mother-infant bonding: associations between foster mothers' oxytocin production, electrophysiological brain activity, feelings of commitment, and caregiving quality. Child. Dev. 84 (3), 826–840. https://doi.org/10.1111/cdev.12008.

Boris, N.W., Renk, K., 2017. Beyond reactive attachment disorder: how might attachment research inform child psychiatry practice? Child. Adolesc. Psychiatr. Clin. N. Am. 26 (3), 455–476. https://doi.org/10.1016/j.chc.2017.03.003.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5 (6), 514–516. https://doi.org/10.1038/nn849.

Borowiak, K., von Kriegstein, K., 2020. Intranasal oxytocin modulates brain responses to voice-identity recognition in typically developing individuals, but not in ASD. Transl. Psychiatry 10 (1), 221. https://doi.org/10.1038/s41398-020-00903-5.

Bos, P.A., Spencer, H., Montoya, E.R., 2018. Oxytocin reduces neural activation in response to infant faces in nulliparous young women. Soc. Cogn. Affect. Neurosci. 13 (10), 1099–1109. https://doi.org/10.1093/scan/nsy080.

Bowlby, J., 1977. The making and breaking of affectional bonds: aetiology and psychopathology in the light of attachment theory. Br. J. Psychiatry 130, 201–210. https://doi.org/10.1192/bjp.130.3.201.

Bradley, E.R., Seitz, A., Niles, A.N., Rankin, K.P., Mathalon, D.H., O'Donovan, A., Woolley, J.D., 2019. Oxytocin increases eye gaze in schizophrenia. Schizophr. Res. 212, 177–185. https://doi.org/10.1016/j.schres.2019.07.039.

Buchheim, A., Heinrichs, M., George, C., Pokorny, D., Koops, E., Henningsen, P., Gundel, H., 2009. Oxytocin enhances the experience of attachment security. Psychoneuroendocrinology 34 (9), 1417–1422. https://doi.org/10.1016/j.psyneuen.2009.04.002.

Chen, F.S., Mayer, J., Mussweiler, T., Heinrichs, M., 2015. Oxytocin increases the likeability of physically formidable men. Soc. Cogn. Affect. Neurosci. 10 (6), 797–800. https://doi.org/10.1093/scan/nsu116.

Cohen, D., Perry, A., Mayseless, N., Kleinmintz, O., Shamay-Tsoory, S.G., 2018. The role of oxytocin in implicit personal space regulation: an fMRI study. Psychoneuroendocrinology 91, 206–215. https://doi.org/10.1016/j.psyneuen.2018.02.036.

Cohen, D., Shamay-Tsoory, S.G., 2018. Oxytocin regulates social approach. Soc. Neurosci. 13 (6), 680–687. https://doi.org/10.1080/17470919.2017.1418428.

Crowell, J., & Owens, G. (1996). Current Relationship Interview and scoring system. Unpublished Manuscript.

Cuijpers, P. (2016). Meta-analyses in mental health research. A practical guide. Amsterdam, the Netherlands: Pim Cuijpers Uitgeverij.

Daigle, K.M., Heller, N.A., Sulinski, E.J., Shim, J., Lindblad, W., Brown, M.S., Hayes, M.J., 2020. Maternal responsivity and oxytocin in opioid-dependent mothers. Dev. Psychobiol. 62 (1), 21–35. https://doi.org/10.1002/dev.21897.

Diamond, G., Russon, J., Levy, S., 2016. Attachment-based family therapy: a review of the empirical support. Fam. Process 55 (3), 595–610. https://doi.org/10.1111/famp.12241.

Ditzen, B., Nater, U.M., Schaer, M., La Marca, R., Bodenmann, G., Ehlert, U., Heinrichs, M., 2013. Sex-specific effects of intranasal oxytocin on autonomic nervous system and emotional responses to couple conflict. Soc. Cogn. Affect. Neurosci. 8 (8), 897–902. https://doi.org/10.1093/scan/nss083.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatr. 65 (9), 728–731. https://doi.org/10.1016/j.biopsych.2008.10.011.

Eapen, V., Dadds, M., Barnett, B., Kohlhoff, J., Khan, F., Radom, N., Silove, D.M., 2014. Separation anxiety, attachment and inter-personal representations: disentangling the role of oxytocin in the perinatal period. PLoS One 9 (9), 107745. https://doi.org/10.1371/journal.pone.0107745.

Ebner, N.C., Lin, T., Muradoglu, M., Weir, D.H., Plasencia, G.M., Lillard, T.S., Connelly, J.J., 2019. Associations between oxytocin receptor gene (OXTR) methylation, plasma

oxytocin, and attachment across adulthood. Int. J. Psychophysiol. 136, 22–32. https://doi.org/10.1016/j.ijpsycho.2018.01.008.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629.
Elmadih, A., Wan, M.W., Numan, M., Elliott, R., Downey, D., Abel, K.M., 2014. Does oxytocin modulate variation in maternal caregiving in healthy new mothers? Brain Res. 1580, 143–150. https://doi.org/10.1016/j.brainres.2014.01.020.
Feldman, R., Gordon, I., Schneiderman, I., Weisman, O., Zagoory-Sharon, O., 2010. Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent-infant contact. Psychoneuroendocrinology 35 (8), 1133–1141. https://doi.org/10.1016/j.psyneuen.2010.01.013.
Feldman, R., Gordon, I., Zagoory-Sharon, O., 2011. Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: considering stress and affiliation components of human bonding. Dev. Sci. 14 (4), 752–761. https://doi.org/10.1111/j.1467-7687.2010.01021.x.
Feldman, R., Weller, A., Zagoory-Sharon, O., Levine, A., 2007. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. Psychol. Sci. 18 (11), 965–970. https://doi.org/10.1111/j.1467-9280.2007.02010.x.
Feng, C., Lori, A., Waldman, I.D., Binder, E.B., Haroon, E., Rilling, J.K., 2015. A common oxytocin receptor gene (OXTR) polymorphism modulates intranasal oxytocin effects on the neural response to social cooperation in humans. Genes Brain Behav. 14 (7), 516–525. https://doi.org/10.1111/gbb.12234.
Flanagan, J.C., Fischer, M.S., Nietert, P.J., Back, S.E., Maria, M.M., Snead, A., Brady, K. T., 2018. Effects of oxytocin on cortisol reactivity and conflict resolution behaviors among couples with substance misuse. Psychiatry Res 260, 346–352. https://doi.org/10.1016/j.psychres.2017.12.003.
Gamer, M., Buchel, C., 2012. Oxytocin specifically enhances valence-dependent parasympathetic responses. Psychoneuroendocrinology 37 (1), 87–93. https://doi.org/10.1016/j.psyneuen.2011.05.007.
Gong, P.Y., Wang, Q.H., Liu, J.T., Xi, S.M., Yang, X., Fang, P.P., Zhang, M.F., 2020. The OXTR polymorphisms are not associated with attachment dimensions: a three-approach study. Psychoneuroendocrinology 120, 104780. https://doi.org/10.1016/j.psyneuen.2020.104780.
Gordon, I., Pratt, M., Bergunde, K., Zagoory-Sharon, O., Feldman, R., 2017. Testosterone, oxytocin, and the development of human parental care. Horm. Behav. 93, 184–192. https://doi.org/10.1016/j.yhbeh.2017.05.016.
Gordon, I., Zagoory-Sharon, O., Leckman, J.F., Feldman, R., 2010. Oxytocin and the development of parenting in humans. Biol. Psychiatry 68 (4), 377–382. https://doi.org/10.1016/j.biopsych.2010.02.005.
Gordon, I., Zagoory-Sharon, O., Schneiderman, I., Leckman, J.F., Weller, A., Feldman, R., 2008. Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. Psychophysiology 45 (3), 349–352. https://doi.org/10.1111/j.1469-8986.2008.00649.x.
Grebe, N.M., Kristoffersen, A.A., Grontvedt, T.V., Emery Thompson, M., Kennair, L.E.O., Gangestad, S.W., 2017. Oxytocin and vulnerable romantic relationships. Horm. Behav. 90, 64–74. https://doi.org/10.1016/j.yhbeh.2017.02.009.
Grewen, K.M., Girdler, S.S., Amico, J., Light, K.C., 2005. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom. Med. 67 (4), 531–538. https://doi.org/10.1097/01.psy.0000170341.88395.47.
Harari-Dahan, O., Bernstein, A., 2014. A general approach-avoidance hypothesis of oxytocin: accounting for social and non-social effects of oxytocin. Neurosci. Biobehav. Rev. 47, 506–519. https://doi.org/10.1016/j.neubiorev.2014.10.007.
Hesse, E., 2008. The Adult Attachment Interview: Protocol, method of analysis, and empirical studies. Handbook of Attachment Theory & Research. The Guilford Press, New York.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558. https://doi.org/10.1002/sim.1186.
Hoge, E.A., Anderson, E., Lawson, E.A., Bui, E., Fischer, L.E., Khadge, S.D., Simon, N.M., 2014. Gender moderates the effect of oxytocin on social judgments. Hum. Psychopharmacol. 29 (3), 299–304. https://doi.org/10.1002/hup.2402.
Jobst, A., Padberg, F., Mauer, M.-C., Daltrozzo, T., Bauriedl-Schmidt, C., Sabass, L., Zill, P., 2016. Lower oxytocin plasma levels in borderline patients with unresolved attachment representations. Front. Hum. Neurosci. 10, 125. https://doi.org/10.3339/tnhum.2015.00125.
Kemp, A.H., Guastella, A.J., 2011. The role of oxytocin in human affect: a novel hypothesis. Curr. Dir. Psychol. 20 (4), 222–231. https://doi.org/10.1177/0963721411417547.
Kiss, I., Levy-Gigi, E., Kéri, S., 2011. CD 38 expression, attachment style and habituation of arousal in relation to trust-related oxytocin release. Biol. Psychol. 88 (2–3), 223–226. https://doi.org/10.1016/j.biopsycho.2011.08.005.
Koch, S.B.J., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., Olff, M., 2019. Effects of intranasal oxytocin on distraction as emotion regulation strategy in patients with post-traumatic stress disorder. Eur. Neuropsychopharmacol. 29 (2), 266–277. https://doi.org/10.1016/j.euroneuro.2018.12.002.
Kohlhoff, J., Eapen, V., Dadds, M., Khan, F., Silove, D., Barnett, B., 2017. Oxytocin in the postnatal period: associations with attachment and maternal caregiving. Compr. Psychiat. 76, 56–68. https://doi.org/10.1016/j.comppsych.2017.03.010.
Krause, S., Boeck, C., Gumpp, A.M., Rottler, E., Schury, K., Karabatsiakis, A., Waller, C., 2018. Child maltreatment is associated with a reduction of the oxytocin receptor in peripheral blood mononuclear cells. Front. Psychol. 9, 173. https://doi.org/10.3389/fpsyg.2018.00173.
Kreuder, A.K., Scheele, D., Wassermann, L., Wollseifer, M., Stoffel-Wagner, B., Lee, M.R., Hurlemann, R., 2017. How the brain codes intimacy: The neurobiological substrates of romantic touch. Hum. Brain Mapp. 38 (9), 4525–4534. https://doi.org/10.1002/hbm.23679.
Kubzansky, L.D., Mendes, W.B., Appleton, A.A., Block, J., Adler, G.K., 2012. A heartfelt response: oxytocin effects on response to social stress in men and women. Biol. Psychol. 90 (1), 1–9. https://doi.org/10.1016/j.biopsycho.2012.02.010.
Lebowitz, E.R., Silverman, W.K., Martino, A.M., Zagoory-Sharon, O., Feldman, R., Leckman, J.F., 2017. Oxytocin response to youth-mother interactions in clinically anxious youth is associated with separation anxiety and dyadic behavior. Depress Anxiety 34 (2), 127–136. https://doi.org/10.1002/da.22585.
Leng, G., Ludwig, M., 2016. Intranasal oxytocin: myths and delusions. Biol. Psychiatry 79 (3), 243–250. https://doi.org/10.1016/j.biopsych.2015.05.003.
MacKinnon, A.L., Gold, I., Feeley, N., Hayton, B., Carter, C.S., Zelkowitz, P., 2014. The role of oxytocin in mothers' theory of mind and interactive behavior during the perinatal period. Psychoneuroendocrinology 48, 52–63. https://doi.org/10.1016/j.psyneuen.2014.06.003.
Mah, B.L., Van Ijzendoorn, M.H., Out, D., Smith, R., Bakermans-Kranenburg, M.J., 2017. The effects of intranasal oxytocin administration on sensitive caregiving in mothers with postnatal depression. Child Psychiat. Hum. Dev. 48 (2), 308–315. https://doi.org/10.1007/s10578-016-0642-7.
Marazziti, D., Baroni, S., Giannaccini, G., Catena-Dell'Osso, M., Piccinni, A., Massimetti, G., Dell'Osso, L., 2015. Plasma oxytocin levels in untreated adult obsessive-compulsive disorder patients. Neuropsychobiology 72 (2), 74–80. https://doi.org/10.1159/000438756.
Marazziti, D., Dell'Osso, B., Baroni, S., Mungai, F., Catena, M., Rucci, P., Dell'Osso, L., 2006. A relationship between oxytocin and anxiety of romantic attachment. Clin. Pract. Epidemiol. Ment. Health 2 (1), 28. https://doi.org/10.1186/1745-0179-2-28.
Markova, G., 2018. The games infants play: social games during early mother-infant interactions and their relationship with oxytocin. Front. Psychol. 9, 1041. https://doi.org/10.3389/fpsyg.2018.01041.
Markova, G., Siposova, B., 2019. The role of oxytocin in early mother-infant interactions: variations in maternal affect attunement. Infant. Behav. Dev. 55, 58–68. https://doi.org/10.1016/j.infbeh.2019.03.003.
Marsh, A.A., Yu, H.H., Pine, D.S., Gorodetsky, E.K., Goldman, D., Blair, R.J., 2012. The influence of oxytocin administration on responses to infant faces and potential moderation by OXTR genotype. Psychopharmacology 224 (4), 469–476. https://doi.org/10.1007/s00213-012-2775-0.
Martins, D.A., Mazibuko, N., Zelaya, F., Vasilakopoulou, S., Loveridge, J., Oates, A., Paloyelis, Y., 2020. Effects of route of administration on oxytocin-induced changes in regional cerebral blood flow in humans. Nat. Commun. 11 (1), 1160. https://doi.org/10.1038/s41467-020-14845-5.
McCullough, M.E., Churchland, P.S., Mendez, A.J., 2013. Problems with measuring peripheral oxytocin: can the data on oxytocin and human behavior be trusted? Neurosci. Biobehav. Rev. 37 (8), 1485–1492. https://doi.org/10.1016/j.neubiorev.2013.04.018.
Mikulincer, M., Birnbaum, G., Woddis, D., Nachmias, O., 2000. Stress and accessibility of proximity-related thoughts: exploring the normative and intraindividual components of attachment theory. J. Pers. Soc. Psychol. 78 (3), 509–523. https://doi.org/10.1037/0022-3514.78.3.509.
Mikulincer, M., Gillath, O., Shaver, P.R., 2002. Activation of the attachment system in adulthood: threat-related primes increase the accessibility of mental representations of attachment figures. J. Pers. Soc. Psychol. 83 (4), 881–895. https://doi.org/10.1037/0022-3514.83.4.881.
Mikulincer, M., Shaver, P.R., 2009. An attachment and behavioral systems perspective on social support. J. Soc. Pers. Relatsh. 26 (1), 7–19. https://doi.org/10.1177/0265407509105518.
Miura, A., Fujiwara, T., Osawa, M., Anme, T., 2015. Inverse correlation of parental oxytocin levels with autonomy support in toddlers. J. Child Fam. Stud. 24 (9), 2620–2625. https://doi.org/10.1007/s10826-014-0064-8.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Grp, P., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLos Med. 8 (5), 336–341. https://doi.org/10.1016/j.ijsu.2010.02.007.
Monin, J.K., Goktas, S.O., Kershaw, T., DeWan, A., 2019. Associations between spouses' oxytocin receptor gene polymorphism, attachment security, and marital satisfaction. PLoS One 14 (2), 0213083. https://doi.org/10.1371/journal.pone.0213083.
Naber, F., van Ijzendoorn, M.H., Deschamps, P., van Engeland, H., Bakermans-Kranenburg, M.J., 2010. Intranasal oxytocin increases fathers' observed responsiveness during play with their children: a double-blind within-subject experiment. Psychoneuroendocrinology 35 (10), 1583–1586. https://doi.org/10.1016/j.psyneuen.2010.04.007.
Neumann, I.D., Maloumby, R., Beiderbeck, D.I., Lukas, M., Landgraf, R., 2013. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. Psychoneuroendocrinology 38 (10), 1985–1993. https://doi.org/10.1016/j.psyneuen.2013.03.003.
Norman, G.J., Cacioppo, J.T., Morris, J.S., Malarkey, W.B., Berntson, G.G., Devries, A.C., 2011. Oxytocin increases autonomic cardiac control: moderation by loneliness. Biol. Psychol. 86 (3), 174–180. https://doi.org/10.1016/j.biopsycho.2010.11.006.
Paetzold, R.L., Rholes, W.S., Kohn, J.L., 2015. Disorganized attachment in adulthood: theory, measurement, and implications for romantic relationships. Rev. Gen. Psychol. 19 (2), 146–156. https://doi.org/10.1037/gpr0000042.
Pearce, E., Wlodarski, R., Machin, A., Dunbar, R.I.M., 2019. Correction to Supporting Information for Pearce et al., Variation in the β-endorphin, oxytocin, and dopamine receptor genes is associated with different dimensions of human sociality, 22410-22410 Proc. Natl. Acad. Sci. USA 116 (44), 22410. https://doi.org/10.1073/pnas.1917121116.
Peled-Avron, L., Abu-Akel, A., Shamay-Tsoory, S., 2020. Exogenous effects of oxytocin in five psychiatric disorders: a systematic review, meta-analysis and a personalized

approach through the lens of the social salience hypothesis. Neurosci. Biobehav. Rev. 114, 70–95. https://doi.org/10.1016/j.neubiorev.2020.04.023.

Perry, A., Mankuta, D., Shamay-Tsoory, S.G., 2015. OT promotes closer interpersonal distance among highly empathic individuals. Soc. Cogn. Affect. Neurosci. 10 (1), 3–9. https://doi.org/10.1093/scan/nsu017.

Plasencia, G., Luedicke, J.M., Nazarloo, H.P., Carter, C.S., Ebner, N.C., 2019. Plasma oxytocin and vasopressin levels in young and older men and women: functional relationships with attachment and cognition. Psychoneuroendocrinology 110, 104419. https://doi.org/10.1016/j.psyneuen.2019.104419.

Quintana, D.S., Lischke, A., Grace, S., Scheele, D., Ma, Y.N., Becker, B., 2021. Advances in the field of intranasal oxytocin research: lessons learned and future directions for clinical research. Mol. Psychiatr. 26 (1), 80–91. https://doi.org/10.1038/s41380-020-00864-7.

Ramseyer, F., Ebert, A., Roser, P., Edel, M.A., Tschacher, W., Brune, M., 2020. Exploring nonverbal synchrony in borderline personality disorder: a double-blind placebo-controlled study using oxytocin. Br. J. Clin. Psychol. 59 (2), 186–207. https://doi.org/10.1111/bjc.12240.

Ravitz, P., Maunder, R., Hunter, J., Sthankiya, B., Lancee, W., 2010. Adult attachment measures: a 25-year review. J. Psychosom. Res. 69 (4), 419–432. https://doi.org/10.1016/j.jpsychores.2009.08.006.

Riem, M.M., van, I.M.H., Tops, M., Boksem, M.A., Rombouts, S.A., Bakermans-Kranenburg, M.J., 2012. No laughing matter: intranasal oxytocin administration changes functional brain connectivity during exposure to infant laughter. Neuropsychopharmacology 37 (5), 1257–1266. https://doi.org/10.1038/npp.2011.313.

Riem, M.M., Voorthuis, A., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 2014. Pity or peanuts? Oxytocin induces different neural responses to the same infant crying labeled as sick or bored. Dev. Sci. 17 (2), 248–256. https://doi.org/10.1111/desc.12103.

Riem, M.M.E., Kunst, L.E., Bekker, M.H.J., Fallon, M., Kupper, N., 2020. Intranasal oxytocin enhances stress-protective effects of social support in women with negative childhood experiences during a virtual Trier Social Stress Test. Psychoneuroendocrinology 111, 104482. https://doi.org/10.1016/j.psyneuen.2019.104482.

Samuel, S., Hayton, B., Gold, I., Feeley, N., Carter, C.S., Zelkowitz, P., 2015. Attachment security and recent stressful life events predict oxytocin levels: a pilot study of pregnant women with high levels of cumulative psychosocial adversity. Attach. Hum. Dev. 17 (3), 272–287. https://doi.org/10.1080/14616734.2015.1029951.

Scheele, D., Kendrick, K.M., Khouri, C., Kretzer, E., Schlapfer, T.E., Stoffel-Wagner, B., Hurlemann, R., 2014. An oxytocin-induced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. Neuropsychopharmacology 39 (9), 2078–2085. https://doi.org/10.1038/npp.2014.78.

Schmidt, A., Davies, C., Paloyelis, Y., Meyer, N., De Micheli, A., Ramella-Cravaro, V., Fusar-Poli, P., 2020. Acute oxytocin effects in inferring others' beliefs and social emotions in people at clinical high risk for psychosis. Transl. Psychiatry 10 (1), 203. https://doi.org/10.1038/s41398-020-00885-4.

Schneiderman, I., Zagoory-Sharon, O., Leckman, J.F., Feldman, R., 2012. Oxytocin during the initial stages of romantic attachment: relations to couples' interactive reciprocity. Psychoneuroendocrinology 37 (8), 1277–1285. https://doi.org/10.1016/j.psyneuen.2011.12.021.

Schroder, M., Ludtke, J., Fux, E., Izat, Y., Bolten, M., Gloger-Tippelt, G., Schmid, M., 2019. Attachment disorder and attachment theory -Two sides of one medal or two different coins? Compr. Psychiatry 95, 152139. https://doi.org/10.1016/j.comppsych.2019.152139.

Serati, M., Grassi, S., Redaelli, M., Pergoli, L., Cantone, L., La Vecchia, A., Buoli, M., 2021. Is there an association between oxytocin levels in plasma and pregnant women's mental health?, 1078390319890400 J. Am. Psychiatr. Nurses Assoc. 27, 222–230. https://doi.org/10.1177/1078390319890400.

Shpigel, M.S., Diamond, G.M., Diamond, G.S., 2012. Changes in parenting behaviors, attachment, depressive symptoms, and suicidal ideation in attachment-based family therapy for depressive and suicidal adolescents. J. Marital Fam. Ther. 38, 271–283. https://doi.org/10.1111/j.1752-0606.2012.00295.x.

Skvortsova, A., Veldhuijzen, D.S., de Rover, M., Pacheco-Lopez, G., Bakermans-Kranenburg, M., van, I.M., Evers, A.W.M., 2020. Effects of oxytocin administration and conditioned oxytocin on brain activity: An fMRI study. PLoS One 15 (3), 0229692. https://doi.org/10.1371/journal.pone.0229692.

Smith, N.B., Mota, N., Tsai, J., Monteith, L., Harpaz-Rotem, I., Southwick, S.M., Pietrzak, R.H., 2016. Nature and determinants of suicidal ideation among U.S. veterans: results from the national health and resilience in veterans study. J. Affect. Disord. 197, 66–73. https://doi.org/10.1016/j.jad.2016.02.069.

Spengler, F.B., Schultz, J., Scheele, D., Essel, M., Maier, W., Heinrichs, M., Hurlemann, R., 2017. Kinetics and dose dependency of intranasal oxytocin effects on amygdala reactivity. Biol. Psychiatry 82 (12), 885–894. https://doi.org/10.1016/j.biopsych.2017.04.015.

Strathearn, L., Fonagy, P., Amico, J., Montague, P.R., 2009. Adult attachment predicts maternal brain and oxytocin response to infant cues. Neuropsychopharmacology 34 (13), 2655–2666. https://doi.org/10.1038/npp.2009.103.

Strathearn, L., Iyengar, U., Fonagy, P., Kim, S., 2012. Maternal oxytocin response during mother-infant interaction: associations with adult temperament. Horm. Behav. 61 (3), 429–435. https://doi.org/10.1016/j.yhbeh.2012.01.014.

Taylor, J.H., Carp, S.B., French, J.A., 2019. Vasopressin, but not oxytocin, modulates responses to infant stimuli in marmosets providing care to dependent infants. Dev. Psychobiol. 62 (7), 932–940. https://doi.org/10.1002/dev.21892.

Taylor, S.E., Saphire-Bernstein, S., Seeman, T.E., 2010. Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships? Psychol. Sci. 21 (1), 3–7. https://doi.org/10.1177/0956797609356507.

Teed, A.R., Han, K., Rakic, J., Mark, D.B., Krawczyk, D.C., 2019. The influence of oxytocin and vasopressin on men's judgments of social dominance and trustworthiness: an fMRI study of neutral faces. Psychoneuroendocrinology 106, 252–258. https://doi.org/10.1016/j.psyneuen.2019.04.014.

Tops, M., van Peer, J.M., Korf, J., Wijers, A.A., Tucker, D.M., 2007. Anxiety, cortisol, and attachment predict plasma oxytocin. Psychophysiology 44 (3), 444–449. https://doi.org/10.1111/j.1469-8986.2007.00510.x.

Ulmer-Yaniv, A., Avitsur, R., Kanat-Maymon, Y., Schneiderman, I., Zagoory-Sharon, O., Feldman, R., 2016. Affiliation, reward, and immune biomarkers coalesce to support social synchrony during periods of bond formation in humans. Brain Behav. Immun. 56, 130–139. https://doi.org/10.1016/j.bbi.2016.02.017.

Van Cappellen, P., Way, B.M., Isgett, S.F., Fredrickson, B.L., 2016. Effects of oxytocin administration on spirituality and emotional responses to meditation. Soc. Cogn. Affect. Neurosci. 11 (10), 1579–1587. https://doi.org/10.1093/scan/nsw078.

Verhees, M., van, I.M.H., Bakermans-Kranenburg, M.J., Ceulemans, E., de Winter, S., Santens, T., Bosmans, G., 2020. Combining oxytocin and cognitive bias modification training in a randomized controlled trial: effects on trust in maternal support. J. Behav. Ther. Exp. Psychiatry 66, 101514. https://doi.org/10.1016/j.jbtep.2019.101514.

Vittner, D., Butler, S., Smith, K., Makris, N., Brownell, E., Samra, H., McGrath, J., 2019. Parent engagement correlates with parent and preterm infant oxytocin release during skin-to-skin contact. Adv. Neonatal Care. 19 (1), 73–79. https://doi.org/10.1097/ANC.0000000000000558.

Waller, C., Wittfoth, M., Fritzsche, K., Timm, L., Wittfoth-Schardt, D., Rottler, E., Gundel, H., 2015. Attachment representation modulates oxytocin effects on the processing of own-child faces in fathers. Psychoneuroendocrinology 62, 27–35. https://doi.org/10.1016/j.psyneuen.2015.07.003.

Wang, D., Ma, Y., 2020. Oxytocin facilitates valence-dependent valuation of social evaluation of the self. Commun. Biol. 3 (1), 433. https://doi.org/10.1038/s42003-020-01168-w.

Weisman, O., Zagoory-Sharon, O., Schneiderman, I., Gordon, I., Feldman, R., 2013. Plasma oxytocin distributions in a large cohort of women and men and their gender-specific associations with anxiety. Psychoneuroendocrinology 38 (5), 694–701. https://doi.org/10.1016/j.psyneuen.2012.08.011.

Wilkinson, R.B., Mulcahy, R., 2010. Attachment and interpersonal relationships in postnatal depression. J. Reprod. Infant Psychol. 28 (3), 252–265. https://doi.org/10.1080/02646831003587353.

Wittfoth-Schardt, D., Grunding, J., Wittfoth, M., Lanfermann, H., Heinrichs, M., Domes, G., Waller, C., 2012. Oxytocin modulates neural reactivity to children's faces as a function of social salience. Neuropsychopharmacology 37 (8), 1799–1807. https://doi.org/10.1038/npp.2012.47.

Yee, J.R., Kenkel, W.M., Frijling, J.L., Dodhia, S., Onishi, K.G., Tovar, S., Carter, C.S., 2016. Oxytocin promotes functional coupling between paraventricular nucleus and both sympathetic and parasympathetic cardioregulatory nuclei. Horm. Behav. 80, 82–91. https://doi.org/10.1016/j.yhbeh.2016.01.010.

Zhao, W., Ma, X., Le, J., Ling, A., Xin, F., Kou, J., Kendrick, K.M., 2018. Oxytocin biases men to be more or less tolerant of others' dislike dependent upon their relationship status. Psychoneuroendocrinology 88, 167–172. https://doi.org/10.1016/j.psyneuen.2017.12.010.