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Review article

A meta-analysis of hormone administration effects on cooperative behaviours: Oxytocin, vasopressin, and testosterone

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ABSTRACT

The hormones oxytocin, vasopressin, and testosterone have been implicated in cooperative behaviours and have attracted increasing research interest for their potential to regulate human cooperation in both healthy and clinical populations. However, the behavioural effects of the administration of these hormones remain to be verified. The current analysis included 41 studies involving 3,269 participants with a narrow age range. We examined the administration effects of these hormones on cooperative behaviour and the regulatory effects of individual characteristics, hormone interventions, and task structure and context. Results revealed a moderate positive effect size of oxytocin intranasal administration, a large negative effect size of vasopressin intranasal administration, and nonsignificant effects of testosterone administration on cooperative behaviours. Participants with mental dysfunctions were less sensitive to oxytocin and vasopressin administration. Oxytocin administration was effective in an in-group situation and for initial choices, corroborating a Tit-for-Tat strategy.

1. Introduction

Cooperation is one of the decisive reasons for the prosperity of human social life, providing mutual benefits for survival and development (Lieberman and Eisenberger, 2009; Decety et al., 2004; Bear and Rand, 2016). Cooperation is defined as an interactive behaviour in which people pay costs (e.g., money, time, effort) to benefit others while performing tasks with others or groups (Rand, 2016; Bear and Rand, 2016). Various canonical paradigms have been developed for assessing and quantifying an individual's cooperation in simulated situations, including the prisoner's dilemma game, trust game, ultimatum game, and so on, in which the individuals pay real costs (e.g., monetary costs) to provide real benefits to the other party or groups (Camerer, 2003; Stallen and Sanfey, 2013; Rand, 2016). The performance pattern observed in these experimental tasks is relatively stable over time in adults and can be used as a moderately accurate predictor of real-world social competition and cooperation (Rand, 2016; Glaeser et al., 2000). Moreover, the cooperative behaviours displayed in these social interaction games are regulated by the posterior pituitary and sex hormones, particularly oxytocin, vasopressin, and testosterone (Donaldson and Young, 2008; Caldwell, 2017; Bos et al., 2010). These findings have triggered a surge of empirical research aimed at examining the extent to which administration of these hormones promotes human cooperative behaviours in both healthy and clinical populations.

In this paper, we briefly summarize extant findings on the administration effects of the aforementioned hormones on human cooperation under experimental conditions. Based on these findings, we discuss the need for a synthetic meta-analysis to verify the administration effects of these hormones, investigate their interactive effects and identify biological and environmental factors that regulate these hormonal effects.

Oxytocin, a peptide hormone, is known for its role in attachment and bonding (Insel and Young, 2001), as well as in promoting prosocial cooperative behaviours (e.g., Donaldson and Young, 2008). After intranasal administration of oxytocin, individuals were more likely to exhibit cooperative behaviours compared to those in the placebo administration condition (Kosfeld et al., 2005; De Dreu et al., 2010). Intranasal administration of oxytocin results in an increase in both the willingness to cooperate and the expectation that others will cooperate

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in social interactions (Israel et al., 2012). A previous meta-analytic review found that oxytocin administration enhanced levels of perceived facial trustworthiness and trust choices (Van IJzendoorn and Bakermans-kranenburg, 2012). However, other studies either were unable to confirm the positive effects of oxytocin administration on cooperative behaviours (e.g., Ide et al., 2018; Baumgartner et al., 2008) or observed the opposite effects (Venta et al., 2017). An evolutionary analysis suggested that the partner's group identification played a critical role in determining whether oxytocin administration affects cooperative decisions. In support of this hypothesis, oxytocin administration only affected cooperative interactions between in-group members but not out-group members (De Dreu et al., 2010; Daughters et al., 2017). Another study revealed that oxytocin, as an "in-group hormone", motivates non-cooperation in intergroup conflict to protect vulnerable in-group members (Ten Velden et al., 2017). In addition, oxytocin administration facilitated cooperative behaviours only when the interactive partners were perceived as trustworthy but inhibited cooperative behaviours when the partners were perceived as untrustworthy (*Mikolajczak et al., 2010).

Vasopressin (*arginine vasopressin*) is a neuropeptide hormone known for its negative impact on human prosocial behaviour and its augmenting effects on aggression (Heinrichs et al., 2009; Albers, 2012; Riedl and Javor, 2012; Carter, 2014). A body of studies has suggested an antagonistic relationship between vasopressin and oxytocin in regulating human social interactions. Cooperative behaviours were suppressed after vasopressin administration compared to placebo administration (Donaldson and Young, 2008; Heinrichs and Domes, 2008; Feng et al., 2015b; Chen et al., 2016). For instance, Chen et al. (2016) found that vasopressin administration significantly reduced the number of cooperation choices in a prisoner's dilemma game compared to placebo administration. However, the effects of vasopressin administration appear to be dependent on the type and context of the task. For example, compared to oxytocin administration, vasopressin did not increase cooperation in general but only increased reciprocated cooperation (Rilling et al., 2013). Additionally, participants exhibited decreased risk-taking behaviour after vasopressin intranasal administration when the task was related to personal safety (Patel et al., 2015) but showed no behavioural changes in risk-taking when the task involved monetary payoffs (Brunnlieb et al., 2013).

The administration route of oxytocin and vasopressin of all the studies included in this meta-analysis was intranasal. Despite striking effects of intracerebral oxytocin/vasopressin delivery on animal social behavior, this mode of delivery is impractical for studying human behaviors. Intranasal delivery provides a noninvasive alternative as long as the substance can get into the brain. Earlier research with rats concluded that oxytocin and vasopressin can cross the blood-brain-barrier (BBB) in amounts sufficient to induce neural activities in the brain (Mens et al., 1983). Human studies with intranasal administration have provided evidence that consistent with the idea that intranasal oxytocin/vasopressin can reach the central nervous system and regulate brain activity (Martins et al., 2020; Quintana et al., 2018). Research so far suggests three possible routes for the absorption of intranasally administered neuropeptides into the brain: (1) the olfactory nerve pathway into the olfactory bulb, (2) the trigeminal nerve pathway into the brainstem, and (3) nasal vasculature vessels of blood circulation (Quintana et al., 2015).

Testosterone, a steroid sex hormone, is implicated in aggression and violent behaviours (Book et al., 2001). Given its influence on competition and dominance, testosterone has been thought to be negatively related to prosocial behaviours during interpersonal interactions (Zak et al., 2005, 2009).

One of the potential drawbacks of oxytocin administration is that it makes a person more susceptible to deception and betrayal due to overgeneralized trust. For instance, Baumgartner et al. (2008) found that following oxytocin administration, participants continued to cooperate with an untrustworthy player in a trust game, despite being told that their trust had been breached by the other player. In contrast, participants receiving a placebo decreased their trust in the same trust game situation. It has been argued that testosterone may counterbalance the effects of oxytocin. Testosterone is often viewed as an inhibitor of sociality and is expected to have antagonistic properties compared to oxytocin (Bos et al., 2010).

However, empirical evidence suggests that the effects of testosterone on sociality and trust have been mixed and are susceptible to task characteristics. Although testosterone administration was reported to significantly reduce interpersonal trust compared to the placebo group (Bos et al., 2010), other studies found no effect in response to testosterone administration on cooperative behaviours, including altruism and trust, in several social interaction games (Zethraeus et al., 2009; van Honk et al., 2012). Boksem et al. (2013) found that following testosterone administration, participants invested less in the proposal stage of the ultimate game but exhibited more generosity in the response stage.

Earlier correlational data suggest that testosterone induces aggression and antisocial behaviours (e.g., Dabbs et al., 1995). However, many researchers have questioned this traditional view and argue that testosterone is primarily involved in status-related behaviours and that its antisocial effects are most likely to be observed in challenging social interactions. In other social situations, such as bargaining for monetary payoffs in an ultimatum game, testosterone administration may even have a prosocial effect, which has been empirically supported (Eisenegger et al., 2010).

The above overview identifies three hormones (oxytocin, vasopressin, and testosterone) and their unique administration effects on human sociality. Extant literature shows some significant but inconsistent effects on human competition and cooperation following the administration of these hormones. Thus, a systematic meta-analysis is necessary to verify these effects and identify their boundary conditions.

This analysis aims to integrate the effect sizes of hormone administration.

There is growing interest in the application of these hormones to improve clinical outcomes. A recent review of this line of research provided preliminary evidence that administration of these hormones alleviates certain social dysfunctions, such as borderline personality disorder and autistic disorder (Peled-Avron et al., 2020). However, the causal relationship between the administration effects of these hormones on cooperation has not yet been systematically reviewed with a meta-analysis. Thus, the primary objective of the present study was to determine whether there is a causal link between the administration of hormones and human cooperative behaviour in both healthy and clinical populations.

Our analysis was performed within a three-level framework of behaviour, biology, and environment. With this overarching framework, we intended to sort the behavioural, biological, and environmental factors that regulate the social effects of these three hormones. For each of the three hormones, we examined (1) how hormone administration causally affects cooperative behaviours and (2) the degree to which the effects of hormone administration are dependent upon individual factors (e.g., sex, age, health condition), biological interventions (e.g., administration dose, dose-to-task interval, plasma level, and route of administration), and contextual variables (e.g., group identification, task type, task role, and experimental design). The results of this analysis will help advance our theoretical and practical understanding of hormonal effects on human cooperation.

2. Methods

We conducted this meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Liberati et al., 2009) and the Meta-Analysis of Observational Studies in Epidemiology (Stroup et al., 2000). We registered this protocol on the PROSPERO platform (http://www.crd.york.ac.uk/PROSPERO/, ID: CRD42020159650). The current meta-analysis primarily included the

steps described below.

2.1. Literature search

After conducting preliminary data retrieval, we determined search terms for the hormones and cooperative behaviours. The literature search was conducted using the following search terms and Boolean operators: ("interpersonal interaction" OR "cooperation" OR "trust" OR "altruism") AND ("oxytocin" OR "vasopressin" OR "testosterone") (see Table S1 for details). Second, we searched for relevant articles in peer-reviewed journals published before 2019 from the following electronic databases: Web of Science, SAGE, Elsevier, PubMed, and Wiley (see Table S2 for details).

2.2. Inclusion/exclusion criteria

Our search resulted in 205 records for eligibility screening. The screening process was conducted based on the following criteria: 1) the paper provided statistics for the original results; 2) the experiment involved human participants, 3) experimental manipulations were double-blind with a placebo control, 4) multiple effect sizes contained within a single study were included, provided that they involved independent samples or examined distinct variables of cooperative behavior, and 5) the paper was in English.

Exclusion criteria were as follows: 1) reviews, comments, case reports, and letters to editor, 2) studies involved no human social interactions (i.e., interaction with computers, estimating the trustworthiness of faces), 3) studies examining hormone genotype, and 4) studies reporting results with insufficient information to compute effect sizes.

2.3. Subgroup coding

Two researchers independently coded the articles included in this meta-analysis. The two coders were trained in data coding and meta-analytic procedures. Articles were coded by their title, authors, publication date, the nationality of the participants, sample size, the age and sex of the participants, health condition of the participants, the design of the study, hormone type, administration method (e.g., dose, dose-to-task interval, plasma level, and route of administration), and experimental paradigm (e.g., prisoner's dilemma game, ultimatum game, trust game, etc.), choice iteration (one-shot or multi-shot), group identification (in-group or out-group), task role (e.g., co-operator, trustor, proposer, etc.) (see Table 1). Missing or additional experimental data were requested from the original authors if needed. If two (or more) studies were based on the identical dataset, only one of them was included in the meta-analysis. Discrepancies in coding were resolved by discussion and by reviewing the relevant articles until complete consensus was reached between the two coders.

2.4. Data collection and synthesis

For all coded subgroups, we extracted the means, standard deviations, and sample sizes under hormone and placebo administration conditions. The contrast between the hormone and placebo groups with a double-blind experimental design allowed us to probe the causal effects of hormone administration on human cooperative behaviour.

2.5. Statistical analysis

All statistical meta-analyses were performed using the "*Metafor*" package (Version 2.0, Viechtbauer, 2010) implemented in *R* programming language (Version 3.6.0, R Core Team, 2015). We conducted the meta-analyses using random-effect models to better handle heterogeneity due to differences in the methods and sample characteristics of the included studies. The "*Metafor*" package also allows for inclusion of moderator variables in these models (Borenstein et al., 2009; DerSimonian and Kacker, 2007; Viechtbauer, 2010).

An aggregated effect size (ES) of hormone interventions was calculated as Cohen's *d* using the standard mean difference (and the standard deviation) between hormone administration and placebo administration (control) conditions in the measures of cooperative behaviours. Effect size coefficients with 95 % confidence intervals were regarded as small ($\geq$ 0.20), medium ($\geq$ 0.50), and large ($\geq$ 0.80) (Cohen, 1988). In the meta-analysis, positive effect sizes indicated that cooperative behaviour increases following hormone administration compared to placebo controls, whereas negative effect sizes indicate that cooperative behaviour decreases following hormone administration compared to controls.

Heterogeneity across studies was computed by Cochran's Q statistic and I^2 index. As an index of heterogeneity across studies, a statistically significant Q indicates that the null hypothesis of homogeneity should be rejected; a statistically significant I^2 indicates the percentage of variability in the treatment estimates, which is attributable to heterogeneity between studies rather than sampling errors (Borenstein et al., 2017). In line with Higgins et al. (2003), we regard I^2 values of 25 %, 50 %, and 75 % as low, moderate, and high heterogeneity, respectively.

Quality assessment of each study was independently performed by two graders according to the criteria provided by the Jadad Scale (see Table S3, Jadad et al., 1996; Brouwers et al., 2005) based on the three quality standards (randomization, double-blinding, and descriptions for withdrawals and dropouts). The quality score for each study was the sum of the ratings of each of the three standards on a scale ranging from 0 to 5. The graders' internal consistency coefficient was 0.815 ($p <$ 0.001).

For initial analysis, funnel plots were conducted to visually inspect any potential publication bias based on the symmetry structure of the studies. Furthermore, Egger's test was applied to estimate the risk of publication bias (Egger et al., 1997). Once the risk was detected, a "Fail-Safe N" was calculated to determine the number of unpublished null studies that could invalidate the findings (Orwin, 1983). Moreover, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis (i.e., "one study removed" procedure).

Moderator effects were assessed from three aspects: 1) sample characteristics, including age, sex, and health condition of the participants (healthy or clinical sample); 2) experimental intervention, including hormone type, administration dose, dose-to-task interval, plasma level, and the route of administration; and 3) task characteristics, including experimental paradigm (e.g., trust game or ultimatum game), choice iteration (e.g., one-shot or repeated game), task role (e.g., being a proposer or responder in an ultimatum game, or being a trustor or a trustee in a trust game, see Figure S1 and Table S4), and group identification (e.g., in-group or out-group). In-group *vs*. out-group identification was determined based on the design of the social dilemma games or choice tasks (see Figure S1 for more detailed illustrations and descriptions of the cooperation tasks used in the studies included in the current meta-analysis). For instance, for a resource allocation task, the participant made allocations to his or her local in-group members or members of an unknown out-group. In some studies, the in-group or out-group identification was assigned. Nevertheless, in other studies, in-group members were decision recipients of the same race and nationality, and outgroup members were decision recipients of a different race and nationality.

The impact of categorical moderators (i.e., sex of the participants, mental health conditions, experimental design, choice iteration, group identification, task role, and route of administration) was estimated using subgroup analyses to generate aggregated effect sizes of hormone administration on cooperative behaviour compared to the control condition for each of these variables (see Table 1).

Regarding sex information in the original data provided by each study, included studies can be classified into four different types: females only, males only, both females and males with separate data, and both females and males with aggregated data. Our mediation analysis of

Table 1
The design characteristics of the studies included in the meta-analysis.

	Sample characteristics					Hormone administration				Cooperation task and context				Quality
	Sample size	Population	Mean Age	Sex	Nation	Hormone and Dose	Dose-to-task interval	Plasma level	Route	Experimental task	Role	Group identity	Design	Jadad score
*Mikolajczak et al. (2010)	60	Healthy	21.2	Male	USA	32 IU[a] OT	45 min	NA	Intranasal	One-shot TG	Trustor	NA	Between	2
Kosfeld et al. (2005)	58	Healthy	22	Male	Switzerland	24 IU[a] OT	50 min	NA	Intranasal	One-shot TG	Trustor	NA	Between	4
Klackl et al. (2013)	40	Healthy	23.67	Male	Germany	24 IU[a] OT	40 min	NA	Intranasal	One-shot TG	Trustor	NA	Between	3
Baumgartner et al. (2008)	49	Healthy	21.7	Male	Switzerland	24 IU[a] OT	50 min	NA	Intranasal	One-shot TG	Trustor	NA	Between	4
Yao et al. (2014)	94 (46 F)	Healthy	21.2	Mixed	China	24 IU[a] OT	45 min	NA	Intranasal	One-shot TG	Trustor	NA	Between	4
Yan et al. (2018)	29	Healthy	23.24	Male	China	24 IU[a] OT	35 min	NA	Intranasal	One-shot TG	Trustor	NA	Within	4
Kret and De Dreu (2017)	118 (62 F)	Healthy	22	Female/ Male	Netherlands	24 IU[a] OT	30 min	NA	Intranasal	One-shot TG	Trustor	In/ Outgroup	Between	3
Venta et al. (2017)	46 (32 F)	Healthy	14.43	Mixed	US	24 IU[a] OT	50 min	NA	Intranasal	Iterative TG	Trustor	NA	Between	4
Daughters et al. (2017)	99 (64 F)	Healthy	21.83	Mixed	UK	24 IU[a] OT	30 min	NA	Intranasal	One-shot TG	Trustor	In/ Outgroup	Between	3.5
Ide et al. (2018)	17	Healthy	25.4	Male	US	40 IU[a] OT	60 min	NA	Intranasal	Iterative TG	Trustor	NA	Within	4
Ebert et al. (2013)	13 (10 F)	Healthy	25.7	Mixed	Germany	24 IU[a] OT	30 min	NA	Intranasal	One-shot TG	Trustor	NA	Within	2.5
Ebert et al. (2013)	14 (8 F)	BPD	28.6	Mixed	Germany	24 IU[a] OT	30 min	NA	Intranasal	One-shot TG	Trustor	NA	Within	2.5
De Dreu et al. (2010)	49	Healthy	19.14	Male	Netherlands	24 IU[a] OT	30 min	NA	Intranasal	One-shot PDG	Cooperator	In/ Outgroup	Between	3
Feng et al. (2015)	104	Healthy	20.7	Male	USA	24 IU[a] OT	40 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	3.5
Chen et al. (2016)	203 (100 F)	Healthy	20.7	Female/ Male	USA	24 IU[a] OT	40 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	4
Rilling et al. (2013)	45	Healthy	20.4	Female	USA	24 IU[a] OT	40 min	Y	Intranasal	Iterative PDG	Cooperator	NA	Between	3
Aydogan et al. (2017)	144	Healthy	23.7	Male	US	24 IU[a] OT	50 min	NA	Intranasal	One-shot PDG	Cooperator	NA	Between	3
Ten Velden et al. (2017)	92 (61 F)	Healthy	22.24	Female/ Male	Netherlands	24 IU[a] OT	25 min	NA	Intranasal	Iterative PDG	Cooperator	In/ Outgroup	Between	4
Zheng et al. (2016)	77	Healthy	23.74	Male	China	24 IU[a] OT	45 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	3
Chen et al. (2019)	204 (100 F)	Healthy	20.7	Female/ Male	US	24 IU[a] OT	40 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	4
Declerck et al. (2010)	131 (70 F)	Healthy	20.2	Mixed	Belgium	24 IU[a] OT	30 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	2
Zhu et al. (2019)	100 (50 F)	Healthy	22.35	Female/ Male	China	24 IU[a] OT	30 min	NA	Intranasal	One-shot UG	Responder	NA	Between	3.5
Radke and de Bruijn (2012)	24	Healthy	21.46	Male	Netherlands	24 IU[a] OT	40 min	NA	Intranasal	One-shot UG	Responder	NA	Within	3
Stanton (2007)	68	Health	21.75	Male	USA	40 IU[a] OT	60 min	NA	Intranasal	One-shot UG	Proposer / Responder	NA	Between	2.5
Israel et al. (2012)	24	Healthy	25.48	Male	Israel	24 IU[a] OT	40 min	NA	Intranasal	One-shot NSD	Cooperator	In/ Outgroup	Between	2.5
Bartz et al. (2011)	13 (6 F)	Healthy	35	Mixed	USA	40 IU[a] OT	40 min	NA	Intranasal	Iterative AG	Cooperator	NA	Within	2
Bartz et al. (2011)	14 (10 F)	BPD	35	Mixed	USA	40 IU[a] OT	40 min	NA	Intranasal	Iterative AG	Cooperator	NA	Within	2
Lambert et al. (2017)	30	Healthy	24.0	Female	Belgium	24 IU[a] OT	35 min	NA	Intranasal	One-shot CG	Cooperator	NA	Within	3
Riem et al. (2013)	54	Healthy	19.63	Female	Netherlands	16 IU[a] OT	90 min	NA	Intranasal	Iterative CBG	Cooperator	NA	Between	3
Andari et al. (2010)	26 (4 F)	ASD or HFA	26	Mixed	France	24 IU[a] OT	50 min	Y	Intranasal	Iterative CBG	Cooperator	NA	Within	3
Stanton (2007)	47	Health	21.77	Male	USA	20IU[a] AVP	45 min	NA	Intranasal	One-shot UG	Proposer /Responder	NA	Between	3
Feng et al. (2015)	103	Healthy	20.7	Male	USA	20 IU[a] AVP	40 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	4
Chen et al. (2016)		Healthy	20.7		USA	20 IU[a] AVP	40 min	NA	Intranasal	Iterative PDG	Cooperator	NA	Between	4

(*continued on next page*)

Table 1 (*continued*)

	Sample characteristics					Hormone administration				Cooperation task and context				Quality
	Sample size	Population	Mean Age	Sex	Nation	Hormone and Dose	Dose-to-task interval	Plasma level	Route	Experimental task	Role	Group identity	Design	Jadad score
	203 (101 F)			Female/ Male										
Rilling et al. (2013)	51	Healthy	20.4	Female	USA	20 IU[a] AVP	40 min	Y	Intranasal	Iterative PDG	Cooperator	NA	Between	3
Israel et al. (2012)	48	Healthy	25.48	Male	Israel	20 IU[a] AVP	40 min	NA	Intranasal	One-shot NSD	Cooperator	In/ Outgroup	Between	2
Purushothaman et al. (2020)	27 (8 F)	SCZ	33.07	Mixed	India	40 IU[a] AVP	30 min	NA	Intranasal	Iterative AG	Cooperator	NA	Within	2
Boksem et al. (2013)	54	Healthy	21.6	Female	Netherlands	0.5 mg[a] TES	4.5 h	Y	Sublingually	One-shot TG	Trustor/ Trustee	NA	Between	3
Zethraeus et al. (2009)	134	Healthy	57.5	Female	USA	40 mg/day × 28day[b] TES	12 h	Y	Tablet	One-shot UG/ TG	Responder /Trustor /Trustee	NA	Between	3
Eisenegger et al. (2010)	60	Healthy	25.16	Female	Switzerland	0.5 mg[a] TES	4 h	Y	Sublingually	One-shot UG	Proposer/ Responder	NA	Between	4
Zak et al. (2009)	25	Healthy	20.8	Male	USA	100mg[a] TES	16 h	Y	Cutaneous (shoulders and back)	One-shot UG	Proposer	NA	Within	4.5
Cueva et al (2016)	38	Healthy	22.4	Male	UK	100 mg/day× 3day[b] TES	1−2 h	NA	Cutaneous (shoulders and back)	One-shot UG	Responder	NA	Between	3
Dreher et al. (2016)	40	Healthy	21.25	Male	France	250mg[a] TES	20 h	Y	IM	Iterative UG	Responder	NA	Between	3
Bird et al. (2018)	400	Healthy	22.8	Male	Canada	11 mg[a] TES	1 h	NA	Cutaneous (nose)	One-shot PGG	Cooperator	NA	Within	2

Note. OT = oxytocin; AVP = vasopressin; TES = testosterone; F = female.

[a] Represents the single dose administration.

[b] Represents the multiple dose administration. min (Unit) = minutes; hr (Unit) = hours; BPD = Borderline personality disorder; ASD = Asperger syndrome; HFA = high-functioning autism; SCZ = Schizophrenia; PDG = Prisoner's dilemma game; TG = Trust game; UG = Ultimatum game; PGG = Public goods game; AG = Assurance game; NSD = Nested social dilemma; CBG = Cyber-ball game; IM = Intramuscular injection; Cutaneous = Nasal cutaneous spread (spread the testosterone gel on nostril walls); Design = within or between subject design; within = within subject design; between = between subject design.

sex effects included only the first three types of studies, and dummy coded females as 1 and males as 0.

All categorical moderators were dummy coded when computing their effects using the *factor* function. The relationship between continuous moderators, such as age, dose administration, and dose-to-task interval, and regression coefficients was explored using meta-regression.

3. Results

3.1. Included studies and study characteristics

The screening process is illustrated in Fig. 1. Eligible data were obtained from a total of 3,269 participants (35.5 % females) across 41 articles and 63 independent effect sizes of hormone administration. Sample characteristics are summarized in Table 1. The mean age of participants was 23.9 ± 6.5 years, ranging from 14 to 58. The majority of studies were conducted with healthy participants (n = 3,188). Only four studies were conducted with samples from clinical populations with mental dysfunctions (n = 81).

3.2. Effect sizes and publication bias

3.2.1. Effect sizes

Twenty-eight studies (n = 2,039, 36.9 % females) investigated the effects of intranasal oxytocin administration on cooperative behaviours (see Table 1). Results demonstrated a significant positive effect of oxytocin administration on cooperative behaviours (k = 30, n = 2,039, ES = 0.53, se = 0.25, z = 2.15, p = 0.031, 95 % CI = [0.05 1.02]), although significant heterogeneity was found among studies (Q = 504.46, $p < 0.001$, I^2 = 94.25 %) (see Fig. 2).

Six studies (n = 479, 33.4 % females) investigated the effects of intranasal vasopressin administration on cooperative behaviours (see Table 1). Results showed a significant negative effect of vasopressin administration on cooperative behaviours (k = 6, n = 479, ES = -0.93, se = 0.39, z = -2.41, p = 0.016, 95 % CI = [-1.69−0.17]) with evidence of heterogeneity among studies (Q = 37.62, $p < 0.001$, I^2 = 86.71 %) (see Fig. 3).

Seven studies with healthy samples (n = 751, 33.0 % females) were included in the meta-analysis investigating the effects of testosterone administration on cooperative behaviours (see Table 1). Results showed a nonsignificant negative effect of testosterone on cooperative behaviours (k = 7, n = 751, ES = -0.28, se = 0.32, z = -0.87, p = 0.384, 95 % CI = [-0.89 0.34]) with significant heterogeneity among studies (Q = 40.12, $p < 0.001$, I^2 = 85.04 %) (see Fig. 4).

3.2.2. Publication bias

Visual inspection of the funnel plots revealed that they were roughly centered on mean effect size, indicating the absence of publication bias among studies (see Figures S2, S3, and S4). Indeed, Egger's regression tests for asymmetry of the funnel plots did not approach statistical significance (z (oxytocin) = 0.35, p = 0.730; z (vasopressin) = 1.63, p = 0.103; z (testosterone) = 1.02, p = 0.310). The following sensitivity analyses showed that the above result of no significant publication bias did not change with the removal of any one study. The sensitivity analysis of the oxytocin effects on cooperative behaviours showed that with the removal of any one study, the effect size d remained in the range of 0.46 to 0.65. The sensitivity analysis of the vasopressin effects on cooperative behaviours showed that with the removal of any one study, the effect size d remained in the range of -0.67 to -1.15. The sensitivity analysis of the testosterone effects on cooperative behaviours showed that with the removal of any one study, the effect size d remained in the range of -0.41 to 0.01.

3.2.3. Subgroup categorical analysis: Sex, health condition, choice interaction, experimental design, group identification, task role, and route of administration

To further determine sources of heterogeneity in the overall effect-

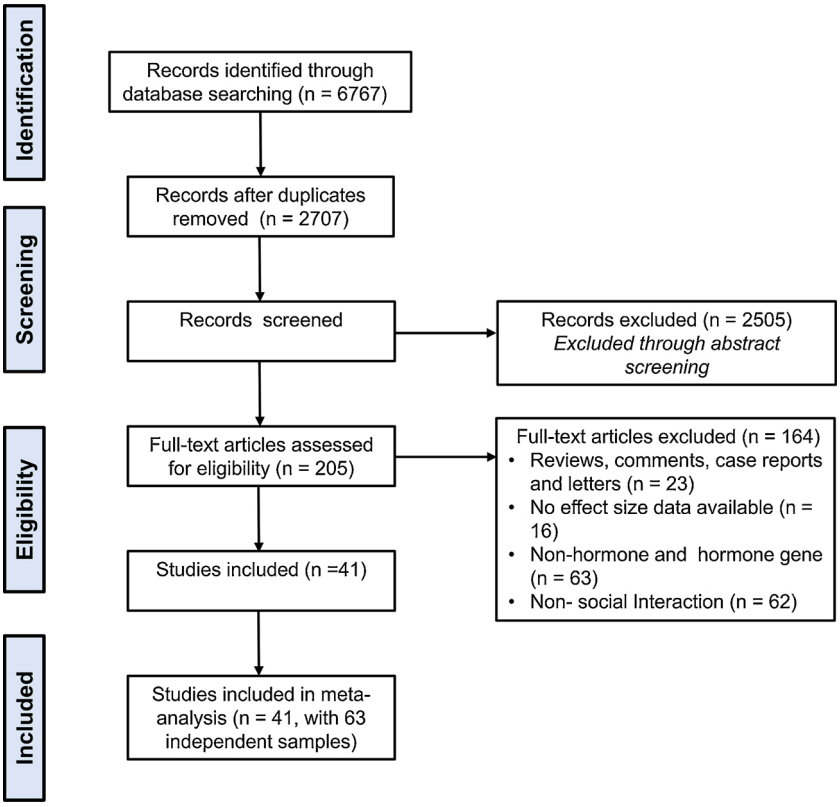

Fig. 1. PRISMA flow chart of the study selection process for the current meta-analysis of hormone administration effects on cooperation behaviours.

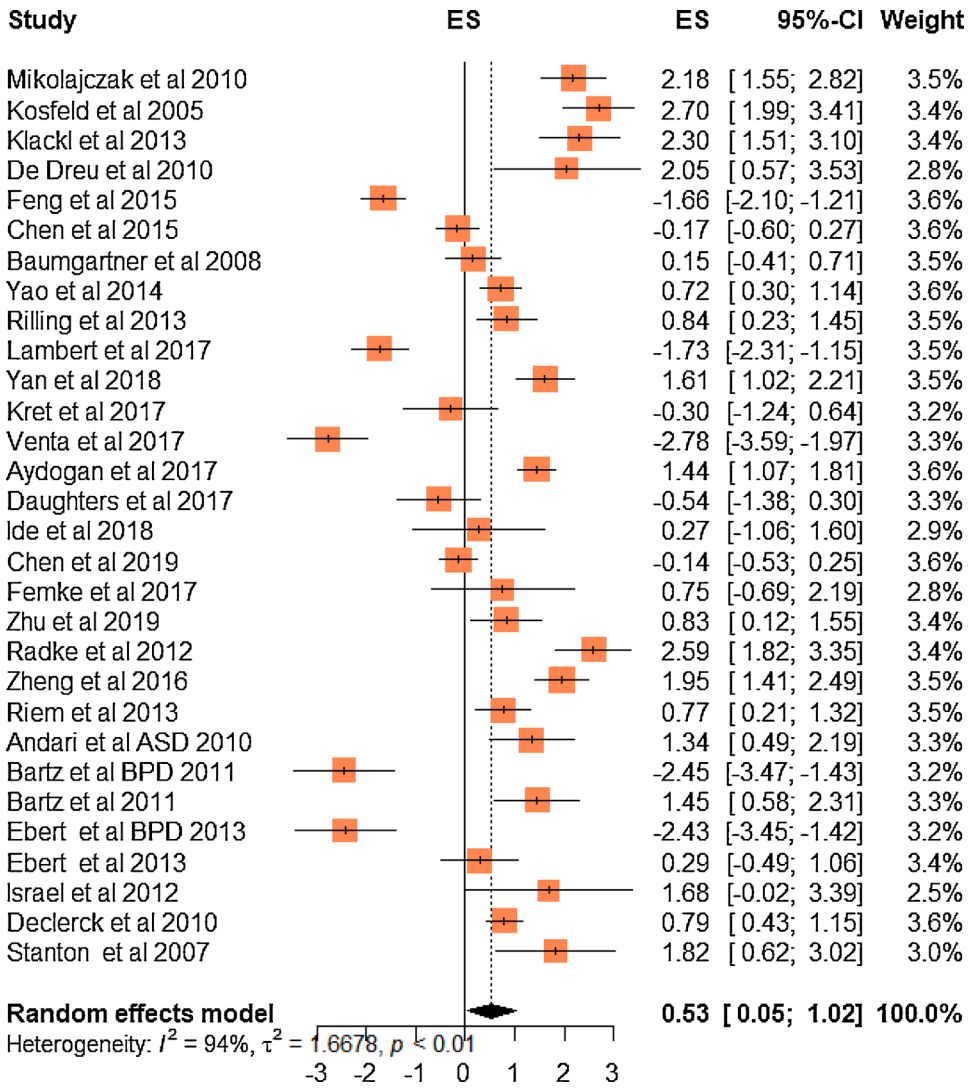

Fig. 2. Effects of oxytocin administration *vs.* placebo on cooperation behaviours. Positive effect sizes indicate improved cooperation following oxytocin administration; negative effect sizes indicate reduced cooperation following oxytocin administration. Box size represents the weighting of the study. The diamond represents the overall effect size and the 95 % confidence intervals.

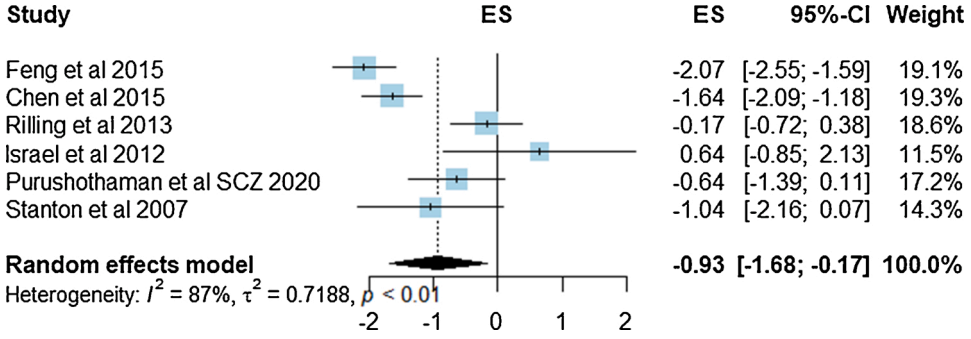

Fig. 3. Effects of vasopressin administration *vs.* placebo on cooperation behaviours. Positive effect sizes indicate improved cooperation following vasopressin administration; negative effect sizes indicate reduced cooperation following vasopressin administration. Box size represents the weighting of the study. The diamond represents the overall effect size and the 95 % confidence intervals.

size analysis, we conducted a series of subgroup analyses to explore the effects of different categorical moderators. Results are shown in Tables 2–4 (also see Table S5). Below, we summarize key findings from these moderator analyses.

3.2.3.1. Sex. Subgroup analysis suggested that the positive effects of oxytocin administration on cooperative behaviour were significant for males (ES = 1.17, p = 0.004), but not females (ES = -0.06, p = 0.867) (see Table 2). The negative effects of vasopressin administration on cooperative behaviour were significant for both males (ES = -1.72, p <

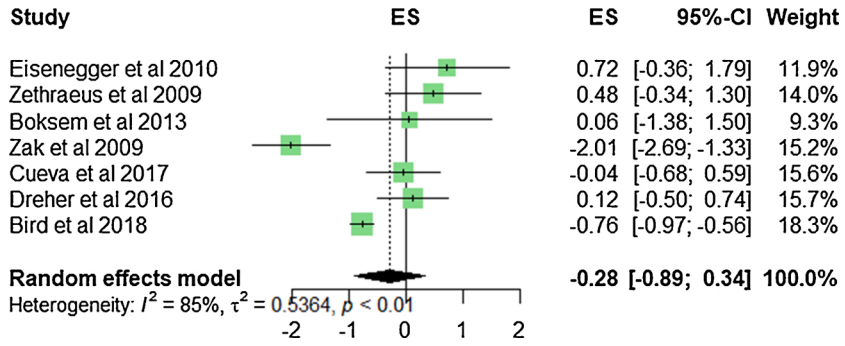

Fig. 4. Effects of testosterone administration *vs.* placebo on cooperation behaviours. Positive effect sizes indicate improved cooperation following testosterone administration; negative effect sizes indicate reduced cooperation following testosterone administration. Box size represents the weighting of the study. The diamond represents the overall effect size and the 95 % confidence intervals.

Table 2
Subgroup analyses of the oxytocin administration effects on cooperative behaviours.

Moderator variables	Sample		Meta-analysis						Heterogeneity		
	k	n	Effect size *d*	se	z	p	95 % CI LL	95 % CI UL	Q statistic	p	I^2 value
Health condition									477.17	<0.001	95.0%
Healthy	27	1,985	0.72	0.28	2.57	**0.010**	0.17	1.26	432.91	<0.001	94.0%
Clinical	3	54	−1.15	0.85	−1.36	0.175	−2.81	0.51	44.26	<0.001	95.5%
Sex									631.61	<0.001	95.9%
Male	18	1,087	1.17	0.38	3.05	**0.002**	0.42	1.93	412.56	<0.001	95.9%
Female	8	502	−0.06	0.39	−0.17	0.867	−0.83	0.70	95.74	<0.001	92.7%
Group identity									219.90	<0.001	95.9%
Ingroup	5	425	1.47	0.60	2.47	**0.014**	0.30	2.65	98.49	<0.001	95.9%
Outgroup	5	425	−0.47	0.44	−1.09	0.277	−1.33	0.38	58.69	<0.001	93.2%
Task									590.39	<0.001	94.9%
TG	12	637	0.37	0.45	0.83	0.406	−0.51	1.25	200.61	<0.001	94.5%
PDG	9	1,049	0.88	0.41	2.12	**0.034**	0.07	1.69	218.60	<0.001	95.9%
UG	3	192	1.74	0.59	2.92	**0.003**	0.57	2.90	10.78	0.005	81.5%
CBG	2	80	0.96	0.27	3.56	**<0.001**	0.43	1.48			
AG	2	27	−0.49	1.95	−0.25	0.677	−4.31	3.33			
CG	1	30	−3.35	0.40	−8.38	**<0.001**	−4.13	−2.57			
NSD	1	24	1.68	0.87	1.94	0.052	−0.02	3.39			
Task role									679.33	<0.001	95.3%
Trustor	12	637	0.28	0.45	0.62	0.533	−0.61	1.17	205.65	<0.001	94.7%
Proposer	1	68	2.43	1.60	1.52	0.130	−0.71	5.58			
Responder	3	192	1.08	1.49	0.72	0.471	−1.85	4.00			
Cooperator	15	1,210	0.51	0.37	1.39	0.165	−0.21	1.23	353.92	<0.001	95.8%
One-shot vs multi-shot game									454.89	<0.001	95.2%
One-shot	17	1,013	0.89	0.36	2.45	**0.014**	0.18	1.60	231.76	<0.001	93.1%
Multi-shot	13	1,026	0.08	0.41	0.18	0.854	−0.73	0.88	223.13	<0.001	94.6%
Within or between-subject design									498.90	<0.001	95.5%
Within	9	180	0.12	0.51	0.24	0.809	−0.88	1.13	164.86	<0.001	95.2%
Between	21	1,859	0.71	0.33	2.13	**0.033**	0.05	1.36	334.04	<0.001	94.0%

Note. The data were analyzed using a random-effect model. Q = Heterogeneity Q statistic. K = the number of independent sampling. n = the number of participants. LL = lower limit, UL = upper limit. Bold suggested the statistical significance level was less than 0.05.

0.001) and females (ES = -1.21, p < 0.001) (see Table 3). The effects of testosterone administration on cooperative behaviour were not significant for either males (ES = -0.67, p = 0.073) or females (ES = 0.48, p = 0.114) (see Table 4). Given the lack of a main effect of sex, more evidence is needed to verify possible moderating effects of sex on the relationship between the administration of oxytocin/vasopressin and cooperative behaviours.

3.2.3.2. Mental health condition (clinical vs. Healthy participants). For oxytocin administration, three studies included participants with borderline personality disorders, Asperger syndrome, or high-functioning autism. Subgroup analysis showed the positive effects of oxytocin administration only in the healthy group (ES = 0.72, p = 0.010) but disappeared in the clinical group (ES = -1.15, p = 0.175). It needs to be mentioned that the sample size of the clinical group was small (n=3), which made this analysis underpowered and its result of no significant oxytocin effects inconclusive. One of the six studies investigated the effects of vasopressin administration on cooperative behaviours, including in participants diagnosed with schizophrenia. The negative effects of vasopressin administration on cooperative behaviours remained in healthy participants (ES = -0.98, p = 0.029) but disappeared in schizophrenic participants (ES = -0.64, p = 0.095).

Table 3
Subgroup analyses of the vasopressin administration effects on cooperative behaviours.

Moderator variables	Sample		Meta-analysis						Heterogeneity		
	K	n	Effect size *d*	se	z	p	95 % CI LL	95 % CI UL	Q statistic	p	I^2 value
Health Condition									37.62	< 0.001	86.7%
Healthy	5	452	−0.98	0.47	−2.18	**0.029**	−1.86	−0.10	34.85	< 0.001	88.5%
Clinical	1	27	−0.64	1.02	−1.67	0.095	−1.39	0.11			
Sex									14.43	0.013	65.3%
Male	4	300	−1.72	0.31	−5.55	**< 0.001**	−2.33	−1.11	7.24	0.065	58.6%
Female	2	152	−1.21	0.22	−5.62	**< 0.001**	−1.64	−0.79			
Task									38.14	<0.001	89.3%
PDG	3	357	−1.30	0.54	−2.41	**0.016**	−2.36	−0.24	27.64	< 0.001	92.8%
NSD	1	48	0.64	0.76	0.84	0.400	−0.85	2.13			
AG	1	27	−0.64	0.38	−1.67	0.100	−1.39	0.11			
UG	1	47	−1.04	0.22	−4.70	**0.001**	−1.48	−0.61			
Task role									38.14	< 0.001	84.3%
Cooperator	5	432	−0.90	0.437	−2.06	**0.040**	−1.76	−0.04	37.50	< 0.001	89.3%
Proposer	1	47	−1.01	0.313	−3.24	**0.001**	−1.62	−0.40			
Responder	1	47	−1.08	0.315	−3.42	**0.001**	−1.69	−0.46			
One-shot vs multi-shot game									37.62	< 0.001	86.7%
One-shot	2	95	−0.28	0.84	−0.33	0.740	−1.92	1.37			
Multi-shot	4	384	−1.15	0.45	−2.58	**0.010**	−2.02	−0.28	31.14	< 0.001	90.4%
Within or between-subject design									37.62	< 0.001	86.7%
Within	1	27	−0.64	1.02	−1.67	0.095	−1.39	0.11			
Between	5	452	−0.98	0.47	−2.18	**0.029**	−1.86	−0.10	34.85	< 0.001	88.5%

Note. The data were analyzed using a random-effect model. Q = Heterogeneity Q statistic. K = the number of independent sampling. n = the number of participants. LL = lower limit, UL = upper limit. Bold suggested the statistical significance level was less than 0.05.

3.2.3.3. Choice iteration. For oxytocin administration, we found that the positive effect of oxytocin on cooperative behaviour was only significant in the one-shot choice situation (ES = 0.89, $p = 0.014$) but not in the multi-shot choice station (ES = 0.08, $p = 0.854$). For vasopressin administration, we found that the negative effect of vasopressin administration on cooperative behaviours was significant in the multi-shot choice situation (ES = -1.15, $p = 0.010$) but not in the one-shot choice station (ES = -0.28, $p = 0.740$). For the testosterone administration, we did not found the significant effects of testosterone on cooperative behaviour neither one-shot (ES = -0.34, $p = 0.341$) nor multi-shot choice (ES = 0.12, $p = 0.706$).

3.2.3.4. Within-subject vs. Between-subject design. Subgroup analyses suggested that the effect of oxytocin administration on within-subject design was not significant positive effects on cooperative behaviour (ES = 0.22, $p = 0.843$), but significant positive effects on between-subject design (ES = 0.69, $p = 0.034$). Also, the effects of vasopressin administration on between-subject design was significant negative effects on cooperative behaviour (ES = -0.98, $p = 0.029$), but not on with-subject design(ES = -0.64, $p = 0.095$). The effects of testosterone administration on within-subject design was significant negative effects on cooperative behaviour (ES = -1.34, $p = 0.031$), but not on between-subject design (ES = 0.20, $p = 0.278$).

3.2.3.5. Group identification. The oxytocin administration had a significant positive effect on cooperative behaviours in an in-group situation (ES = 1.47, $p = 0.014$) but not out-group situation (ES = -0.47, $p = 0.277$). We found only one study with vasopressin administration that tested the moderation effect of group identification on cooperative behaviour and found no significant difference in cooperative behaviours between in-group and out-group conditions (Israel et al., 2012). We found no eligible studies with testosterone administration that would allow a meta-analysis of moderation effects of group identification on cooperative behaviour following hormone administration.

3.2.3.6. Task role. The only situation where oxytocin administration had task role-dependent effects was in the trust game. The positive effects of oxytocin administration on cooperative behaviours were not found in the trustors. There were significant negative effects on cooperative behaviour following vasopressin administration among all task roles. There were significant positive or negative effects of testosterone administration among the trustees (n = 2, ES = 2.42, $p < 0.001$) and cooperators (n =1, ES = -0.76, $p < 0.001$), but not among the trustors, proposer and responder (all $p > 0.05$).

3.2.3.7. Route of administration. As shown in Table 1, all studies on oxytocin and vasopressin administration used the intranasal spray as the administration route. However, different routes of administration were involved in studies with testosterone. Subgroup analysis found that except for **nasal cutaneous spread** (ES = -0.76, $p < 0.001$), the other routes of testosterone administration (including oral medication, shoulders and upper backs cutaneous spread, and intramuscular injection) did not significantly change cooperative behaviour compared to the control condition (all $p > 0.05$).

3.2.4. Subgroup meta-regression analysis: Age, length and dose of administration, and dose-to-task interval

3.2.4.1. Age. The age range was narrow across all included studies in the current meta-analysis (see Table 1). The average age of the participants varied from 19 to 35 years except for one study (Venta et al., 2017, M_{age} = 14y) on oxytocin effects in adolescents. The average age of the participants varied from 20 to 33 years on vasopressin administration effects. The average age of the participants varied from 20 to 25 years except for one study (Zethraeus et al., 2009, M_{age} = 57y) on testosterone administration effects in older adults.

Meta-regression analysis revealed that age was not a significant modulator for the effects of oxytocin administration on cooperative behaviours, k = 30, n = 2,056, β = -0.028, se = 0.07, z = -0.40, $p = 0.689$, 95 % CI = [-0.16 0.11] with significant heterogeneity among the

Table 4
Subgroup analyses of the testosterone administration effects on cooperative behaviours.

Moderator variables	Sample		Meta-analysis						Heterogeneity		
	K	n	Effect size *d*	se	z	p	95 % CI LL	95 % CI UL	Q statistic	p	I^2 value
Healthy	7	751	−0.28	0.32	−0.87	0.38	−0. 90	0.35	40.12	< 0.001	85.0%
Sex									40.13	< 0.001	85.0%
Male	4	503	−0.67	0.37	−1.79	0.073	−1.40	0.06	25.30	< 0.001	88.1%
Female	3	248	0.48	0.30	1.58	0.114	−0.12	1.07	0.51	0.773	0.0%
Administration dose									40.13	<0.001	85.0%
Single	5	579	−0.47	0.40	−0.79	0.240	−1.25	0.31	28.92	< 0.001	86.2%
Chronic	2	172	0.15	0.26	0.59	0.555	−0.35	0.65			
Administration route									40.13	<0.001	85.0%
Oral medication	3	248	0.48	0.30	1.58	0.114	−0.12	1.07	0.51	0.77	0.0%
Cutaneous (shoulders & back)	2	63	−1.02	0.98	−1.04	0.297	−2.95	0.90			
Cutaneous (nose)	1	400	−0.76	0.10	−7.36	**< 0.001**	−0.97	−0.56			
IM	1	40	0.12	0.32	0.38	0.706	−0.50	0.74			
Task									65.55	<0.001	89.3%
TG	2	188	0.82	0.55	1.49	0.135	−0.26	1.89			
UG	5	297	−0.49	0.41	−1.20	0.231	−1.30	0.31	34.23	<0.001	88.3%
PGG	1	400	−0.76	0.10	−7.36	**< 0.001**	−0.97	−0.56			
Task role									375.46	<0.001	97.3%
Trustor	2	188	−1.17	1.87	−0.62	0.532	−4.85	2.50			
Trustee	2	188	2.42	0.72	3.37	**< 0.001**	1.01	3.82			
Proposer	2	85	0.16	2.17	0.07	0.942	−4.08	4.40			
Responder	4	272	−0.49	0.29	−1.72	0.084	−1.05	0.07	13.70	<0.001	78.1%
Cooperator	1	400	−0.76	0.10	−7.36	**< 0.001**	−0.97	−0.56			
One-shot vs multi-shot game									40.13	<0.001	85.1%
One-shot	6	711	−0.34	0.36	−0.95	0.341	−1.05	0.36	34.24	<0.001	85.4%
Multi-shot	1	40	0.12	0.32	0.38	0.706	−0.50	0.74			
Within or between-subject design									40.13	0.017	85.0%
Within	2	425	−1.34	0.62	−2.16	**0.031**	−2.56	−0.12			
Between	5	326	0.20	0.18	1.08	0.278	−0.16	0.55	11.85	<0.001	91.6%

Note. The data were analyzed using a random-effect model. Q = Heterogeneity Q statistic. K = the number of independent sampling. n = the number of participants. LL = lower limit, UL = upper limit. Bold suggested the statistical significance level was less than 0.05.

studies, Q = 500.28, $p < 0.001$, $I^2 = 95.63$ %]. This result remained the same after excluding adolescent samples ((Venta et al., 2017), k = 29, n = 2,010, β = -0.104, se = 0.07, z = -1.52, $p = 0.128$, 95 % CI = [-0.24 0.03]) with significant heterogeneity among studies (Q = 439.36, $p < 0.001$, $I^2 = 94.58$ %]).

Similarly, there were no significant moderating effects of age between vasopressin administration and cooperative behaviours (k = 6, n = 479, β = 0.067, se = 0.09, z = 0.76, $p = 0.447$, 95 % CI = [-0.10 0.24]) with significant heterogeneity among studies (Q = 33.45, $p < 0.001$, $I^2 =$ 88.28 %). There was also no significant moderating effect of age between testosterone administration and cooperative behaviours (k = 7, n =751, β = 0.028, se = 0.03, z = 0.98, $p = 0.325$, 95 % CI = [-0.03 0.08]) with significant heterogeneity among the studies (Q = 31.86, $p < 0.001$, $I^2 = 88.84$ %). After removing the sample with older adults (Zethraeus et al., 2009), the moderation effect of age remained nonsignificant (k = 6, n = 617, β = 0.382, se =0.26, z = 1.47, $p = 0.142$, 95 % CI = [-0.13 0.89]) with the significant heterogeneity among the studies (Q = 28.99, $p < 0.001$, $I^2 = 86.08$ %).

3.2.4.2. Length of administration. Since all the studies involving oxytocin and vasopressin administration used a single dose, the analysis of the effects of the length of administration applied to only the studies of the testosterone administration. The analysis of meta-regression did not find the moderator effect of length of administration between testosterone administration and cooperative behaviours (k = 7, n = 751, β = 0.033, se = 0.04, z = 0.86, $p = 0.390$, 95 % CI = [-0.04 0.11]) with the significant heterogeneity (Q = 31.95, $p < 0.001$, $I^2 = 89.00$ %).

3.2.4.3. Dose of administration. All of the studies of oxytocin and vasopressin effects used single-dose administration. The dose of oxytocin administration ranged from 16 IU to 40 IU. The dose of vasopressin administration ranged from 20 IU to 40 IU. The testosterone administrations included both single-dose and multiple doses, ranging from 0.5 mg to 1120 mg (see Table S6 for further details).

Meta-regression analysis suggested that there were no significant moderating effects of dose of administration between oxytocin administration and cooperative behaviours (k = 30, n = 2,056, β = -0.005, se = 0.05, z = -0.10, $p = 0.924$, 95 % CI = [-0.10 0.09]) with the significant heterogeneity (Q = 503.96, $p < 0.001$, $I^2 = 95.67$ %), and between vasopressin administration and cooperative behaviours (k = 6, n = 479, β = 0.017, se = 0.06, z = 0.30, $p = 0.768$, 95 % CI = [-0.09 0.13]) with the significant heterogeneity (Q = 34.84, $p < 0.001$, $I^2 = 89.45$ %), and also between testosterone administration and cooperative behaviours (k = 7, n =751, β = 0.001, se < 0.01, z = 0.19, $p = 0.851$, 95 % CI = [-0.01 0.01]) with the significant heterogeneity among studies (Q = 33.04, $p < 0.001$, $I^2 = 87.18$ %).

Considering that the dose of testosterone administration included the single administration and chronic administration, we further examined the effects of the single and chronic administration. Both the effects of the single and chronic administration dose were not significant effects on cooperative behaviour ($ES_{single} = -0.47$, p = 0.240; $ES_{chronic} = 0.15$, p = 0.555).

3.2.4.4. Dose-to-task interval. The dose-to-task intervals of oxytocin administration ranged from 25 min to 90 min. The dose-to-task intervals of vasopressin administration ranged from 30 min to 45 min. The dose-to-task intervals of testosterone administration ranged from 1 h to 20 h

(see Table S7 for further details).

Meta-regression analysis revealed that dose-to-task interval was not a significant modulator for the effects of oxytocin administration on cooperative behaviours ((k = 30, n = 2,056, β = 0.022, se = 0.02, z = 0.97, p = 0.334, 95 % CI = [-0.02 0.07]) with the significant heterogeneity (Q = 485.81, p < 0.001, I^2 = 95.41 %), for the effects of vasopressin administration on cooperative behaviours (k = 6, n = 479, β = -0.029, se = 0.10, z = -0.30, p = 0.763, 95 % CI = [-0.21 0.16]) with the significant heterogeneity among the studies (Q = 35.59, p < 0.001, I^2 = 89.66 %), and for the effects of testosterone administration on cooperative behaviours (k = 7, n = 751, β = -0.024, se = 0.05, z = -0.44, p = 0.661, 95 % CI = [-0.13 0.08]) with the significant heterogeneity among the studies (Q = 31.95, p < 0.001, I^2 = 89.00 %).

4. Discussion

The objective of the current meta-analysis was twofold: (1) to determine causal links between three social hormones (oxytocin, vasopressin, and testosterone) and human cooperative behaviours tested in social interaction games and (2) to better understand how hormone-behaviour relationships are regulated by individual factors (e.g., sex, age, health condition), biological variables (e.g., administration dose, dose-to-task interval, plasma level, and route of administration), and cooperation task and contextual variables (e.g., group identification, task type, task role, and experimental design).

4.1. Oxytocin administration and cooperative behaviours

Our analysis revealed that a single dose of intranasal oxytocin administration is sufficient to significantly improve cooperation in the experimental settings of interactive games involving trust, reciprocity, and resource allocation and acquisition (ES = 0.53). Subgroup analyses revealed that the cooperation-enhancing effects of oxytocin were significant in males but not in females (see Table 2). This result is consistent with some previous findings of sex-differentiated brain (the caudate/putamen) reactions to oxytocin underlying increased cooperative behaviours among males (Feng et al., 2015a).

Consistent with the view that oxytocin is an “in-group” hormone (e.g., De Dreu et al., 2010; Daughters et al., 2017; *Mikolajczak et al., 2010), the significant cooperation-enhancing effects of oxytocin administration were found only in the in-group situations but not in out-group situations (see Table 2). The present meta-analysis results support the argument that oxytocin motivates in-group favouritism and benevolent views for in-group members (De Dreu, 2012; De Dreu et al., 2016). Individuals with oxytocin administration cooperate with potentially favored “in-group” members but not with potentially threatening “out-group” members (Olff et al., 2013; Zik and Roberts, 2015; Van Ijzendoorn and Bakermans-Kranenbrug, 2012). From the perspective of group emotion, the reason why the prosocial cooperation effects of oxytocin were regulated by subjective social boundaries might be related to negative emotions triggered by out-group threats (Mackie et al., 2000; Riek et al., 2006). Altnativenatively, the effects of oxytocin are related to a general enhancement in the sensitivity to emotional cues in social situations. For instance, a meta-analysis by Leppanen et al. (2017) shows that a single dose of intranasal oxytocin significantly improved the recognition of both positive and negative basic emotions among healthy individuals.

Interestingly, the positive effect of oxytocin intranasal administration on cooperation was only evident in one-shot games but not in multi-shot games (see Table 2). A key difference between one-shot and multiple-round social dilemma games is the “interaction-based” learning process (Fouragnan et al., 2013). Previous studies have demonstrated that reputation learning is a key process in repeated social dilemma games (Delgado et al., 2005; Fouragnan et al., 2013; Osinsky et al., 2014). Combined with the results of the current meta-analysis, it is conceivable that oxytocin administration is only effective on the initial choice and thus promotes a Tit-for-Tat strategy (i.e., never defect first). Thus, oxytocin does not unconditionally improve cooperation but instead increases the social acuity of the players (Heinrichs et al., 2009).

Consistent with a myriad study, our analysis shows that oxytocin improves cooperation. This meta-analysis further reveals that the cooperation-enhancing effect of oxytocin was evident only in one-shot games, but disappeared in repeated games. This conditional effect of oxytocin indicates a Tit-for-Tat strategy in social interactions (Axelrod and Hamilton, 1981). For the participants using a Tit-for-Tat strategy, they would always begin with cooperation in a one-shot game. In a repeated game, the actions would be contingent upon the other player’s action: either continue to cooperate, if the other also cooperates, or begin to defect, if the other defects. So, if oxytocin were a Tit-for-Tat enhancing hormone, it would promote the choice of cooperation in one-shot games and mixed choices of cooperation and defection in repeated games.

This novel hypothesis was inferred based on indirect evidence and needs further verifications. The postulation that oxytocin serves as a neuroendocrine substrate of the Tit-for-Tat strategy is an important insight we gleaned from the present meta-analytical work. This hypothesis provides a new theoretical direction for future research on oxytocin functionality.

Regarding oxytocin administration, another finding was that participants with mental dysfunctions were not sensitive to oxytocin administration. However, it needs to be noted that the sample size (n = 3) of this analysis was small and involved in different clinical disorders. Thus, it would be premature to derive any conclusion from the finding. Previous studies suggest that the effects of oxytocin are mental condition-specific. For instance, oxytocin administration significantly suppressed cooperative behaviours among the patients with borderline personality disorders (Bartz et al., 2011a,b; Ebert et al., 2013), however, increased the cooperation among the patients with autism spectrum disorders (Andari et al., 2010). Also, the observed insensitivity of clinical populations to intranasal oxytocin administration might be dose-dependent or involve more complicated mechanisms (e.g., receptor insensitivity). Future research should examine possible oxytocinergic deficiencies associated with different mental disorders and dose-response relationships on prosocial behaviours.

4.2. Vasopressin administration and cooperative behaviours

In contrast to the role of oxytocin as a prosocial in-group hormone, a single dose of intranasal vasopressin administration significantly reduced interpersonal cooperation. This effect was only significant in healthy samples but not in clinical participants with schizophrenia (see Table 3). Considering the small sample size (n = 1), the effects of vasopressin administration on schizophrenic patients needs further investigation.

The inhibitory effect of vasopressin administration on cooperative behaviours suggests that sociality is regulated via a balance between the genetically and structurally related oxytocin and vasopressin. While oxytocin promotes interpersonal cooperation, vasopressin boosts interpersonal competition. Vasopressin is critical for social adaptations in a hostile environment and has been implicated in the behaviour profile associated with pair-bonding, maternal defense, and attachment to kith and kin (Carter, 2014).

The antisocial effects of vasopressin were prominent in multi-shot games but not in one-shot games (see Table 3). In contrast to oxytocin, which promotes in-group cooperation, the social competition augmented by vasopressin is more prominent in situations of repeated interpersonal interactions rather than one-time encounters.

4.3. Testosterone administration and cooperative behaviours

The overall effect of testosterone on cooperative behaviours was not significant (ES = -0.28). However, subgroup analysis revealed a negative

effect of testosterone administration on cooperation in studies with a within-subject design but not those with a between-subject design (see Table 4). This second result indicates that a negative effect of testosterone administration on social cooperation may become more evident after reducing experimental noise and variance.

One possible explanation for this lack of overall effect is that the included studies were too heterogeneous to draw firm conclusions about the effects of testosterone administration.

Another possible reason is that testosterone had little effect on the type of human cooperation as measured in social dilemma games. In other words, the lack of effect might be related to the tasks used in the studies included in the meta-analysis. Administration of testosterone may exert more significant effects if cooperation and competition are employed in the context of mating and intrasexual competition (Peters et al., 2007). Testosterone responses during competition depend upon the presence of potential, immediate mating opportunities associated with the competition (Miller et al., 2012). In the context of financial resource allocation and acquisition, as measured in most of the social dilemma games included in the current meta-analysis, the behavioural effects of testosterone administration become less evident. Thus, the effects of testosterone administration are likely to be task domain-specific.

4.4. Limitations and future directions

The current meta-analysis has several limitations. First, the age range of research subjects included in the current meta-analysis was narrow, consisting primarily of young adults. Although no significant moderating effect of age was found in the current analysis, it is conceivable that the effects of the three social hormones in question would vary as a function of developmental stages across the lifespan.

Second, the majority of subjects were young adults. Therefore, the significant results revealed in the current analysis may not be readily generalizable to other age groups. Since the neuroendocrine system changes with age, the effects of oxytocin administration are likely to be different among different age cohorts (e.g., Ishunina and Swaab, 2002; Buisman-Pijlman et al., 2014).

Third, oxytocin and vasopressin are both synthesized from a common ancestral molecule and are structurally different by only two amino acids (Goodson et al., 2012). Due to their structural similarity, the two hormones interact and are capable of binding to each other's receptors (Carter, 2014). Unfortunately, studies included in the current meta-analysis did not directly investigate the interactions between oxytocin and vasopressin. Future research should pay special attention to oxytocin-vasopressin interactions and their joint effects on human cooperation.

5. Conclusions

In this meta-analytic review, we pooled studies investigating the administration effects of three social hormones (oxytocin, vasopressin, and testosterone) on human cooperative behaviours measured in experimental interaction games. Results revealed a moderate positive effect of oxytocin administration, a large negative effect of vasopressin administration, and a nonsignificant effect of testosterone administration on cooperative behaviours. Furthermore, subgroup analyses suggested that the effects of hormone administration are moderated by a variety of individual, biological, and environmental factors. Overall, these results indicate a prosocial property of oxytocin in general and its in-group trust-enhancing role in particular. In contrast, vasopressin administration exerts egoistic and competitive effects, particularly in repeated social interactions. Together, the results of this meta-analytic work suggest that oxytocin and vasopressin may serve as a neural underpinning of reciprocal altruisms (Trivers, 1971).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.03.033.

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