Frontiers in Neuroendocrinology 52 (2019) 144–155

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Menstrual cycle-related fluctuations in oxytocin concentrations: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Menstrual cycle
Oxytocin
Female
Estrogens
Estradiol
Progesterone
GnRH
FSH
LH

ABSTRACT

Oxytocin affects physiological and psychological functions that are often expressed sex-specifically, suggesting interactions between oxytocin and sex hormones. As female sex hormone concentrations change during the menstrual cycle, oxytocin might fluctuate, too. This systematic review and meta-analysis investigated endogenous oxytocin concentrations across menstrual cycle phases in healthy women. Data from 13 studies (120 women) showed a significant increase of oxytocin concentrations from the early follicular phase to ovulation ($g = 0.39$ [0.25; 0.53], $p < .001$) and a significant decrease from ovulation to the mid-luteal phase ($g = -0.50$ [−0.81; −0.18], $p < .001$). There were no significant differences between the early follicular and mid-luteal phase ($g = -0.19$ [−0.70; −0.32], $p = .471$). These findings contribute to a deeper understanding of differences in normal and abnormal psychobiological processes in women. They highlight the necessity to consider the menstrual cycle phase in studies on oxytocin in women.

1. Introduction

Oxytocin is a neuropeptide that is synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei and in parvocellular neurons of the paraventricular nucleus of the hypothalamus (Jurek and Neumann, 2018). Through axonal and somato-dendritic release, oxytocin acts centrally as neurotransmitter and neuromodulator (Jurek and Neumann, 2018; Landgraf and Neumann, 2004), targeting receptors in the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis and brain stem (Gimpl and Fahrenholz, 2001; Meyer-Lindenberg et al., 2011). Furthermore, through projections of the hypothalamic magnocellular neurons (Jurek and Neumann, 2018), oxytocin is transmitted to the posterior pituitary, from where it is released into the peripheral bloodstream, acting as a hormone (Ludwig and Leng, 2006; Meyer-Lindenberg et al., 2011). Consequently, oxytocin's functions can be distinguished between its central role as a neurotransmitter and modulator and its peripheral role as a hormone. In humans, several options exist to measure endogenous oxytocin concentrations in different body fluids. At least some of oxytocin's central actions are assumed to be reflected in cerebrospinal fluid (CSF; Veening, de Jong and Barendregt, 2010). Alternatively, the physiological and psychological consequences of increased central oxytocin availability can be observed after intranasal administration of the peptide (Born et al., 2002). Its peripheral actions can be examined by measuring oxytocin concentrations in blood plasma and serum, urine or saliva (Rutigliano et al., 2016). Originating from research on oxytocin's physiological functions related to sexual behavior and reproduction, in recent years, the scientific interest in the neuropeptide has expanded into psychology. Oxytocin's impact on social behavior and stress reduction contributes to understanding the biological underpinnings of these basic psychological functions and makes it a promising candidate as a biomarker for mental disorders (Meyer-Lindenberg et al., 2011). Notably, these functions are often expressed sex-specifically and studies point towards interactions between oxytocin and sex hormones such as estrogens.

1.1. Sex-specificity of oxytocin's physiological and psychological functions

Concerning oxytocin's peripheral functions, it correlates with sexual stimulation, sexual arousal and muscular contractions during orgasm in both sexes (Carmichael et al., 1994; Carter, 1992). In men, oxytocin plays a key role in the central regulation of the penile erection and in ejaculation (Carter, 1992, Filippi et al., 2003). For example, it enhances the contraction of the seminiferous tubule that is involved in

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https://doi.org/10.1016/j.yfrne.2018.11.002
Received 8 August 2018; Received in revised form 14 November 2018; Accepted 16 November 2018
Available online 17 November 2018

ejaculation (Gimpl and Fahrenholz, 2001). In women, oxytocin release stimulates uterine contractions during birth and milk ejection during lactation (for an overview, see MacDonald and MacDonald (2010)). As breastfeeding is assumed to be highly relevant for the formation of a strong bond between a mother and her child (Carter, 1998), the role of oxytocin in interpersonal relationships attracted increasing interest. In mothers and fathers, a parenting-related increase of endogenous peripheral oxytocin concentrations was observed (Gordon et al., 2010).

Whereas in mothers, the oxytocin system is naturally activated due to birth and lactation, parental care activates it not only in mothers, but also in fathers (Feldman, 2012). Notably, parenting styles and behaviors associated with peripheral oxytocin differ between men and women and are thus illustrative, although not exclusive, examples for the sex-specificity of some of oxytocin's behavioral functions.

It has been suggested that mothers' parenting is often expressed by means of affectionate behaviors (Feldman et al., 2007), inducing feelings of predictability and safety (Feldman, 2012), whereas fathers tend to engage in arousing, exploratory, rough-and-tumble contact (Paquette, 2004), preparing for novelty and excitement (Feldman, 2012). Accordingly, peripheral oxytocin was correlated with maternal gaze, affect, vocalizations and affectionate touch in mothers, while in fathers, it was associated with positive arousal, object exploration and stimulatory touch (Gordon et al., 2010). These oxytocin-related parenting behaviors positively impact children's neurocognitive and attachment-related development (Feldman, 2003; Feldman and Eidelman, 2003).

As strong social bonds facilitate adaptive stress responses (Olff et al., 2013), the oxytocin system has also been discussed as possible biological underpinning of the buffering impact of social support on stress (Ditzen and Heinrichs, 2014). Indeed, intranasal administration of synthetic oxytocin has anxiolytic and stress-reducing effects (Acheson et al., 2013; Eckstein et al., 2015; Heinrichs et al., 2003) in men and women, but sex differences exist with regard to behavioral stress coping. On a behavioral level, men tend to show stress-induced fight-and-flight reactions that were mainly attributed to testosterone, whereas in women, peripheral oxytocin was hypothesized to promote tend-and-befriend behaviors (Taylor et al., 2000). On a physiological level, intranasally administered oxytocin has been shown to decrease stress parameters, such as alpha-amylase concentrations, in a partner conflict paradigm in women, while it increased alpha-amylase concentrations and emotional arousal in men (Ditzen et al., 2012).

Because of oxytocin's involvement in social behavior and stress regulation it is also relevant as a biomarker of psychological disorders. Alterations in basal peripheral oxytocin have been investigated in psychological disorders such as autism, schizophrenia or depression (for an overview, see Cochran et al. (2013)). Furthermore, the use of oxytocin nasal spray in some studies improved symptoms of autism (Andari et al., 2010; Parker et al., 2017) and lowered emotional stress responses in patients with borderline personality disorder (Amad et al., 2015).

1.2. Interactions between sex hormones and oxytocin

Sex-differences in the above described physiological and psychological functions suggests that the oxytocin system might interact with sex hormones. Most research addressing this association, to date, has focused on the interactions between estrogens and oxytocin. On a behavioral level, experiments with rats and mice showed that estrogens intensify oxytocin-related stress reduction (McCarthy et al., 1996; Ochedalski et al., 2007). On a neurophysiological level, the oxytocin system is regulated by estrogens (Lim and Young, 2006), which promote the synthesis of oxytocin and oxytocin receptor mRNA and thereby increase the transcription rate of oxytocin receptor genes (Gabor et al., 2012). To date, there is only one study in humans that specifically investigated these interactions: In female anorexia and bulimia patients as well as in healthy control women, pharmacological treatment with estrogen resulted in increased blood oxytocin concentrations (Chiodera et al., 1991). This preliminary evidence is supported by more detailed evidence from animal and in-vitro studies, indicating an estrogen-stimulated oxytocin release in neurons of the supraoptic hypothalamic nucleus (Wang et al., 1995). Moreover, oxytocin production in the hypothalamic paraventricular nucleus of mice was mediated by estrogen receptor beta functioning (Patisaul et al., 2003). Exogenous administration of estrogens increased oxytocin receptor mRNA levels in rats by activating estrogen receptor alpha (Amico et al., 1997; Breton and Zingg, 1997). This effect was also observed for a combined administration with progesterone, but not for progesterone as stand-alone drug (Amico et al., 1997; Breton and Zingg, 1997). However, studies on human tissues revealed correlations of both, estrogens and progesterone, with oxytocin in the corpus luteum, when measured in ovarian tissue and ovarian veins (Dawood and Khan-Dawood, 1986). Furthermore, progesterone and oxytocin seem to follow similar concentration patterns during the estrous cycle in sheep and in the mid-luteal phase in cows (Walters et al., 1984; Webb et al., 1981).

In summary, there is only little systematic research on interactions between sex hormones and oxytocin in humans until now. Evidence that is mainly derived from animal studies indicates that estrogens might regulate and progesterone might co-vary with oxytocin release.

1.3. Hormonal fluctuations across the menstrual cycle

The menstrual cycle is a precisely orchestrated sequence of reciprocally interconnected hormone releases, preparing a possible pregnancy. A regular cycle lasts about 28 days (notably, only a minority of women experience regular menstrual cycles of exactly 28 days) and can be divided into different phases. The follicular phase begins with the first day of the menstruation. The ovulation marks a specific timeframe that initiates the luteal phase, which lasts until the next menstruation. Each of these three phases or timeframes is characterized by a specific hormonal constellation. Besides the steroid hormones estradiol and progesterone, hormonal regulation of the menstrual cycle involves the polypeptide hormones gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH) and luteinizing hormone (LH) (Bale and Epperson, 2017).

During the follicular phase, the hypothalamus secrets GnRH with increased frequency. This stimulates the pituitary gland to produce gonadotropins, more precisely, FSH and LH. FSH stimulates the growth of follicles in the ovary, which produce estradiol. Estradiol, in turn, prepares the uterus for a possible pregnancy and blocks FSH and LH release in the pituitary gland. Lacking possibilities to cause follicle growth, FSH and LH accumulate there until they peak and finally cause ovulation i.e., the release of the mature follicle from the ovary into the fallopian tube. At this point, LH, FSH and estradiol reach their highest concentrations during the course of the menstrual cycle. In the subsequent luteal phase, the corpus luteum, which develops in the ovary where the follicle was released, produces progesterone. Progesterone, in turn, prepares the body for a possible pregnancy, for instance by inhibiting GnRH synthesis and thereby preventing further follicles from growing. If there is no fertilization, the corpus luteum demises and through menstrual bleeding the follicle is excreted along with the inner layer of the endometrium (Bale and Epperson, 2017; Reed and Carr, 2015).

1.4. Scientific gap and objectives

The precisely coordinated fluctuations of female sex hormones during the course of the menstrual cycle as well as their interactions with the oxytocin system suggest that oxytocin concentrations might also fluctuate between menstrual cycle phases (Insel, 2010). This hypothesis is supported by studies in rats demonstrating that oxytocin concentrations change during the estrous cycle (Ho and Lee, 1992;

Sarkar et al., 1992). Empirical studies have addressed possible fluctuations of endogenous oxytocin concentrations during the course of the human menstrual cycle, as well. In their qualitatively oriented systematic review, Macdonald and Feifel (2013) pointed out that "data on fluctuations in plasma OT levels across the menstrual cycle are mixed, with studies in different healthy and clinical populations showing both variation and lack of variation in normally cycling women" (p. 10).

To date, no systematic review and meta-analysis exists that quantitatively summarized evidence on these possible fluctuations and tested heterogeneity of these effects. Therefore, we conducted a systematic review and meta-analysis to summarize evidence on differences in basal oxytocin concentrations between menstrual cycle phases. Specifically, we investigated whether differences exist between the early follicular phase, ovulation and the mid-luteal phase. We defined our main review question according to the PICOS framework, as recommended by the PRISMA group (Moher et al., 2009). In terms of study population, we included healthy, naturally cycling women. We did not include intervention studies. Comparisons were conducted within subjects, comparing the same women in at minimum two different cycle phases. Concerning the outcome, we were interested in differences in endogenous oxytocin concentrations between the early follicular phase, ovulation and the mid-luteal phase, respectively. Accordingly, we included longitudinal within-subjects study designs.

2. Methods

2.1. Protocol and registration

This study is based on a subset of data from a larger methodological review that investigated potential confounders of basal endogenous oxytocin concentrations in healthy humans (Engel et al., in preparation) It was pre-registered at PROSPERO (Registration number: CRD42017072306) on the 17th of July 2017[2].

2.2. Eligibility criteria

We applied the following inclusion and exclusion criteria: Study participants were required to be healthy women with a mean age of 18 years or older. Participants with physical diseases, injuries or mental disorders were excluded. Furthermore, women with irregular menstrual cycles were excluded, which also applied for women who took any kind of hormonal contraceptives and menopausal women. Due to the critical role of oxytocin during labor and lactation (Nissen et al., 1995), women who were pregnant or had given birth less than a year ago were excluded, as well. Studies were excluded if there was a psychological or medical intervention before oxytocin measurement. As necessary for the intended comparisons, the same women had to be assessed at least twice at different menstrual cycle phases. In terms of outcomes, we were interested in possibly differing basal endogenous oxytocin concentrations measured in blood, saliva, urine or cerebrospinal fluid. Studies were required to report such differences between the follicular phase, ovulation and the luteal phase, respectively or to provide sufficient data to calculate an effect size. Concerning study design, longitudinal, within-subjects studies were eligible. Cross-sectional studies and between-subjects designs were excluded unless there was a subgroup for which within-subjects comparisons were possible. We included quantitative, empirical, published or unpublished studies in English or German language. Qualitative studies and reviews were excluded. We did not define an exclusion criterion with regard to publication year.

[2] It is available online from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017072306.

2.3. Identification and selection of studies

In order to identify all eligible primary studies, we conducted a systematic literature search which followed the strategies recommended by Lipsey and Wilson (2001). The electronic databases *PsycINFO, PubPsych, PsycARTICLES, PubMed, Web of Science, BIOSIS, ProQuest Dissertations and Theses Global* and *Clinicaltrials.gov* were searched up to 28th March 2017. Search terms were "oxytocin AND (blood OR plasma OR serum OR CSF OR cerebrospinal fluid OR urine OR urinary OR saliva OR salivary)". Additionally, we screened abstracts of conference contributions, posters and commentaries. A snowball search system was applied by screening reference lists of overview articles and by contacting experts in the field. All published and unpublished studies in English or German language were screened.

In order to select all relevant studies from the results of the database research, titles and abstracts of studies were screened at first. Secondly, full-text articles were read to decide whether studies were eligible for inclusion. These two steps were performed by one researcher (SE) and resulted in a pool of studies that assessed basal endogenous oxytocin concentrations in healthy humans. In a third step, all studies that met the precise inclusion criteria were identified from this pool. Studies that measured basal oxytocin concentrations in at least two phases of the menstrual cycle were included in the descriptive part of the review. Studies that provided all necessary data were also considered in the meta-analytic procedure. Step three was performed by two independent raters (HK and SE). In case of discrepancies, a third independent rater decided about study inclusion (SSch).

If full-texts or abstracts were not available, we contacted the corresponding authors via email and asked for access to the paper in order to take it into consideration. We also contacted authors of study registers and asked whether unpublished data was already available.

2.4. Data extraction and preparation

A standardized coding scheme was used to extract relevant information from the included studies. Two raters (SE, HK) extracted the data from each study independently. In case of discrepancies, a third rater (SSch) decided.

For the qualitative review, we extracted the number of days and in which cycle phases oxytocin was measured, the measurement method (e.g. blood or saliva), the kind of assay, whether extraction preceded the biochemical analysis, the time of day of sampling, and information about the participants' age.

For the quantitative synthesis, we labeled day 1 as the first day of the follicular phase, and day 14 as ovulation or LH peak. We extracted mean or median oxytocin concentrations of all available days during the course of the cycle. Standard deviations, standard errors and ranges were extracted as measures of variance. If studies provided oxytocin concentrations of the individual participants, exclusively, we calculated the mean and standard deviation. If oxytocin concentrations were provided by graphs, exclusively, we used a web based plot digitizer (Rohatgi, 2010) to extract them. To ensure accuracy, two raters (HK, SE) extracted the data from each study, independently. Additionally, we calculated the correlation (r) of the values that were extracted by the two raters assuring reliability. In case of discrepancies, a third rater (SSch) decided which value to use. As required for the statistical procedures, we estimated means and standard deviations from medians, standard errors or ranges with the formulas provided by Hozo et al. (2005). Correlations and effect sizes of differences between the cycle phases were extracted, if available. If studies did not report within-subjects correlations but provided the individual concentrations of oxytocin for each participant at the respective cycle phases, we calculated them. For studies that neither provided correlations nor individual oxytocin concentrations, we estimated the correlation by calculating the mean correlation of the other included studies, using a set of formulas by Olkin and Pratt (1958) which was recommended for meta-

analyses by Schulze (2004). Furthermore, sample sizes were extracted. If the exact sample size was not reported for each cycle phase or if it varied across phases, we used the smallest sample size for the meta-analytic calculations.

If a study did not provide all necessary information for the meta-analytic procedure, we contacted the authors via e-mail, if contact details were found, and asked for the information. In the case of no response we sent reminders after 10 days. If no response was received or the authors indicated that they no longer had access to the data, we considered the data unavailable.

2.5. Risk of bias of individual studies

Risk of bias was assessed for all studies that were included into the meta-analytic procedures by means of the Cochrane Risk of Bias Assessment Tool for interrupted time series studies (Higgins et al., 2016). In accordance with the scale, we rated risk of specific biases for interrupted time series studies (i.e., whether menstrual cycle-related changes of oxytocin concentrations occurred independently of other changes over time, whether the expected effect of menstrual cycle phases on oxytocin concentrations was pre-specified and whether the menstrual cycle itself was unlikely to affect data collection), risk of attrition bias (incomplete outcome data), risk of reporting bias (selective outcome reporting), and risk of other bias (i.e., whether exclusion of women who used hormonal contraception was explicitly stated). We decided not to rate the items for performance bias and detection bias, as we considered the respective items as inappropriate for the purposes of our study. Concerning performance bias, we considered it impossible to blind participants for their menstrual cycle phase. With regard to detection bias, as biochemical analyses are relatively objective and less prone to interpretation biases (e.g., in contrast to psychometric interviews), we considered it unnecessary to ensure blinding of laboratory workers. The ratings were performed by two independent researchers (SE, HK) and in case of disagreements, a third person (SSch) decided.

2.6. Descriptive presentation of menstrual-cycle related fluctuations of oxytocin concentrations

In order to provide a visualization of possible fluctuations of oxytocin concentrations during the course of the menstrual cycle, we created a line graph of standardized means. We selected all studies that provided oxytocin values for more than 10 days during the cycle and z-standardized the oxytocin concentration of the single days. These values were then averaged for each day across all studies.

2.7. Meta-analytic procedures

In order to test possible fluctuations during the course of the menstrual cycle statistically, we conducted within-studies comparisons between the early follicular phase, ovulation and the mid-luteal phase, respectively, under the random effects model. We used reference days to mark these phases. Day 4 was used as reference day for the follicular phase since the risk of bias caused by an early ovulation is low and the early follicular phase is frequently used as a reference point in the literature (Altemus et al., 2001; Rubin et al., 2015). Day 14 was used as a reference day for ovulation since it is considered as the average day of ovulation (Hoffbauer, 2005). Day 22 was used as a reference day for the luteal phase to exclude the risk of influence through a late ovulation or an early menstruation. The mid-luteal phase is also frequently used as a reference point for the luteal phase (Altemus et al., 2001; Rubin et al., 2015). If oxytocin concentrations were not provided at days 4, 14, or 22, we used the day closest to the reference day. If there were two days in the same distance to the reference day, we applied the following rules: If one of the two days provided data for more individuals, the data of this day were used. If the participant number was the same, the data of the day that was more distant from ovulation were chosen in order to exclude the risk of bias by hormonal change through ovulation.

We used Hedges' *g*, corrected for small sample sizes, to test differences in oxytocin concentrations between the three phases, as recommended by Borenstein et al. (2011). Specifically, we determined standardized mean differences between the early follicular phase and ovulation, between ovulation and the mid-luteal phase, as well as between the early follicular and mid-luteal phase. Furthermore, we calculated a synthesized effect size across the three phases as an indicator of overall fluctuations of oxytocin concentrations during the course of the menstrual cycle (Borenstein et al., 2011). In this synthesized effect size calculation, we used the early follicular phase as the baseline measurement. This implies that we investigated the contrast of the differences between the early follicular phase and ovulation and the differences between the early follicular and mid-luteal phase, as recommended by Borenstein et al. (2011).

Heterogeneity was examined using the Q-statistic and the I^2-index Borenstein et al. (2011). Significant Q coefficients ($p < .05$) indicate heterogeneity. I^2 values of 25, 50, and 75 were interpreted as the minimum for indicating low, moderate and high heterogeneity, respectively (Crombie and Davies, 2009). If these coefficients indicated heterogeneity, we applied subgroup analyses. As possible moderators, we pre-defined measurement method of oxytocin, age, and risk of bias.

To test for publication bias, Egger's regression test (Egger et al., 1997), Begg and Mazumdar's rank correlation (Begg and Mazumdar, 1994), and Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie, 2000) were applied to all homogeneous data sets including at least six primary studies (Ioannidis et al., 2005). All calculations were conducted with the Comprehensive Meta-Analysis software (Biostat, 2014).

3. Results

3.1. Included studies

Fig. 1 visualizes the results of the literature search and study selection. We included 19 studies (228 participants) into the descriptive part of this systematic review. When reviewing the included studies, we contacted authors who were involved in multiple included studies and asked if data overlapped between the studies. Subsequently, two studies were excluded from the meta-analytic procedure (Rubin, 2009; Rubin et al., 2015), due to data overlap with Rubin et al. (2010). Four studies were excluded due to insufficient data for the meta-analysis. Finally, we were able to include 13 studies (120 participants) into the meta-analytic procedure.

3.2. Qualitative review of included studies

The 19 studies included in the qualitative synthesis were published between the years 1981 and 2015 (see Table 1). The sample sizes consisted of three to 31 women per study. All included studies measured oxytocin in blood plasma. Studies measuring endogenous oxytocin in other fluids would have been eligible for inclusion, but such studies were not identified in the literature search. The studies reported oxytocin concentrations in two to 28 days and in three (k = 7) or two (k = 8) cycle phases. Four studies measured oxytocin in different cycle phases, but did not report the concentrations, explicitly. Fourteen studies analyzed oxytocin with radioimmunoassay, four studies with enzyme immunoassay and one study did not report which kind of assay was used. Extraction was performed in 10 studies, three studies analyzed unextracted samples and six studies did not provide information on this issue. The day time of sampling varied between studies. While seven studies measured oxytocin in the morning (between 6 am and 11:59 am) and three in the afternoon (between 12 and 5.59 pm), two studies used sampling protocols including morning and afternoon measurements. Seven studies did not report on time of day of sampling. The women's mean ages were between 20.40 and 39.00 years. The

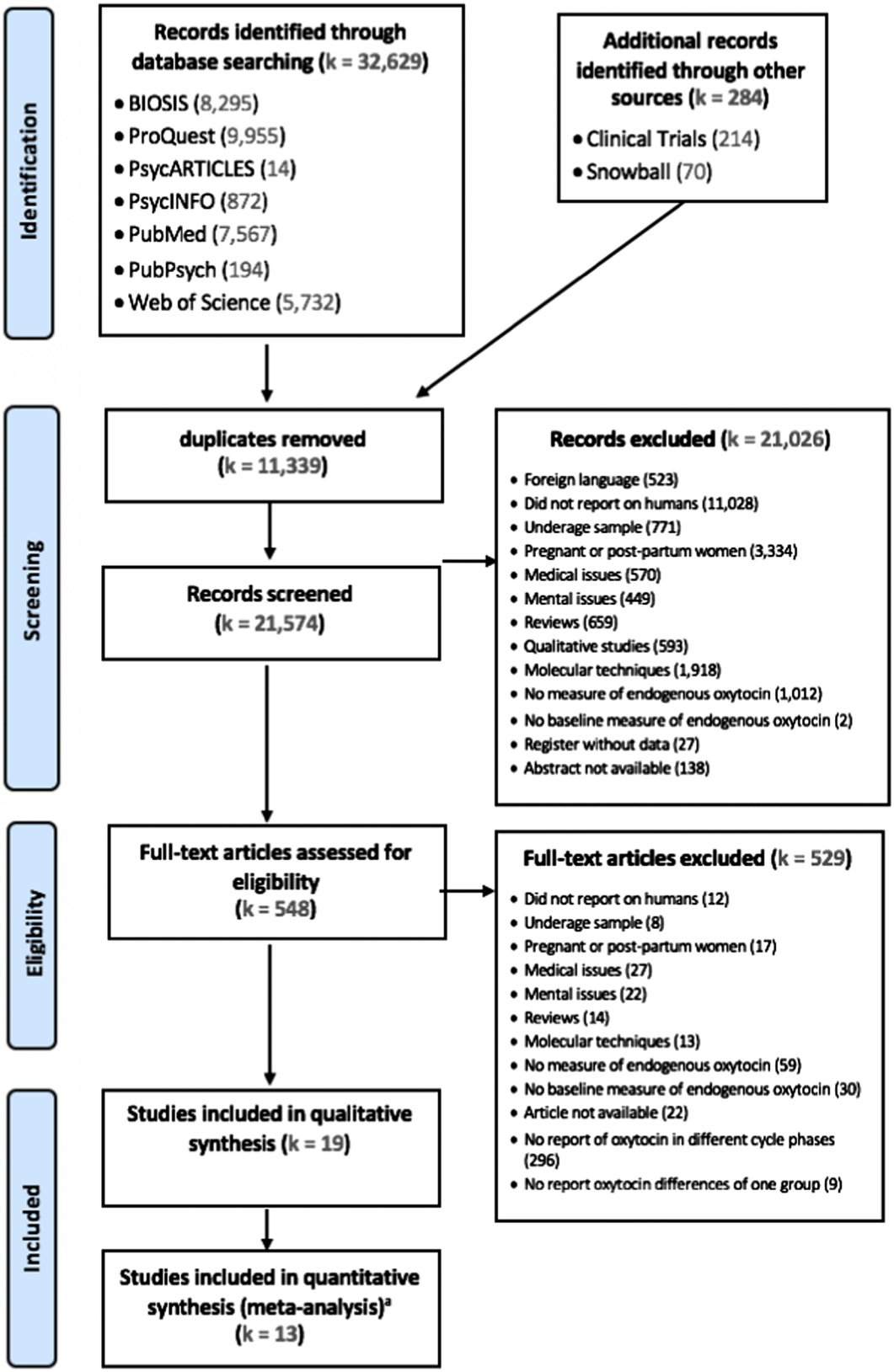

Fig. 1. Flowchart illustrating the steps of the literature search. *Note.* k = number of studies; [a] Four studies were excluded because of insufficient reported data and two studies because of overlapping data to another included study.

Table 1
Characteristics of included studies.

Author (year)	Number of Days[a]	Number of Phases[b]	Phases reported[c]	*n*	Assay	Extraction[d]	Unit	Age[e]	Sampling daytime[f] [g]
Altemus et al. (2001)	2	2	●○●	8	RIA	1	pmol/L	34.20 ± 1.80	Morning
Amico et al. (1981)	14	3	●●●	5	RIA	1	μU/ml	26.00 ± 2.00	Morning
Anderberg and Uvnäs-Moberg (2000)	2	2	○○○	16	RIA	1	pmol/l	–	Morning
Challinor et al. (1994)	2	2	●○●	4	RIA	1	μU/ml	18.00–35.00[h]	Morning–afternoon
Kostoglou-Athanassiou et al. (1998)	2	2	●○●	8	RIA	1	pmol/l	–	Afternoon
Kostoglou-Athanassiou et al. (1996)	2	2	○○○	8	–	–	μU/ml	20 0.00–22.00[h]	Afternoon
Kumaresan et al. (1983)	28	3	●●●	3–10	RIA	0	μU/ml	24.00 ± 10.80	Morning
Leake et al. (1984)	2	2	●○●	9	RIA	–	–	25.00–45.00[h]	Morning–afternoon
Le Mellédo et al. (2001)	–	–	○○○	–	RIA	–	pg/ml	27.00 ± 7.00	–
Liedman et al. (2008)	10	3	○○○	5	EIA	1	pg/ml	20.40 ± 0.50	–
Mitchell et al. (1981)	22	3	●●●	6	RIA	–	pg/ml	20.00–45.00[h]	–
Rubin (2009)	2	2	●○●	30	EIA	–	pg/ml	27.57 ± 6.79	–
Rubin et al. (2010)	2	2	●○●	31	EIA	0	pg/ml	27.55 ± 6.67	Afternoon
Rubin et al. (2015)	2	2	●○●	31	EIA	0	pg/ml	27.55 ± 6.67	–
Salonia et al. (2005)	3	3	●●●	20	RIA	1	pg/ml	33.80 ± 0.50	Morning
Shukovski et al. (1989)	27	3	●●●	4	RIA	1	pmol/l	–	–
Stock et al. (1991)	11	3	●●●	4–15	RIA	1	fmol ml^{-1}	22.00–39.00[h]	–
Uvnäs-Moberg et al. (1989)	28	3	●○●	14	RIA	–	pM	39.00 ± 1.70	Morning
Williams et al. (1985)	28	3	●●●	4	RIA	1	pmol/l	20.00–22.00[h]	Morning

Note. RIA = radioimmunoassay; EIA = enzyme immunoassay.
[a] Number of days measured.
[b] Number of phases measured.
[c] Black points show phases with available values of oxytocin (either numbers or extractable from graphs with extraction tool), the first point represents the follicular phase, the second point the ovulation and the third point the luteal phase.
[d] 1 = extraction, 0 = no extraction.
[e] Reported as mean ± standard deviation.
[f] Morning = 6:00 am to 11:59 am; afternoon = 12 pm to 5.59 pm; evening = 6:00 pm–11:59 pm; night = 12:00 am–5:59 am.
[g] Oxytocin was measured in blood in all included studies, therefore, this the category measurement method is not stated in this table.
[h] Mean age was not available; therefore, the age range was reported.

results of the risk of bias ratings are shown in supplementary material 1. Overall, the general study quality can be regarded as sufficient.

3.3. Cycle-related changes in oxytocin

3.3.1. Descriptive presentation of oxytocin concentrations during the menstrual cycle

Fig. 2 presents the fluctuation of oxytocin across the six studies that provided data for more than 10 days during the course of the menstrual cycle. The graph demonstrates that, on a descriptive level, mean oxytocin concentrations increased from the follicle phase to ovulation and decreased after ovulation. Furthermore, the graph shows fluctuations of the mean oxytocin concentrations not only between menstrual cycle phases but also between single days.

3.3.2. Meta-analytic results

The mean correlation for data extracted with an online plot digitizer (Rohatgi, 2010) by two raters was $r = 0.99$. Concerning the three cycle

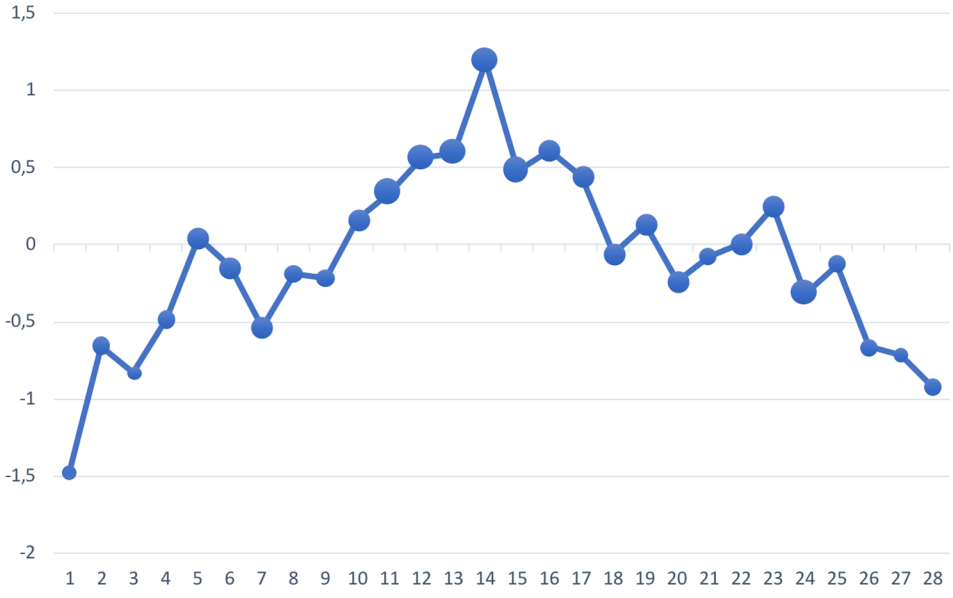

Fig. 2. Descriptive analysis of mean z-standardized oxytocin concentrations during the menstrual cycle. *Note.* y-axis: mean of z-standardized oxytocin concentrations for 6 studies that measured oxytocin on more than 10 days during the menstrual cycle. x-axis: days of the menstrual cycle starting with day one as the first day of bleeding. Size of points estimates the precision of the values, as sample sizes varied between $n = 14$ (smallest point) and $n = 45$ (biggest point): larger points indicate that more samples of oxytocin were provided on that day.

Table 2
Overview of effect estimates.

Comparison	*k*	Hedges' *g*	*SEM*	s^2	CI (95%)	*Z*	*p*
Follicular phase Ovulation	7	0.39	0.07	0.01	0.25–0.53	5.31	< 0.001
Ovulation Luteal phase	7	−0.50	0.16	0.03	−0.81 to (−0.18)	−3.06	< 0.002
Follicular phase Luteal phase	7	−0.19	0.26	0.07	−0.70 to 0.32	−0.72	0.471
Follicular phase Luteal phase	13	0.00	0.11	0.01	−0.21 to 0.22	0.03	0.975

Note. *k* = number of studies, *SEM* = standard error, s^2 = variance, CI = Confidence interval.

phases or timeframes, the maximum difference of the chosen days to the pre-specified reference days was two days to the follicular and luteal phase, and one day to ovulation.

The calculation of effect estimates between early follicular phase, ovulation and the mid-luteal phase included data from 7 studies (48 participants) for each comparison. As 6 additional studies provided data for the follicular and the luteal phase only, they were used to replicate this comparison with a larger number of studies (120 participants) and thereby create more robust results. The overview of the effects is listed in Table 2. The forest plots are reported in supplementary material 2.

When comparing the early follicular phase with ovulation, a small but significant effect estimate was determined ($g = 0.39$ [0.25, 0.53], $p < .001$), indicating higher oxytocin concentrations around the time of ovulation than in the early follicular phase. The effect was homogeneous ($Q = 5.13$, $p = .528$, $I^2 = 0.00$). A significant, medium-sized effect estimate was found for changes from ovulation to the mid-luteal phase ($g = -0.50$ [−0.81, −0.18], $p = .002$), indicating higher endogenous oxytocin concentrations around the time of ovulation than in the luteal phase. Again, the effect was homogeneous ($Q = 8.28$, $p = .222$, $I^2 = 27.07$). Concerning changes in oxytocin concentrations from the early follicular to mid-luteal phase, no significant effect was detected ($g = -0.19$ [−0.7, 0.32] $p = .471$). This result was homogeneous ($Q = 9.03$, $p = .172$, $I^2 = 33.57$). This analysis was replicated by adding six studies that provided oxytocin concentrations in the follicular and luteal phase, exclusively. The previous result revealing no effect ($g = 0.00$ [−0.21, 0.22], $p = .975$; $Q = 20.92$, $p = .052$, $I^2 = 42.64$) was confirmed.

The synthesized effect size across the three time points was significant and of medium size ($g = 0.51$ [0.01, 1.01], $p = .044$), indicating that the change in oxytocin concentrations from the follicular phase to ovulation was larger than the change from the follicular to the luteal phase. Again, the effect was homogeneous ($Q = 10.91$, $p = .091$, $I^2 = 45.02$). The forest plots are illustrated in Fig. 3.

3.3.2.1. Effect of sample extraction. There is ongoing debate about the comparability between measures of endogenous oxytocin in extracted and unextracted samples (Szeto et al., 2011). Therefore, we tested whether the effects remained stable when repeating our analyses only in those studies that explicitly stated that samples had been extracted before biochemical analysis. Accordingly, we performed the same comparisons of endogenous oxytocin concentrations between follicular phase, ovulation, and luteal phase, but excluded studies that clearly mentioned that samples were unextracted as well as those studies that did not report whether extraction was performed.

The comparison between the follicular phase and ovulation (across five studies, $n = 37$) still displayed a small, but now non-significant effect ($g = 0.20$ [−1.2, 0.53], $p = .216$). The direction of the effect remained the same, indicating higher oxytocin concentrations around the time of ovulation, and the effect was homogeneous ($Q = 3.34$, $p = .503$, $I^2 = 0.00$). The comparison between ovulation and mid-luteal phase (across five studies, $n = 37$) remained to be of medium size and significant. As in the previous analysis, it indicated that oxytocin concentrations were higher around the time of ovulation ($g = -0.50$ [−0.93, −0.06], $p = .025$). The effect was homogeneous ($Q = 8.12$, $p = .870$, $I^2 = 50.71$). The comparison between the follicular phase and mid-luteal phase (across five studies, $n = 37$) now displayed a small, significant effect, indicating higher oxytocin concentrations during the follicular phase ($g = -0.48$ [−0.93, −0.03], $p = .038$). The effect was homogeneous ($Q = 2.90$, $p = .575$, $I^2 = 0.00$). However, when including the total number of available studies that extracted the samples prior to analysis ($k = 8$, $n = 57$), the significant difference between follicular and mid-luteal phase disappeared ($g = -0.15$ [−0.44, 0.15], $p = .330$). This effect was homogeneous, as well ($Q = 11.85$, $p = .106$, $I^2 = 40.92$).

The synthesized effect size across the three time points remained significant and of medium size ($g = 0.69$ [0.17, 1.21], $p = .009$). This result indicates that the change in oxytocin concentrations from the

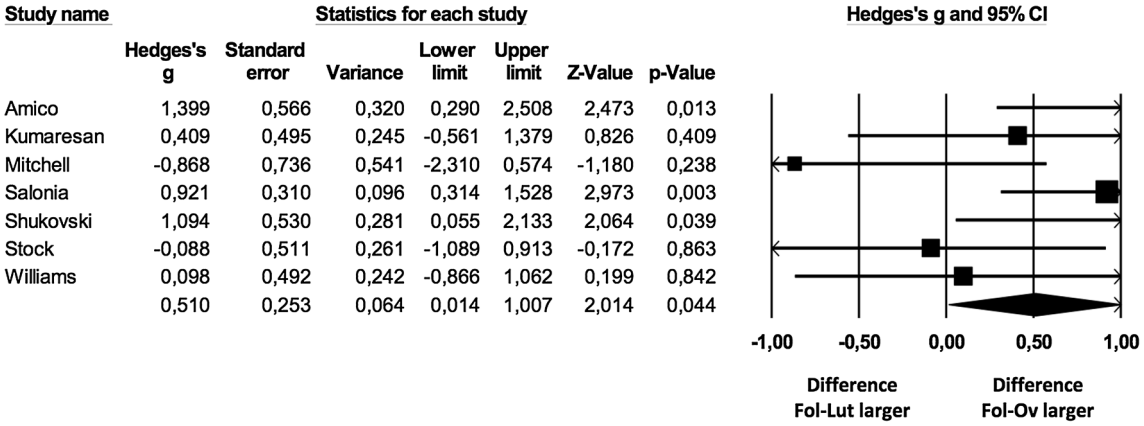

Fig. 3. Synthesized effect size of the differences between the follicular and luteal phase and the follicular phase and ovulation.

follicular phase to ovulation was larger than the change from the follicular to the luteal phase and that there is an overall change in oxytocin concentrations during the course of the menstrual cycle. The synthesized effect size was also homogeneous ($Q = 6.46$, $p = .157$, $I^2 = 38.07$).

3.3.3. Publication bias

None of the data sets of the main analyses indicated publication bias according to Begg and Mazumdar's rank correlation (Begg and Mazumdar, 1994) and Egger's regression test (Egger et al., 1997). The trim-and-fill-procedure (Duval and Tweedie, 2000) imputed one possible missing study in the comparison between the follicular and luteal phase on the larger pool of studies ($k = 13$). The resulting adjusted effect did not differ significantly from the original one. All other data sets showed no imputed studies when the trim-and-fill-procedure (Duval and Tweedie, 2000) was applied. The detailed results of the tests for publication bias can be seen in supplementary material 3.

4. Discussion

4.1. Summary of evidence

The results of this systematic review and meta-analysis indicate that endogenous oxytocin concentrations fluctuate during the course of the menstrual cycle. Data suggests that oxytocin concentrations peak around the time of ovulation. There seems to be no difference between the early follicular phase and the mid-luteal phase, but oxytocin increases from the early follicular phase to ovulation and decreases again during the luteal phase. Most effects were based on a relatively small number of studies ($k = 7$). However, we were able to replicate the effect from the comparison between the early follicular and mid-luteal phase on a larger subset of studies ($k = 13$). All effects were homogeneous. Additional analyses for publication bias indicated that, despite a minor tendency toward bias, the findings on menstrual-cycle related fluctuations of oxytocin concentrations were robust. In subgroup analyses of all studies that definitely performed an extraction before the biochemical analysis, the directions of all effects remained the same. The loss of significance of the difference between follicular phase and ovulation might be attributable to the reduced number of included studies and participants, and accordingly, loss of statistical power. Interestingly, the difference between mid-luteal and follicular phase was significant within this smaller set of studies, but this effect disappeared when including the complete set of studies that extracted their samples, which was available for this specific comparison.

4.2. Integration of results and future directions

Our results hold several implications on both, a practical and a theoretical level. Our qualitative description of the current state of research provided a comprehensive evaluation of previous efforts to understand and consider the impact of the menstrual cycle on the oxytocin system. Practical implications can be derived from the data that might help to extend the generalizability and increase the reliability of future studies. Our quantitative summary provided a description and statistical test of the fluctuations of oxytocin concentrations during the course of the menstrual cycle. Based on our data, theoretical implications for promising future studies addressing for instance the sex-specificity of oxytocin's functions and the interactions between oxytocin and sex hormones can be given.

4.2.1. Generalizability and reliability of evidence on the oxytocin system

First, to date, only a small number of studies addressed menstrual cycle-related fluctuations of endogenous oxytocin concentrations, resulting in a small number of studies that were eligible for inclusion. Notably, the majority of studies was published in the 1980s and the 1990s and comprised small samples ($n = 3$ to $n = 31$). In general, the investigation of oxytocin's psychological functions, its impact on psychopathology and therapeutic potential can be regarded as a growing field of research. Nevertheless, menstrual-cycle related variations, as a basic and important influence on the oxytocin system, have been neglected. Therefore, to confirm the robustness of our results, more studies are needed that repeatedly measure oxytocin concentrations during the course of the menstrual cycle using state-of-the-art biochemical assays.

As reviewed by Rutigliano et al. (2016), many results in research on oxytocin and psychiatric disorders are heterogeneous, which the authors attributed to a lack of consideration of confounders amongst other explanations. With regard to the results of our systematic review and meta-analysis, it seems likely that the menstrual cycle might be one of these influencing confounders. Our findings indicate that oxytocin concentrations fluctuate in a coordinated manner with other female sex hormones. Women in different phases of their menstrual cycle, women using hormonal contraceptives and menopausal women all differ with regard to the basal concentrations and the extent of fluctuations of these hormones. This suggests that any study on the oxytocin system, regardless of its specific scientific question, should take these variations into account to derive valid results and enabling to draw firm conclusions.

Moreover, our study revealed that oxytocin fluctuates not only between the menstrual phases, but also between single days. This implies a high overall variability of oxytocin concentrations and suggests a potentially high number of additional confounders. The assumed interactions between oxytocin and sex hormones suggest that it might be worthwhile to investigate the influence of contraceptives, the fertility status or number of pregnancies and births on endogenous oxytocin concentrations. However, other confounders are conceivable as well, and efforts should be taken to identify them ensuring appropriate confounder control in future studies. After all, this might contribute to less heterogeneous and more reliable study results.

4.2.2. Sex-specificity of oxytocin's functions and their cycle-related fluctuations

Second, the results of this review and meta-analysis contribute to a better understanding of oxytocin's sex-specific functions and their variations across the menstrual cycle. Sex-specific functions, such as oxytocin's influence on social behavior or stress response, might not only differ between men and women but also within women, depending on their current cycle phase. It is possible that these functions are reinforced around the time of ovulation compared to the luteal or follicular phase, as already suggested by some findings. For instance, social perception seems to change during the course of the menstrual cycle. During the time of ovulation women seem to be able to categorize faces, especially male faces, more easily (Macrae et al., 2002). Furthermore, face characteristics that are perceived as more socially dominant are preferred around the time of ovulation (Penton-Voak et al., 2003). Besides, some studies show a fluctuation of certain social behaviors across the menstrual cycle. Buser (2012) reported that in a trust game, women scored highest during the late follicular and ovulatory phase. Additionally, sexual activity seems to be increased during the late-follicular and the ovulatory phase (Matteo and Rissman, 1984) which – according to our data - would be paralleled by the increase in oxytocin concentration during that time. From an evolutionary perspective, an increase in social behaviors and trust seems plausible since the ovulation phase is also the phase where fertilization is possible. With regard to stress and the menstrual cycle, studies investigated mainly physiological stress parameters, that seem to be decreased, when circulating estradiol is high (Kirschbaum et al., 1999). Subjective stress measures also differed in different cycle phases and women reported to feel less

stressed at ovulation (Albert et al., 2015). Combining these two aspects, recent data suggests that in women, preferences for masculine faces increased during ovulation while estradiol was high and, above this, preferences interacted with stress with a shift towards more feminine faces after stress (Ditzen et al., 2017).

As trust, stress and social behaviors are also relevant in the context of psychological disorders which have been associated with alterations in the oxytocin system, it can be speculated that oxytocin-related symptoms of psychological disorders also fluctuate during the course of the menstrual cycle in accordance with oxytocin concentrations. Specifically, symptoms might decrease during ovulation. In fact, studies with animals and healthy human samples indicate menstrual cycle-related variability in areas crucial for mental health such as stress and affect (Guo et al., 2018; Ross et al., 2003). However, there is a lack of studies investigating menstrual-cycle related fluctuations of psychopathological symptoms in clinical populations. Further research in this field is highly relevant to understand the exact role and the impact of oxytocin and other sex hormones in psychopathology. Furthermore, a lot of oxytocin-related functions such as stress regulation, further social behaviors or parental care are not yet examined in the context of the menstrual cycle. From a biological point of view further research is needed to determine why oxytocin fluctuates during the menstrual cycle. The question which hormone(s) influences oxytocin is still unanswered and the assumptions that are made in this study need to be further investigated.

4.2.3. Interactions between oxytocin and sex hormones

Third, the observed ovulation-related increase of oxytocin concentrations might inform theory on interactions between oxytocin and sex hormones that is, until today, mainly based on results from animal studies. Those provided preliminary evidence that estrogens stimulate oxytocin production by means of estrogen receptor beta functioning (Patisaul et al., 2003). The results of the current meta-analysis seem to confirm this finding, as estradiol concentrations reach their highest level during the menstrual cycle right before ovulation (Bale and Epperson, 2017). Accordingly, the ovulation-related peak of oxytocin might be thought of as a consequence of increased estradiol availability and estrogen receptor beta functioning. Furthermore, our results seem to be in line with evidence pointing towards an inverse interaction between oxytocin and progesterone (Dawood and Khan-Dawood, 1986; Walters et al., 1984; Webb et al., 1981). Whereas our results indicated that oxytocin concentrations are highest at ovulation, progesterone concentrations are still low at ovulation and reach their peak during the luteal phase (Bale and Epperson, 2017). This implies that the association between both hormones might be chronologically delayed. More studies investigating the dynamic interactions between estrogens, progesterone and oxytocin are needed, especially in human samples. Moreover, this field of research could be extended to other hormones regulating the menstrual cycle, specifically GnRH, FH, and LH. Evidence on interactions between oxytocin and these hormones is even sparser, even though associations might be assumed. Additionally, as the sex-specificity of oxytocin's functions suggests an interaction with female sex hormones, an interaction with testosterone might be assumed, as well. This is supported by the fact that many psychological functions of testosterone seem opposite to those that are usually ascribed to oxytocin (MacDonald, 2013). To sum up, our results clearly point towards interactions between oxytocin and sex and cycle-related hormones. However, the lack of robust research on humans makes it difficult to integrate these findings into theory. This underlines the statement by Gimpl and Fahrenholz (2001) that "the regulation by gonadal and adrenal steroids is one of the most remarkable features of the oxytocin system and is, unfortunately, the least understood" (p. 630).

4.3. Limitations

This systematic review and meta-analysis needs to be interpreted in consideration of its limitations. The most remarkable one refers to the small number of studies we were able to include. Higher numbers of studies and participants would be necessary to gain more robust meta-analytic effects. Nevertheless, it seems remarkable that even with relatively low statistical power, significant, homogeneous, and even across the subgroup analyses of studies that extracted the samples before analysis, relatively stable effects were found. Still, we cannot exclude the possibility that few studies or participants with especially pronounced fluctuations of oxytocin might have biased our findings. Therefore, more primary studies with larger samples are definitely needed. It might be worthwhile to update this meta-analysis if the number of eligible studies can be significantly extended in upcoming years.

Additionally, it should be considered that many of the included studies are rather old, only three were published after the year 2000. Especially in the field of biological research, this might be problematic since the methods and designs used to assess and determine oxytocin concentrations are subject to continuous development. Again, more primary studies using state-of-the-art biological assays, including extraction procedures, and a subsequent update of this meta-analysis are recommended.

Concerning our methodological approach, it needs to be critically mentioned that our analyses on oxytocin concentrations were partially based on data extracted from graphs. We considered a higher exclusion rate from the meta-analytic procedure and a resulting reduction of eligible studies as more problematic than possibly imprecise oxytocin values. It can be assumed that the extracted data is valid as the correlation between the extractions of the two independently rating researchers was very high ($r = 0.99$). However, a direct extraction of the exact values as reported by the authors would have been our method of choice.

It is worth noting that the menstrual cycle-related variability in endogenous oxytocin concentrations detected by this meta-analysis does not allow for conclusions about oxytocin's function as a neuromodulator (Lefevre et al., 2017). It remains unclear to which extent endogenous measurements reflect central processes (Valstad et al., 2017). Above this, oxytocin functions in the brain and in the body are determined through oxytocin receptor sensitivity and limited data is available on oxytocin receptor sensitivity over the course of the menstrual cycle to date (Einspanier et al., 1998). It might be worthwhile to integrate according parameters into future studies to detect whether the menstrual cycle-related variability of peripheral oxytocin concentrations also extends to its central actions.

4.4. Conclusions

In conclusion, the available data suggests that peripheral oxytocin concentrations fluctuate during the course of the menstrual cycle. Specifically, an increase from the follicular phase to ovulation was detected as well as a decrease during the luteal phase compared to ovulation. It needs to be considered that peripheral oxytocin concentrations cannot give a valid picture of the neuropeptide's function in the brain or even specific brain areas. In addition, the small number of included studies and participants highlight the need for more studies with larger samples that underpin our findings. Furthermore, endogenous oxytocin concentrations might be influenced by a number of physiological factors. A comprehensive investigation of possible influencing factors such as sex, age, daytime, sleep or medication intake is warranted for the future. In this regard, our study can be viewed as a first step.

On the one hand, the results of this meta-analysis provide practical

implications. They highlight the necessity for researchers to control for menstrual cycle phase when measuring oxytocin concentrations in women, in order to draw valid and unbiased conclusions. On the other hand, our results might provide theoretical implications. They indicate that oxytocin, which is related to important psychological functions might also interact with sex hormones. Therefore, it might have the potential to contribute to a better understanding of sex differences in psychological functions and symptoms. Considering that men and women differ regarding prevalence, symptomatology and course of mental disorders (Boyd et al., 2015) this study might have discovered one possible underpinning of these sex differences.

Funding

The "Stiftung der Deutschen Wirtschaft" provided doctoral funding for SE. The foundation had no influence on the study design, the collection, analysis and interpretation of data, the writing of the report or the decision to submit the manuscript for publication. Apart from this doctoral scholarship, this research did not receive any specific funding.

Contributors

HK, SE, CK and SSch designed the study. SE developed the search strategy and performed the literature research. HK contacted the authors of all primary studies for which data was missing. SE and HK performed the study selection, data collection and inspection, as well as the risk of bias rating. SSch acted as independent rater in the study selection, data collection and risk of bias rating. HK and SE performed the statistical analyses and drafted the manuscript. SSch, CK and BD supervised the meta-analysis and revised the manuscript for important intellectual content.

Conflicts of interest

Mrs. Engel, Mrs. Klusmann, Prof. Dr. Ditzen, Prof. Dr. Knaevelsrud and Dr. Schumacher have no conflicts of interest to declare.

Acknowledgements

We would like to thank Ludwig Ohse for his support in the grey literature research and his correspondence with authors of registered trials. We are grateful to Anya Deubel and Annika Walinski who assisted in gathering full-text articles. Furthermore, we would like to thank Johannes Bohn for his statistical advice. Finally, we deeply appreciate the generosity of all authors of the included studies, who provided us with the full-texts and requested data for the present meta-analysis.

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