Psychoneuroendocrinology 101 (2019) 138–149

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

The endogenous oxytocin system in depressive disorders: A systematic review and meta-analysis

Sinha Engel*, Sebastian Laufer, Christine Knaevelsrud, Sarah Schumacher

Division of Clinical Psychological Intervention, Department of Education and Psychology, Freie Universität Berlin, Schwendenerstraße 27, 14195 Berlin, Germany

ARTICLE INFO

Keywords:
Oxytocin
Depression
Depressive disorder
Systematic review
Meta-analysis

ABSTRACT

The oxytocin system is involved in psychological functions and interacts with biological systems that are altered in patients suffering from depressive disorders. This suggests a possible role of oxytocin in the development and maintenance of depression. We provide the first systematic review and meta-analysis that specifically addresses differences in basal endogenous oxytocin concentrations between patients with depressive disorders and healthy controls.

A systematic literature search was conducted to identify studies that measured basal endogenous oxytocin concentrations in depressive patients and healthy controls. We included $k = 13$ studies ($n = 368$ patients and $n = 346$ healthy controls) in the qualitative review and $k = 9$ studies ($n = 273$ patients and $n = 273$ healthy controls) in the meta-analytic procedure.

Standardized mean group differences were non-significant ($g = -0.02$, CI = [−0.41; 0.36]), indicating that depressive patients and healthy controls did not differ in basal endogenous oxytocin concentrations. The overall effect was heterogeneous. Effects within studies showing comparable risks of biases, as rated according to the Newcastle-Ottawa Quality Assessment Scale, were non-significant as well, but homogeneous.

The findings suggest that more complex research designs and methodological approaches should be employed to detect and understand a possible role of the oxytocin system in depressive disorders. We provide recommendations for subsequent promising study designs, involving the consideration of illness phase, comorbidities and correlations with psychological functions or symptoms. We point out the strengths of reactivity designs and multidimensional measurement approaches and recommend to linking future research questions to theories of depression.

1. Introduction

Depressive disorders are characterized by affective symptoms such as depressed mood, loss of interest and enjoyment, reduced energy, increased fatiguability, and diminished activity (American Psychiatric Association, 2013). They are complex disorders, as they comprise various subtypes, characterized by co-occuring symptoms and chronicity, and are often accompanied by comorbidities. Furthermore, depressive disorders are influenced by multiple psychological, social and biological factors (Kendler et al., 2006, 2002) which has implications for their treatment. Besides the key symptoms, depressive patients often experience impairments in other psychological domains that are relevant for everyday life functioning, such as social behavior or stress regulation. Since oxytocin influences these domains, it appears interesting to investigate it as a possible biomarker for depression.

1.1. The physiological basis of the oxytocin system

The neuropeptide oxytocin is synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei and in parvocellular neurons of the paraventricular nucleus of the hypothalamus (Meyer-Lindenberg et al., 2011). Its neurotransmissive and neuromodulatoty actions are an essential part of the hypothalamo-neurohypophysial system (Neumann, 2008). Through both, diffuse dendritic release and targeted neuronal projections, oxytocin exerts its central impact, mediated by function of its receptors (Meyer-Lindenberg et al., 2011; Neumann, 2008). Oxytocin's target brain regions are the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis and brainstem (Landgraf and Neumann, 2004; Meyer-Lindenberg et al., 2011). In addition to its central distribution, oxytocin is released from the neurohypophysial terminal into the bloodstream

* Corresponding author.
E-mail addresses: s.engel@fu-berlin.de (S. Engel), sebastian.laufer@fu.berlin.de (S. Laufer), christine.knaevelsrud@fu-berlin.de (C. Knaevelsrud), sarah.schumacher@fu-berlin.de (S. Schumacher).

https://doi.org/10.1016/j.psyneuen.2018.11.011
Received 31 May 2018; Received in revised form 10 September 2018; Accepted 6 November 2018

(Neumann, 2008). Peripheral oxytocin receptors have been identified in the reproductive organs, mammary tissue, kidney, heart, thymus, fat cells, pancreas and adrenal gland (Gimpl and Fahrenholz, 2001). Most knowledge about oxytocin's functions has been derived from animal studies (Gimpl and Fahrenholz, 2001), as they provide a large variety of complementary methods to examine the behavioral effects of exogenous oxytocin administration or endogenous oxytocin availability. Approaches range from intracerebroventricular administration of synthetic oxytocin or selective oxytocin receptor antagonists, over transgenic or gene knockout models, to virally mediated gene transfer or administration of antisense oligodeoxynucleotides (Neumann, 2008). However, in humans, the number of methods to investigate the physiological or psychological consequences of oxytocin is more limited. Unlike intravenous administration approaches, intranasally administered neuropeptides were shown to cross the blood-brain barrier (Born et al., 2002). By this means, behavioral consequences of artificially increased central oxytocin availability can be measured. This approach has most frequently been used to assess oxytocin's functions in humans. It is particularly convenient for laboratory settings. Beyond that, it is possible to correlate endogenous oxytocin concentrations to physiological or psychological functions. This approach encompasses both, central and peripheral pathways. Central concentrations can be derived from cerebrospinal fluid, whereas peripheral ones can be measured in blood plasma, blood serum, saliva, or urine (Feldman, 2012). Endogenous oxytocin concentrations have frequently been assessed to investigate possible neuroendocrine dysregulations in the context of mental disorders (Rutigliano et al., 2016). As oxytocin's impact also depends on receptor function, it is reasonable to combine endogenous measurements with measures of oxytocin receptor gene variation or methylation (Meyer-Lindenberg et al., 2011).

1.2. Oxytocin's impact on depression-related psychological and physiological functions

1.2.1. Oxytocin and social behaviors

These approaches have complementarily been applied in order to understand oxytocin's impact on psychological functions, such as social behaviors or stress regulation. Studies demonstrated that oxytocin regulates a range of distinct behaviors that, in general, can be described as prosocial. It has been shown to increase willingness to bind, interact and cooperate with others (for overview articles, see Heinrichs et al., 2009; Meyer-Lindenberg et al., 2011). Specifically, experimental studies that intranasally administered oxytocin or a placebo to healthy humans indicated that oxytocin promotes initial trust (Kosfeld et al., 2005; Mikolajczak et al., 2010a,b; Theodoridou et al., 2009) and trust after betrayal (Baumgartner et al., 2008), perceived attractiveness of faces (Theodoridou et al., 2009), positive communication behavior (Ditzen et al., 2009) and parochial altruism (de Dreu et al., 2010). Moreover, its key role in attachment between parent and child, affiliative and romantic partners, has been extensively studied by means of various complementary approaches comprising endogenous measurements, molecular genetic and intranasal administration approaches (for an overview article, see Feldman, 2012). These effects are assumed to be mediated by oxytocin-induced anxiety reduction, increase of social salience of situational cues and increase of affiliation motivation (Bartz et al., 2011). However, they are also moderated by contextual and interindividual factors, instead of being prosocial in general (Bartz et al., 2011; Olff et al., 2013).

A possible link between the oxytocin system and depression can be established as impairments in social behaviors play a role in the development, maintenance and treatment of depressive disorders. With regard to the development of depressive disorders, loneliness increases the risk for depression (Cacioppo et al., 2006), whereas social support protects against it (Gariépy et al., 2016). In manifest depressive disorders, social withdrawal and decreased social skills represent prominent symptoms (Tse and Bond, 2004). Furthermore, with regard to information processing, cognitive biases might lead depressed patients to interpret social cues more pessimistically (Strunk and Adler, 2009). The promotion of social functioning, by means of a restoration of social contacts, relationships and behavioral skills, are targeted by psychotherapeutic as well as pharmacological treatments (Franck et al., 2016; Hirschfeld et al., 2000; Renner et al., 2014).

1.2.2. Oxytocin and stress regulation

Evidence from animal studies shows that social relationships influence hypothalamic-pituitary-adrenal axis regulation (Levine, 2001; Ros-Simó and Valverde, 2012; Serra et al., 2005) Interestingly, alterations of this neuroendocrine stress system represent a prominent finding in depression, as well (Strawbridge et al., 2017). Specifically, depressive disorders are characterized by hypercortisolism and an attenuated cortisol awakening response with some evidence also pointing towards depression-related elevations in corticotrophin-releasing hormone and adrenocorticotropin hormone levels (Strawbridge et al., 2017). Presumably, this hyperactivated physiological stress system underlies high subjective stress experiences in depressive patients.

Oxytocin is known to dampen both, subjective and physiological stress. Intranasal oxytocin administration was shown to reduce reactivity to psychosocial stress, as measured by salivary cortisol and a psychological questionnaire (Ditzen et al., 2009; Heinrichs et al., 2003). Meta-analytic evidence showed a positive correlation between endogenous oxytocin and cortisol, suggesting that both hormones are initially co-released in response to immediate stress (Brown et al., 2016). Over time, however, oxytocin seems to reduce cortisol release, as a significant decrease of cortisol levels after exogenous oxytocin administration was reported in another meta-analysis (Cardoso et al., 2014). This effect was especially high in clinical populations.

1.3. Current evidence for the role of oxytocin in depression

In conclusion, the oxytocin system is involved in psychological functions that are impaired in depression and interconnected with their biological correlates. Hence, it might be worthwhile to investigate if alterations in the oxytocin system contribute to the development and maintenance of depressive disorders. Several research groups have already compared basal endogenous oxytocin concentrations between depressive patients and healthy controls and first attempts have been made to systematically summarize their findings.

To date, four systematic reviews focused on this topic. Cochran et al. (2013) provided a systematic overview of aberrations in parameters of the oxytocin system in mental disorders, including a section on mood disorders. McQuaid et al. (2014) developed a comprehensive rationale of investigating the oxytocin system in depressive disorders, based on empirical findings on interactions between the oxytocin system and other biological systems that are relevant for depression. Massey et al. (2016) summarized studies on the correlation between depressive symptom severity and endogenous oxytocin concentrations. These three reviews provided detailed overviews on their respective topics but are merely descriptive and lack meta-analytic procedures. Rutigliano et al. (2016), however, applied meta-analytic computations and provided aggregated effect size estimates regarding differences in endogenous oxytocin concentrations between patients with mental disorders and healthy controls. However, they included only two studies investigating these differences with regard to depressive disorders, specifically. No overall effect of depression on oxytocin concentrations was found, but the review clearly lacked a sufficient number of studies to draw robust conclusions.

Addressing this research gap, the present review aimed at systematically summarizing studies that investigated differences in endogenous oxytocin concentrations between patients with depressive disorders and healthy controls. By focusing on depression instead of general psychopathology, we aimed to extend preliminary findings from previous reviews by identifying a sufficiently high number of

studies to perform more robust meta-analytic comparisons.

1.4. Objectives

This is the first systematic review and meta-analysis with the particular focus of comparing endogenous oxytocin concentrations between patients with depressive disorders and healthy controls. We defined our main structured review questions according to the PICOS framework by the PRISMA group (Moher et al., 2009): As target population, we defined in- and outpatients with a depressive disorder. As our meta-analysis focused on basal oxytocin concentrations, we included studies without regard to whether an intervention was evaluated, too. As comparison group, healthy individuals were included. The difference in endogenous oxytocin levels between depressive and healthy individuals was our main outcome. Consequently, we included exclusively between-groups designs.

2. Methods

2.1. Protocol and registration

This study is based on a subset of data from a larger methodological review investigating basal endogenous oxytocin concentrations of healthy humans (Engel et al., in prep.) The larger review was pre-registered at PROSPERO (Registration number: CRD42017072306) on the 17th of July 2017. It is available online from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017072306.

2.2. Eligibility criteria

Studies were eligible for inclusion if they compared endogenous oxytocin concentrations between patients with a depressive disorder and healthy controls. In terms of the target population, we included studies investigating adult (mean age ≥18 years) in- and outpatients with current or chronic depressive disorders. As such, we considered patients diagnosed with current depressive episode, recurrent depressive disorder, or dysthymia. We did not define exclusion criteria with regard to comorbidities. For the meta-analytic procedure, we focused on comparisons of basal oxytocin concentrations. Intervention studies were included only if oxytocin was assessed at baseline. Concerning the comparison population, we included adults without any mental disorder, physical disease, injury or pregnancy. Studies were required to report differences in endogenous oxytocin concentrations in blood plasma, blood serum, saliva, urine or cerebrospinal fluid (CSF) between the target and comparison population as outcomes. We also included studies that did not report such differences but provided sufficient data to calculate an effect size. In terms of study designs, we included cross-sectional and longitudinal between-groups designs. Within- and single group designs, case studies, reviews and meta-analyses were excluded. Published and unpublished studies in English or German language were considered. Qualitative studies and reviews were excluded. There were no restrictions regarding publication year.

2.3. Search strategy and selection of studies

2.3.1. Literature search strategy

As this meta-analysis is based on a subset of studies from a larger systematic review, we applied the same electronic search strategy as in the larger review (Engel et al., in prep.) and then adapted the screening process for the purposes of the present study. The literature search aimed at identifying all studies measuring basal endogenous oxytocin concentrations in healthy humans and followed the search strategies recommended by Lipsey and Wilson (2001). The following electronic bibliographic databases were searched up to 28th of March 2017: *PsycINFO, PubPsych, PsycARTICLES, PubMed, Web of Science, BIOSIS and ProQuest Dissertations and Theses Global*. Furthermore, we searched through study registers at *Clinicaltrials.gov*. As search terms, ((oxytocin) AND (blood OR plasma OR serum OR CSF OR cerebrospinal fluid OR urine OR urinary OR saliva OR salivary)) were applied to search through titles, abstracts and keywords. Additionally, we examined the grey literature in order to identify further published or unpublished studies. Therefore, abstracts of conference contributions, posters and commentaries were screened and we contacted experts in the field. Moreover, we applied a snowball search system by screening the reference lists of reviews and relevant empirical articles.

2.3.2. Study selection

In the process of study selection, we aimed at including all studies that investigated differences in endogenous oxytocin concentrations between healthy individuals and patients with depressive disorders. In a first step, titles and abstracts of all studies that resulted from our systematic literature research were screened, excluding duplicates and studies meeting the exclusion criteria of the larger review. We did not include study registers but contacted the corresponding authors to inquire whether data were already accessible. If abstracts or full-texts were not available, we contacted the corresponding authors and asked for access to the paper.

In a second step, full-texts articles were read to decide if studies met one of the exclusion criteria listed above or were eligible for inclusion. Accordingly, all studies assessing basal endogenous oxytocin concentrations in healthy humans were kept.

In a third step, all studies meeting the inclusion criteria of the present review were identified. Therefore, we included studies that additionally comprised a sample of depressive patients and compared basal oxytocin concentrations between this sample and the healthy controls.

Steps one and two were performed by one researcher (SE). Step three was conducted as follows: Studies considered as eligible were randomized based on a computerized tool and assigned to a team of two researchers (SE and AW or SL and HK), respectively. Researchers within one team independently decided about exclusion or inclusion. In case of disagreements, a third independent researcher (SL or SE, respectively) was consulted for the final decision.

2.4. Data extraction and preparation

2.4.1. Data collection process

We used a pre-defined coding manual to extract relevant data from the primary studies. Extraction was performed by one researcher (SE) and checked by a second, independent researcher (SL). In case of disagreements, a third independent researcher (SSch) was consulted for the final decision. If data that was relevant for the meta-analytic procedure was not obtainable from the original paper, we contacted the corresponding authors via email and asked them to provide us with the information. Studies that did not report sufficient data for the meta-analytic procedures were considered in the descriptive, but not in the statistical part of the review. The same applied for sample overlaps. Concerning overlapping studies, we included the one that provided a larger sample in the meta-analysis.

2.4.2. Extracted data

For the descriptive part of the review, we extracted information about the patient and comparison populations, as well as about methodological aspects of the studies. In terms of the target population, we extracted number, sex distribution and age of depressive patients, their patient status (inpatients vs. outpatients) and exact diagnosis, the diagnostic instruments that were used to assess depression, medications and comorbidities. Concerning the healthy comparison population, we extracted number, sex distribution and age of participants. Furthermore, we assessed if an additional comparison population was investigated. In terms of general methodological aspects, we extracted information about the study design (cross-sectional vs. longitudinal)

and a description of paradigms or interventions that were evaluated. Concerning the assessment of oxytocin, assessment design (e.g. basal, diurnal profile or reactivity), number of measurement points, time of day and the measurement method (e.g. blood or CSF) were extracted.

Differences in basal endogenous oxytocin concentrations between healthy participants and patients with a depressive disorder were statistically compared using meta-analytic procedures. For this purpose, we extracted the means and standard deviations of oxytocin, as well as the number of participants per healthy or depressive sample, respectively. If oxytocin concentrations were not reported in texts or tables but shown in figures, an online plot digitizer was used for extraction (Rohatgi, 2015). This tool was applied in a recent meta-analysis on endogenous oxytocin and yielded good results (Valstad et al., 2017).

2.5. Risk of bias in individual studies

By means of an established and validated scale, we assessed the general quality of primary studies. Specifically, we chose the Newcastle-Ottawa Quality Assessment Scale (Wells et al., 2018) for case-control studies, as the inclusion criteria of the present review required individual studies to apply a between-groups design. The NOS can be used to rate the risk of bias in case-control studies in three different domains, that are, selection of cases and controls, comparability of cases and controls and ascertainment of exposure or, in the case of our review, ascertainment of outcome. A primary study can obtain a pre-defined number of possible stars per domain. The scale is standardized, but adaptable to the specific purpose of a review, for instance by defining important covariates that should be considered. Within the domain selection of cases and controls, four items are rated, implying that primary studies can obtain a maximum of four stars. For instance, studies received one star if cases (i.e. depressive patients) were identified by means of an adequate method, such as a standardized clinical interview or medical records, instead of self-report questionnaire data. With regard to the comparability of cases and controls, a maximum of two stars can be awarded if primary studies controlled for age or sex. Within the domain ascertainment of outcome, by rating three items, a maximum of three stars can be awarded. For instance, primary studies received a star if the same procedure and method to assess endogenous oxytocin was applied for depressive patients and healthy controls. Therefore, by answering eight items, a maximum of nine stars can be obtained by each study, with a higher number of stars indicating higher study quality and lower risk of bias.

Two researchers (SE and SL) applied the NOS independently to estimate the quality of the included studies. In case of disagreements, a third independent researcher (SSch) was consulted for the final decision. The result of these ratings, i.e. the general study quality (low vs. medium vs. high) was used as a moderator in subgroup analyses of the meta-analytic effects. By this means, we tested whether potential heterogeneity of effects might be reduced within groups of studies of similar quality.

2.6. Meta-analytic procedure

To test the standardized mean differences in basal endogenous oxytocin concentrations between healthy participants and patients with a depressive disorder, Hedges' g was used (Borenstein et al., 2009, 2009). This coefficient represents the difference between means of healthy and depressive participants, divided by the pooled standard deviation and adjusted for a small sample bias. Its confidence interval (CI) was used to display the precision of the effects. Positive Hedges' g estimated with a CI above zero indicated that basal oxytocin concentrations were higher in healthy participants compared with patients with a depressive disorder. According to Cohen (1988), Hedges'$g < 0.5$ can be considered as small, $0.5 \leq g < 0.8$ as medium and $g \geq 0.8$ as large.

As indicators of heterogeneity, we used the Q-statistic and the I^2-index (Borenstein et al., 2009). Q represents the sum of the products of weights and squared differences between study and summary effect sizes. Significant Q-statistics indicate heterogeneity of effects. I^2 indicates the proportion of total variance that is attributable to real variance between studies. According to Higgins and Thompson (2002), I^2 values of 25%, 50% and 75% indicate low, moderate, and high heterogeneity, respectively. In case of significant heterogeneity of effects, we applied subgroup analyses to test whether effects are homogeneous within subgroups of studies. As possible moderators, we considered measurement method of oxytocin, chronicity of depressive disorder, time of day of sampling, sex, age differences between groups, and general study quality.

We used Egger's regression test (Egger et al., 1997) and Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie, 2000) to test for publication bias across studies. These tests were only applied for homogenous data sets including at least six primary studies (Ioannidis, 2005; Peters et al., 2007; Rothstein and Bushman, 2012; Terrin et al., 2003). All calculations were conducted with the Comprehensive Meta-Analysis software (Biostat, 2014).

3. Results

3.1. Study selection

The flowchart summarizing the number of studies that were screened, assessed for eligibility, and included in the review is presented in Fig. 1. Thirteen studies fulfilled the criteria and were included in the descriptive part of the review. Nine studies were published in scientific journals (Cyranowski et al., 2008; Jobst et al., 2015; Ozsoy et al., 2009; Parker et al., 2010; Pitts et al., 1995; Sasayama et al., 2012; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014) and four were abstracts of conference contributions (Frasch et al., 1995; Lien et al., 2016; Zetzsche et al., 1996, 1995).

From the pool of thirteen included studies, nine were also used in the meta-analytic procedure. From two studies with overlapping samples (van Londen et al., 1998; van Londen, 1997), the study providing the larger sample was used (van Londen, 1997). Three studies did not provide sufficient data to be included in the meta-analysis (Frasch et al., 1995; Zetzsche et al., 1996, 1995).

3.2. Study characteristics

3.2.1. Sample characteristics

Table 1 provides an overview on the samples of patients with a depressive disorder and Table 2 on the comparison populations. Concerning patients with a depressive disorder, the descriptive part of this review summarizes data from $n = 368$ patients ($n = 357$ patients with valid oxytocin values). Sizes of patient samples ranged from $n = 12$ to $n = 97$. One patient sample was exclusively female (Cyranowski et al., 2008), five were predominantly (> 50%) female (Lien et al., 2016; Parker et al., 2010; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014), two were predominantly (> 50%) male (Jobst et al., 2015; Pitts et al., 1995) and one was exclusively male (Sasayama et al., 2012). The mean age varied between 31 and 48 years between studies. With one exception focusing on chronically depressed patients (Jobst et al., 2015), all studies included patients with current depression (major depressive disorder or major depressive episode, (Cyranowski et al., 2008; Frasch et al., 1995; Lien et al., 2016; Ozsoy et al., 2009; Parker et al., 2010; Pitts et al., 1995; Sasayama et al., 2012; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014; Zetzsche et al., 1996, 1995). The most frequently used instrument to assess depression was the Hamilton Rating Scale for Depression (Hamilton, 1960) (Cyranowski et al., 2008; Jobst et al., 2015; Ozsoy et al., 2009; Parker et al., 2010; Pitts et al., 1995; Sasayama et al., 2012; Yuen et al., 2014). Five studies employed a standardized clinical interview (Cyranowski et al., 2008; Jobst et al., 2015; Pitts et al., 1995; van Londen et al.,

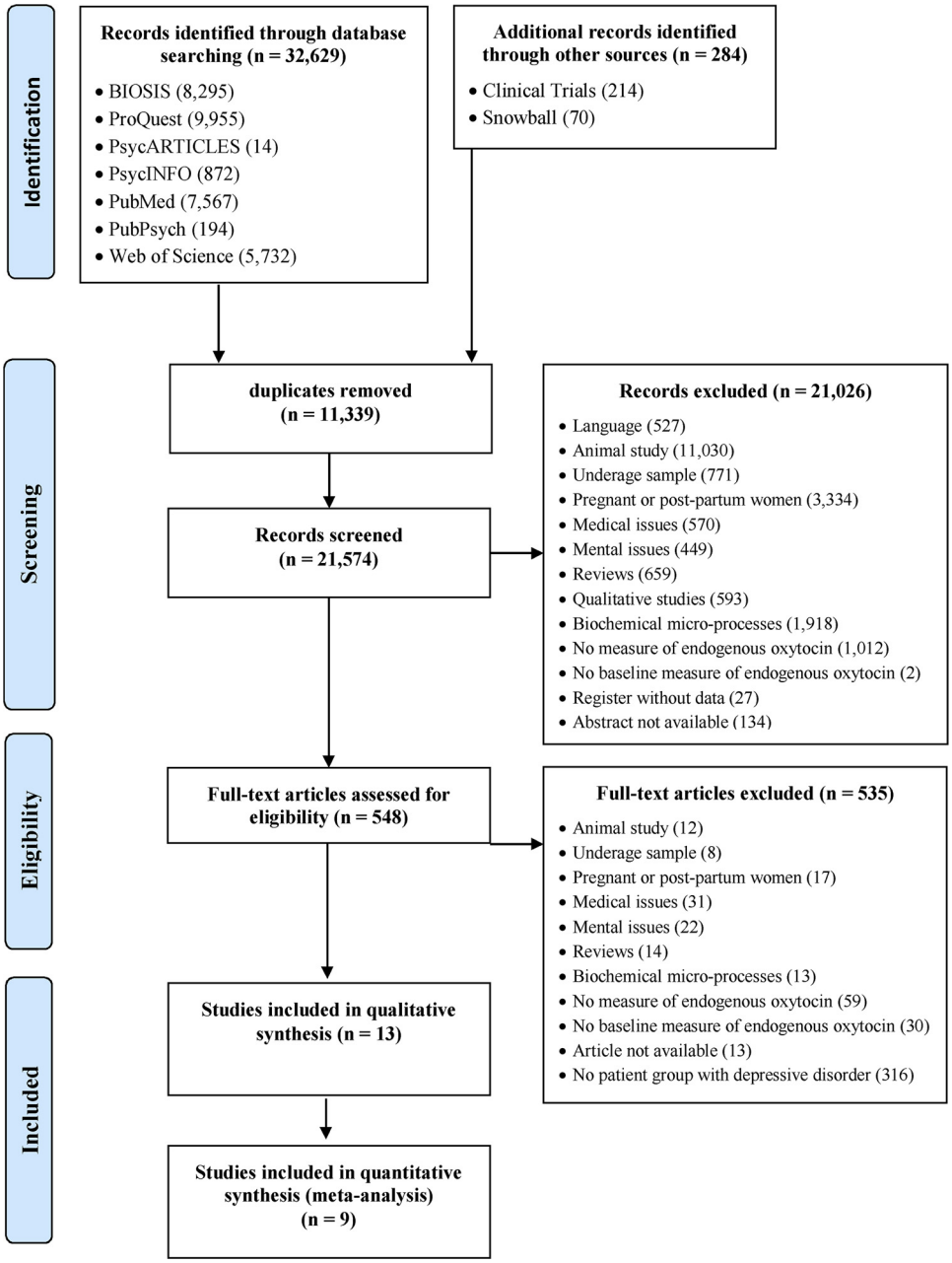

Fig. 1. Flowchart: Identification and selection of primary studies.

1998; van Londen, 1997). Studies were heterogeneous in terms of the patients' status. Four included exclusively inpatients (Cyranowski et al., 2008; Jobst et al., 2015; Ozsoy et al., 2009; Pitts et al., 1995), two exclusively outpatients (Parker et al., 2010; Sasayama et al., 2012) and two included both (van Londen et al., 1998; van Londen, 1997). Information about medication was also heterogeneous. Five studies had medication-free samples (Cyranowski et al., 2008; Lien et al., 2016; Ozsoy et al., 2009; van Londen et al., 1998; van Londen, 1997) and five studies reported the kind of medication each patient used (Jobst et al., 2015; Parker et al., 2010; Pitts et al., 1995; Sasayama et al., 2012; Yuen et al., 2014). Notably, only one study reported comorbid diagnoses (Jobst et al., 2015).

Concerning the healthy control groups, the descriptive part of this review summarizes data from $n = 346$ participants ($n = 339$ participants with valid oxytocin values). Sizes of healthy samples ranged from $n = 12$ to $n = 96$. One sample was exclusively female (Cyranowski et al., 2008), six were predominantly (> 50%) female (Lien et al., 2016; Ozsoy et al., 2009; Parker et al., 2010; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014), in one study, the sex distribution was balanced (Pitts et al., 1995), two studies were predominantly (> 50%) male (Jobst et al., 2015; Parker et al., 2010; Pitts et al., 1995) and one was exclusively male (Sasayama et al., 2012). The mean age varied between 27 and 47 years between studies. Four studies utilized another clinical comparison group. Two studies additionally investigated bipolar disorder patients (Ozsoy et al., 2009), and one inspected schizophrenia patients (Sasayama et al., 2012) and patients with psychotic major depression (Yuen et al., 2014), respectively.

3.2.2. *Methodological aspects*

In terms of study designs, results are summarized in Table 3. Most studies explicitly addressed possible differences in endogenous oxytocin concentrations between depressive patients and healthy controls (Cyranowski et al., 2008; Frasch et al., 1995; Jobst et al., 2015; Parker et al., 2010; Sasayama et al., 2012; van Londen et al., 1998; van

Table 1
Descriptives with regard to patient populations.

Study name	*n* (OT)[a]	% f	Age[b]	Status	Diagnosis	Instruments	Medication	Comorbidities
*Cyranowski et al. (2008)	17 (15)	100	31 (7)	Inpatients	Current major depressive disorder	SCID-I; BDI-II; HRSD	No antidepressant medication 2 weeks prior to the study	N/A
Frasch et al. (1995)	12	N/A	N/A	N/A	Major depression	N/A	N/A	N/A
*Jobst et al. (2015)	21 (19)	32	46 (16)	Inpatients	Dysthymia and depressive episode lasting longer than 2 years	SCID-I (Screening);SCID-II; BDI-II; HRSD	Antidepressants (n = 17); second generation antipsychotics (n = 10); benzodiazepines (n = 8); mood stabilizers (n = 9);	Depressive PD (n = 5); avoidant PD (n = 4); obsessive-compulsive PD (n = 4); paranoid PD (n = 2); dependent PD (n = 2); antisocial PD (n = 2); negativistic PD (n = 1); schizoid PD (n = 1); narcissistic PD (n = 1); borderline PD (n = 1); histrionic PD (n = 1)
*Lien et al. (2016)	97	71	N/A	N/A	Major depressive disorder	N/A	none	N/A
*Ozsoy et al. (2009)	29	N/A	N/A	Inpatients	Major depressive disorder	Clinical interviews; HDRS	none	N/A
*Parker et al. (2010)	11	64	41 (15)	Outpatients	Major depression	HDRS; CES	No medication (n = 4); antidepressants (n = 6); concomitant anxiolytics and antidepressants (n = 1);	N/A
*Pitts et al. (1995)	19	47	37 (14)	Inpatients	Major depressive disorder	SADS; HDRS	Tricyclics (n = 10); monoamine oxidase inhibitors (n = 2); lithium carbonate (n = 2); antipsychotics (n = 1); benzodiazepines (n = 5)	N/A
*Sasayama et al. (2012)	17	0	39 (8)	Outpatients	Major depressive disorder	unstructured interviews; information from medical records; HDRS	Antidepressants (n = 12); antipsychotics (n = 6); benzodiazepines (n = 13); mood stabilizers (n = 1)	N/A
*van Londen (1997)	56 (52)	58	45 (14)	Inpatients (n = 18) and outpatients (n = 34)	Major depressive episode	CPRS; MADRS	Medication free at least 2 weeks prior to the study; except for clorazepate, oxazepam or temazepam (n = 9)	N/A
van Londen et al. (1998)	48	56	45 (14)	Inpatients (n = 15) and outpatiens (n = 33)	Major depressive episode	CPRS; MADRS	Medication free at least 2 weeks prior to the study; except for clorazepate, oxazepam or temazepam (n = 8)	N/A
*Yuen et al. (2014)	17 (14)	64	48 (12)	N/A	Major depressive disorder without psychosis	MCMI-II/III; HAMD	No psychiatric medications (n = 2); antidepressants (n = 10); antipsychotics (n = 8); anxiolytics (n = 4); mood stabilizers (n = 4)	N/A
Zetzsche et al. (1995)	12	N/A	N/A	N/A	Major depression	N/A	N/A	N/A
Zetzsche et al. (1996)	12	N/A	N/A	N/A	Major depression	N/A	N/A	N/A

Notes. % f = percentage of female patients; N/A = information not available; MDBDI-II = Beck Depression Inventory II; CES = Thase Core Endogenomorphic Scale; CPRS = Comprehensive Psychopathological Rating Scale; HRSD = Hamilton Rating Scale for Depression; MADRS = Montgomery and Åsberg Depression Rating Scale; MCMI-II/III = Million Clinical Multiaxial Inventory; SADS = Schedule for Affective Disorders and Schizophrenia; SCID-I = Structured clinical interview for DSM-IV axis I disorders; SCID II = Structured clinical interview for DSM-IV axis II disorders; PD = personality disorder.

[a] Number of participants with valid oxytocin (OT) values are shown in brackets.

[b] Data are presented as M (SD).

* Study was included in meta-analytic procedure.

Table 2
Descriptives with regard to comparison populations.

	Healthy controls				Other control group	
Study name	Description	*n* (OT)[a]	% female	Age[b]	Description
*Cyranowski et al. (2008)	Controls who never met current or lifetime criteria for any mood disorder	17 (15)	100	27 (5)	None
Frasch et al. (1995)	Healthy controls, matched for age	12	N/A	N/A	None
*Jobst et al. (2015)	Healthy controls, matched for gender, age and education, without current psychiatric disorder, lifetime psychiatric treatment and any psychological treatment in the past 10 years	21 (19)	32	47 (14)	None
*Lien et al. (2016)	Healthy controls	96	57	N/A	Bipolar II patients with current depressive episode
*Ozsoy et al. (2009)	Mentally healthy controls	32	62	40 (10)	Bipolar affective disorder patients with current depressive episode
*Parker et al. (2010)	Healthy controls without psychiatric medication use	19	47	34 (15)	None
*Pitts et al. (1995)	Healthy controls without personal or first-degree family history of psychiatric illness	18 (17)	50	31 (11)	None
*Sasayama et al. (2012)	Healthy controls without current or past history of psychiatric treatment and without axis I psychiatric disorder	21	0	38 (15)	Schizophrenia patients
*van Londen (1997)	Healthy controls without lifetime or present mental illness	37	54	41 (15)	None
van Londen et al. (1998)	Healthy controls without history of mental illness	30	57	42 (16)	None
*Yuen et al. (2014)	Healthy controls without history of axis I disorders, without psychiatric medication, without electroconvulsive shock therapy, without substance abuse problems in the last six months	19 (17)	53	37 (13)	Psychotic major depressive patients
Zetzsche et al. (1995))	Normal controls, matched for age	12	N/A	N/A	None
Zetzsche et al. (1996)	Controls, matched for age	12	N/A	N/A	None

Notes. % f = percentage of female participant; N/A = information not available.
[a] Number of participants with valid oxytocin (OT) values are shown in brackets.
[b] Data are presented as M (SD).
* Study was included in meta-analytic procedure.

Londen, 1997; Yuen et al., 2014; Zetzsche et al., 1996, 1995). Interestingly, some studies also investigated other hormones in addition to oxytocin, namely cortisol (Jobst et al., 2015; Zetzsche et al., 1996) and arginine vasopressin (van Londen et al., 1998; van Londen, 1997).

Eleven cross-sectional (Cyranowski et al., 2008; Frasch et al., 1995; Jobst et al., 2015; Parker et al., 2010; Pitts et al., 1995; Sasayama et al., 2012; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014; Zetzsche et al., 1996, 1995) and two longitudinal (study period > 1 day) studies, evaluating the effects of medical treatment (Lien et al., 2016; Ozsoy et al., 2009) were included. Two studies implemented reactivity designs. One assessed oxytocin reactivity to an affiliation-focused guided imagery task and a speech stress task (Cyranowski et al., 2008) and the other one to a social exclusion paradigm (Jobst et al., 2015). Seven studies measured diurnal (van Londen et al., 1998; van Londen, 1997) or nighttime profiles (Frasch et al., 1995; Parker et al., 2010; Yuen et al., 2014; Zetzsche et al., 1996, 1995) and four applied single basal measurements of oxytocin (Lien et al., 2016; Ozsoy et al., 2009; Pitts et al., 1995; Sasayama et al., 2012). The number of collected samples ranged from 1 to 36. The results concerning the time of day of sampling were highly heterogeneous. In terms of measurement methods, most studies measured oxytocin in blood plasma or serum (Cyranowski et al., 2008; Frasch et al., 1995; Jobst et al., 2015; Lien et al., 2016; Ozsoy et al., 2009; Parker et al., 2010; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014; Zetzsche et al., 1996, 1995) and two in CSF (Pitts et al., 1995; Sasayama et al., 2012). Concerning the biochemical assays, six studies measured oxytocin by means of an radioimmunoassay (Cyranowski et al., 2008; Ozsoy et al., 2009; Parker et al., 2010; Pitts et al., 1995; van Londen et al., 1998; van Londen, 1997) and five studies applied an enzyme immunoassay (Jobst et al., 2015; Sasayama et al., 2012; Yuen et al., 2014; Zetzsche et al., 1996, 1995). Two studies did not provide information about the assay (Frasch et al., 1995; Lien et al., 2016). Extraction was performed in five studies (Cyranowski et al., 2008; Parker et al., 2010; van Londen et al., 1998; van Londen, 1997; Yuen et al., 2014). One study reported that extraction was not performed (Pitts et al., 1995) and seven studies did not provide information on this issue (Frasch et al., 1995; Jobst et al., 2015; Lien et al., 2016; Ozsoy et al., 2009; Sasayama et al., 2012; Zetzsche et al., 1996, 1995).

3.3. Risk of bias within studies

The NOS ratings for the individual studies ranged from four to eight stars ($M = 5.69$, $Md = 6$, $SD = 1.07$). Ratings for individual primary studies are reported in Table 3.

3.4. Differences in endogenous oxytocin between healthy and depressive populations

In the meta-analytic part of this review, valid oxytocin data from $n = 273$ healthy participants and patients with a depressive disorder were included, respectively, resulting in a summary sample size of $n = 546$. The result is summarized in Fig. 2.

The mean standardized difference between healthy and depressive populations was $g = -0.02$ and non-significant (CI = [−0.41; 0.36]). The effect was heterogeneous ($Q = 38.41$, $p < .01$, $I^2 = 76.57$). Most of the pre-defined moderators failed to reduce heterogeneity of the effects. For an overview, see Appendix A. Whereas measurement method of oxytocin, chronicity of depressive disorder, time of day of sampling, sex and age differences between groups failed to substantially reduce heterogeneity, study quality contributed to a reduction. Within the three studies of high quality (Cyranowski et al., 2008; Jobst et al., 2015; van Londen, 1997), there was no significant difference between healthy participants and depressive patients ($g = -0.31$, CI = [−0.68; 0.07]). This effect was homogeneous ($Q = 2.66$, $p = .26$, $I^2 = 24.73$). The effect within the three studies of the lowest quality within our study pool (Lien et al., 2016; Parker et al., 2010; Pitts et al., 1995), was

Table 3
Descriptives with regard to study methodology.

Study name	Study aim[a]	Design	Paradigms or intervention	Assessment design	Measurement points	Time of day	Measurement method	Assay	Extraction	NOS rating
*Cyranowski et al. (2008)	To compare patterns of peripheral oxytocin release exhibited by depressed and nondepressed women	CS	Affiliation-focused Guided Imagery task and Speech Stress task	Reactivity (60 min)	24	2 p.m.[b]	Blood	RIA	Yes	7
Frasch et al. (1995)	To measure oxytocin plasma levels in patients suffering from major depression and in a control group of healthy age-matched volunteers	CS	None	Nighttime profile	N/A	N/A	Blood	N/A	N/A	5
*Jobst et al. (2015)	To investigate how social exclusion affects emotions, oxytocin levels, and cortisol levels in patients with chronic depression and healthy controls	CS	Cyberball	Reactivity (40 min)	5	between 8 a.m. and 11 a.m.	Blood	EIA	N/A	8
*Lien et al. (2016)	To investigate the serum oxytocin levels in drug-naïve major depressive disorder patients and bipolar I disorder patients in a depressive episode before and after receiving pharmacological treatment	L	Pharmacological treatment	Basal measurement	1	N/A	Blood	N/A	N/A	4
*Ozsoy et al. (2009)	To test the hypothesis of reduced oxytocinergic activity in depression and to investigate gender differences and the effect of electroconvulsive therapy and antidepressant treatment on oxytocin levels in depressive patients	L	Electroconvulsive therapy or Antidepressant drugs	Basal measurement	1	8 a.m.[b]	Blood	RIA	N/A	6
*Parker et al. (2010)	To test whether depressed subjects exhibit dysregulated oxytocin biology compared to healthy control subjects	CS	None	Nighttime profile	16	hourly from 6 p.m. to 9 a.m. (9 a.m.[b])	Blood	RIA	Yes	5
*Pitts et al. (1995)	To determine relationships among the adrenocorticotropic hormone secretagogues and any changes in the affectively ill	CS	None	Basal measurement	1	4 p.m.[b]	CSF	RIA	No	5
*Sasayama et al. (2012)	To compare the oxytocin levels in CSF of patients with schizophrenia, patients with depression and healthy controls and to investigate the correlation between CSF oxytocin levels and symptom severity of these disorders	CS	None	Basal measurement	1	N/A	CSF	EIA	N/A	6
*van Londen (1997)	To assess plasma concentrations of arginine vasopressin and oxytocin in patients with major depression and healthy controls	CS	None	Diurnal profile	3	8 a.m.[b]; 4 p.m.; 23 p.m.	Blood	RIA	Yes	7
van Londen et al. (1998)	To further explore the finding that mean plasma concentrations of arginine vasopressin, but not of oxytocin were higher in depressed patients than in healthy controls by studying psychomotor retardation by means of an activity monitor	CS	None	Diurnal profile	3	8 a.m.; 4 p.m.; 23 p.m.	Blood	RIA	Yes	5
*Yuen et al. (2014)	To test whether oxytocin concentrations vary systematically in depressive disorders with and without hypercortisolemia, whether gender differences in oxytocin concentrations are observed in depressed vs. healthy control participants, and whether concentrations are predictive of clinical phenotypes	CS	None	Nighttime profile	16	hourly from 6 p.m. to 9 a.m.	Blood	EIA	Yes	6
Zetzsche et al. (1995)	To compare nocturnal patterns of oxytocin secretion in depressive patients and healthy controls	CS	None	Nighttime profile	36	hourly from 8 p.m. to 7 a.m.	Blood	EIA	N/A	5
Zetzsche et al. (1996)	To measure nocturnal oxytocin plasma levels in depressed patients and healthy controls and compare these values with nocturnal cortisol secretion and sleep electroencephalography	CS	None	Nighttime profile	36	hourly from 8 p.m. to 7 a.m.	Blood	EIA	N/A	5

Notes. CS = cross-sectional; L = longitudinal; N/A = information not available; CSF = cerebrospinal fluid; RIA = radioimmunoassay; EIA = enzyme immunoassay; NOS = Newcastle-Ottawa Quality Assessment Scale.
[a] Main scientific question as defined in the primary study.
[b] Value was considered for meta-analytic procedure. If value was not extracted at a specific time, the mean of several timepoints was used.
* Study was included in meta-analytic procedure.

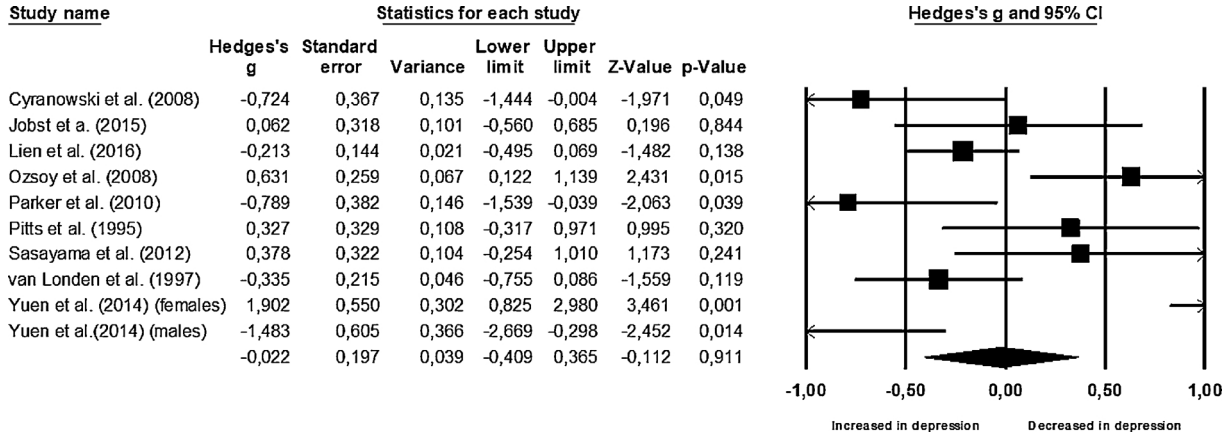

Fig. 2. Summary effect size. Negative values indicate that oxytocin concentrations were lower in healthy controls than in depressive patients.

also non-significant ($g = -0.20$, CI = [−0.69; 0.29]), but as well homogeneous ($Q = 4.95$, $p = .08$, $I^2 = 59.59$).

Due to the high overall heterogeneity and small number of included studies, we refrained from testing publication bias (Ioannidis, 2005; Peters et al., 2007; Rothstein and Bushman, 2012; Terrin et al., 2003).

4. Discussion

4.1. Summary of evidence

The present systematic review and meta-analysis summarized current evidence on differences in basal endogenous oxytocin concentrations between depressive patients and healthy controls. In general, studies varied with respect to clinical and demographic characteristics of patient and control groups as well as concerning methodological aspects of designs, clinical and hormonal assessments. Except for one (Jobst et al., 2015), all studies examined a currently depressed patient group and did not report comorbidities. The standardized mean group difference derived by the meta-analytic procedure was non-significant, indicating that depressive patients did not show altered basal oxytocin concentrations compared with healthy controls. The overall effect was heterogeneous, and so were effects in the subgroup analyses, with the exception of the also non-significant effects within the three studies of low and the three studies of high risk of bias.

As noted before, the assessment of basal concentrations represents a frequently used (Cochran et al., 2013) approach which might be suitable to provide first indications towards aberrations the oxytocin system in mental disorders. Particularly, it is highly questionable whether oxytocin concentrations derived from peripheral body fluids reflect neurotransmissive and neuromodulatoty actions (Valstad et al., 2017). Even though oxytocin concentrations measured in CSF might be more informative in this regard (Meyer-Lindenberg et al., 2011), only two primary studies that were included in the present meta-analysis actually applied this approach. We summarized them separately by means of a subgroup analysis, but the limited available data do not allow for meaningful conclusions based on the statistical synthesis.

Given these theoretical restrictions, the null finding of our meta-analysis does not ultimately implicate that the oxytocin system is not involved in depressive disorders. However, it does implicate that more complex and distinctive research designs and methodological approaches may be more appropriate to detect and understand a possible role of oxytocin in depression. In the following, we integrate our findings into the existing literature and current discussion on this topic and conduct recommendations for promising future research designs.

It needs to be considered that the key affective symptoms of depressive disorders, related to negative mood and loss of energy, do not seem to be closely related to the oxytocin system (Massey et al., 2016). However, impairments in social behavior and stress regulation, two symptoms suggested to be strongly associated with oxytocin (e.g. Feldman, 2012; Heinrichs et al., 2009; Meyer-Lindenberg et al., 2011), are also frequent findings in depression (Cacioppo et al., 2006; Gariépy et al., 2016; Strawbridge et al., 2017; Tse and Bond, 2004). It might be worthwhile to investigate the role of oxytocin with regard to those neuronal processes that result in these symptoms. Even though human studies provide less access to central oxytocinergic mechanisms than animal models, one possible methodological approach might be assessing the consequences of increased central oxytocin availability, established by intranasal peptide administration, on neuronal processes revealed by imaging techniques. Moreover, as the impact of endogenous oxytocin concentrations depends on oxytocin receptor function (Neumann, 2008), the investigation of (epi-)genetic markers of the oxytocin receptor gene might be a meaningful add-on.

In contrast to the non-significant finding of our study, aberrant oxytocin concentrations have been identified as markers for other mental disorders which are more clearly affected by impairments of oxytocin-related functions such as social behavior and stress regulation. The oxytocin system has most frequently been investigated in autism and schizophrenia, but it also seems to play a role in other mental disorders, such as social anxiety disorder or obsessive-compulsive disorder (Cochran et al., 2013). Given the high prevalence of comorbidities in depression, the fact that only one of the primary studies included in this meta-analysis reported them (Jobst et al., 2015) seems worthy of discussion. Insufficient consideration of comorbidities might be an important factor contributing to the heterogeneity of our results. Conversely, missing information and small number of studies prohibited a test of this assumption. We recommend that future studies on oxytocin and depression should take comorbidities into account. This could be done by defining them as an exclusion criterion in order to enable clear conclusions for a well-defined depressive population, by reporting them or controlling for them statistically.

Furthermore, as biomarkers of mental disorders are often criticized for their lack of specificity, it might be promising to correlate hormone concentrations to specific psychological symptoms or functions instead of associating them to the mere presence or absence of a certain disorder. Correlations between affective symptoms and endogenous oxytocin concentrations seem to be weak (Massey et al., 2016). Hence, it might be worthwhile to investigate them in symptoms that on the one hand are prevalent in depression, and on the other hand are known to be strongly influenced by oxytocin. As such, future studies might test associations between oxytocin and social withdrawal or subjective stress in depressive patients.

Moreover, its role in stress regulation suggests that it might be interesting to assess reactivity of the oxytocin system in addition to basal hormone concentrations. Notably, two of the included primary studies

applied reactivity designs (Cyranowski et al., 2008; Jobst et al., 2015). As their paradigms are not comparable, it was not possible to meta-analytically aggregate their effects. However, it is worth noting that preliminary studies on the reactivity of the oxytocin system in socially relevant situations exist, and this approach should be kept in view. Evidence challenging the assumptions that peripheral endogenous concentrations of oxytocin reflect its central availability also recommends the use of reactivity paradigms (Valstad et al., 2017). A meta-analysis showed that central and peripheral concentrations are unrelated under basal, but positively correlated under challenged conditions (Valstad et al., 2017).

A substantial proportion of the theoretical rationale behind the possible involvement of the oxytocin system in depressive disorders is based on its interactions with other depression-related biological systems. As McQuaid et al. (2014) noted, "complex illnesses are typically biochemically heterogeneous". This implies that it might be interesting to apply multi-methodological approaches combining different parameters of the oxytocin system, such as variations or methylation of the receptor gene or reactivity to nasal spray, and multidimensional approaches investigating the co-regulation of the oxytocin and other biological systems. Of particular relevance for depression research are interactions between oxytocin and other biological substances acting on the brain level, such as serotonin norepinephrine, dopamine, growth factors, or cytokines (for an overview article, see McQuaid et al., 2014). Moreover, a combined investigation of parameters of the oxytocin system and the hypothalamic-pituitary-adrenal axis after social stress induction might be an adequate design to understand their respective interactions and impact on depression.

Finally, it could be worthwhile to test assumptions on the influence of oxytocin during specific phases of the course of depressive disorders. Biological systems can be influential during the development, maintenance and treatment of mental disorders. The investigation of basal hormone concentrations, as focused on in this meta-analysis, is an appropriate approach to test if aberrations of the oxytocin systems exists in manifest disorders. Beyond that, empirical findings also propose a possible involvement of oxytocin in the development of depression. For instance, oxytocin has been shown to influence perceived social salience of situations (Bartz et al., 2011), possibly increasing the risk to develop depressive disorders under socially distressing circumstances or in individuals with pre-existing pessimistic cognitive schemata. Moreover, variations of the oxytocin receptor gene were shown to increase the risk to develop depressive symptoms, moderating the impact of early life adversities (Thompson et al., 2014, 2011). Other studies investigated the role of oxytocin with regard to its role in the treatment of depression. Jobst et al. (2018) reported that endogenous oxytocin moderated the outcome of psychotherapy in chronically depressed patients. Preliminary studies evaluated the effects of intranasal oxytocin as adjunctive to psychotherapeutic treatment (MacDonald et al., 2013) and the effects of oxytocin-related pharmacological treatment, especially the agents carbetocin, Mif-1 and nemifitide (Catena-Dell'Osso et al., 2013). Notably, two of the primary studies included in the present review assessed the role of endogenous oxytocin concentrations in pharmacological antidepressant treatment (Lien et al., 2016; Ozsoy et al., 2009).

In line with the reflection about the course of depression, it should be attempted to integrate the assumptions about the involvement of oxytocin in depression into psychopathological theories of this disorder. For instance, an integration of the social salience hypothesis of oxytocin (Bartz et al., 2011) into theories of cognitive biases in depression (Strunk and Adler, 2009) seem interesting. It might be speculated, for instance, that oxytocin increases the subjective salience of social isolation, promoting the impact of loneliness as a risk factor for depression. Considering the broad functions of oxytocin and the large number of theories on depression, many more connections are imaginable.

4.2. Limitations

The results of our study need to be interpreted in the context of its limitations. Even if we succeeded in significantly extending previous meta-analytic evidence, the overall number of primary studies comprised by this meta-analysis was still small, resulting in low statistical power. In connection to this, the meta-analytic effects have mostly been heterogeneous and homogeneity was only present within the small groups of primary studies of comparable risks of biases. It is important to note that even within those two groups, lack of statistical power might have contributed to the non-significant *Q*-test and therefore might have covered actual heterogeneity. The heterogeneity does not seem surprising, considering that our analyses summarized effects across primary studies with diverging populations in terms of clinical and demographic characteristics (ranging from patients in a current depressive episode to dysthymia patients and from exclusively female to exclusively male samples) and methodologies in terms of clinical (ranging from self-report questionnaires to standardized clinical interviews) and hormonal assessments (ranging from blood to CSF oxytocin). Therefore, despite our best efforts, it was not possible to gather sufficient numbers of primary studies within subgroups to substantially reduce heterogeneity and calculate robust effect sizes across them.

Moreover, this review exclusively summarizes evidence on alterations of basal endogenous oxytocin concentrations in depressive patients. Neither does it address reactivity of the oxytocin system, not does it involve multidimensional approaches such as investigations of the oxytocin receptor gene, its methylation or neuronal reactivity to intranasal oxytocin administration. Future research involving these more complex approaches should be kept in view. However, to date, there are not enough studies to summarize evidence beyond the basic approach addressed in our review. At present, no conclusion can be drawn beyond the fact that presumably no alterations in the endogenous oxytocin system in depressive disorders exist.

4.3. Conclusions

To sum up, the results of this systematic meta-analysis showed no significant differences in basal endogenous oxytocin concentrations between depressive patients and healthy controls. We detected significant heterogeneity in the effect that might be attributed to clinical and demographic factors, such as age, sex or comorbidities, as well as to different study designs or hormonal assessments. In order to detect a possible impact of the oxytocin system in disorders, we recommend investigating it with respect to specific oxytocin-related symptoms and functions, to apply reactivity designs as well as multi-methodological or multi-dimensional approaches. It is crucial to control for comorbidities, as they are highly prevalent in depression and interact with the oxytocin system. On a theoretical level, the combination of biological and psychological theories might be useful to inform meaningful future studies that provide a deeper understanding of the oxytocin system in depressive disorders.

Funding

The "Stiftung der Deutschen Wirtschaft" (Germany) 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

SE, SL, CK and SSch designed the study. SE and SL performed the literature research and coordinated the data collection. SE contacted the authors of all primary studies for which data was missing. SE and SL

coordinated the study selection and performed data collection and inspection, as well as the risk of bias rating. SSch acted as independent rater in the data collection and risk of bias rating processes. SE performed the statistical analyses and drafted the manuscript. SSch and CK supervised the meta-analysis. SL, SSch and CK revised the manuscript for important intellectual content.

Conflicts of interest

Mrs. Engel, Mr. Laufer, 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, Hannah Klusmann and Annika Walinski who assisted in gathering full-text articles. We owe thanks to Hannah Klusmann and Annika Walinski for their help in the study selection process, as well. 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.

Appendix A. Results of the subgroup analyses

(Sub)group	Number of studies	Hedges 'g[a]	Confidence interval[a]	Q-value	I^2
All studies	9	−0.02	−0.41 to 0.36	38.41***	76.57
Measurement method	7	−0.12	−0.58 to 0.24	34.46***	79.68
Blood	2	0.35	−0.10 to 0.80	0.01	0.00
CSF					
Depressive disorder	8	−0.03	−0.46 to 0.40	38.22***	79.07
current	1	0.06	−0.56 to 0.68	0.00	0.00
chronic					
Time of day	4	−0.08	−0.65 to 0.49	12.50**	76.00
Morning	5	0.03	−0.58 to 0.64	25.87***	80.67
Others/unknown					
Sex	5	0.13	−0.45 to 0.72	25.85***	84.52
> 50% female	4	−0.35	−1.07 to 0.37	10.76*	72.11
> 50% male					
Age	6	−0.11	−0.70 to 0.49	29.57***	79.71
Depressive patients older	3	0.13	−0.40 to 0.67	8.14*	75.43
Healthy participants older/unknown					
Study quality based on NOS rating	3	−0.31	−0.68 to 0.07	2.66	24.73
> Md	3	0.40	−0.55 to 1.35	17.55**	83.01
= Md	3	−0.20	−0.69 to 0.29	4.95	59.59
< Md					

Notes. Md = Median; NOS = Newcastle-Ottawa Quality Assessment Scale.
[a]Negative values indicate that oxytocin concentrations were lower in healthy controls than in depressive patients.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Arlington, VA.
Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. 15 (7), 301–309. https://doi.org/10.1016/j.tics.2011.05.002.
Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., Fehr, E., 2008. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 58 (4), 639–650. https://doi.org/10.1016/j.neuron.2008.04.009.
Biostat, 2014. Comprehensive Meta Analyses.
Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Introduction to Meta-Analysis. Wiley, Chichester, pp. 225.
Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5 (6), 514–516. https://doi.org/10.1038/nn849.
Brown, C.A., Cardoso, C., Ellenbogen, M.A., 2016. A meta-analytic review of the correlation between peripheral oxytocin and cortisol concentrations. Front. Neuroendocrinol. 43, 19–27. https://doi.org/10.1016/j.yfrne.2016.11.001.
Cacioppo, J.T., Hughes, M.E., Waite, L.J., Hawkley, L.C., Thisted, R.A., 2006. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. Psychol. Aging 21 (1), 140–151. https://doi.org/10.1037/0882-7974.21.1.140.
Cardoso, C., Kingdon, D., Ellenbogen, M.A., 2014. A meta-analytic review of the impact of intranasal oxytocin administration on cortisol concentrations during laboratory tasks: moderation by method and mental health. Psychoneuroendocrinology 49, 161–170. https://doi.org/10.1016/j.psyneuen.2014.07.014.
Catena-Dell'Osso, M., Fagiolini, A., Marazziti, D., Baroni, S., Bellantuono, C., 2013. Non-monoaminergic targets for the development of antidepressants: focus on neuropeptides. Mini Rev. Med. Chem. 13 (1), 2–10.
Cochran, D.M., Fallon, D., Hill, M., Frazier, J.A., 2013. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. Harv. Rev. Psychiatry 21 (5), 219–247. https://doi.org/10.1097/HRP.0b013e3182a75b7d.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. Erlbaum, Hillsdale.
*Cyranowski, J.M., Hofkens, T.L., Frank, E., Seltman, H., Cai, H.-M., Amico, J.A., 2008. Evidence of dysregulated peripheral oxytocin release among depressed women. Psychosom. Med. 70 (9), 967–975. https://doi.org/10.1097/PSY.0b013e318188ade4.
Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatry 65 (9), 728–731. https://doi.org/10.1016/j.biopsych.2008.10.011.
de Dreu, C.K., Greer, L.L., Handgraaf, M.J., Shalvi, S., van Kleef, G.A., Baas, M., ten Velden, F.S., van Dijk, E., Feith, S.W., 2010. The neuropepti de oxytocin regulates parochial altruism in intergroup conflict among humans. Science 328 (5984), 1408–1411. https://doi.org/10.1126/science.1189047.
Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel plot based method of testing and adjusting for publication bias in meta-analysis. Biometrics 65, 455–463. https://doi.org/10.1111/j.0006-341X.2000.00455.x.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ: Br. Med. J. 315 (7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629.
Feldman, R., 2012. Oxytocin and social affiliation in humans. Horm. Behav. 61 (3), 380–391. https://doi.org/10.1016/j.yhbeh.2012.01.008.
Franck, L., Molyneux, N., Parkinson, L., 2016. Systematic review of interventions addressing social isolation and depression in aged care clients. Qual. Life Res. 25 (6), 1395–1407. https://doi.org/10.1007/s11136-015-1197-y.
*Frasch, A., Zetsche, T., Steiger, A., Jirikowski, G.F., 1995. Reduction of plasma oxytocin levels in patients suffering from major depression. Adv. Exp. Med. Biol. 395, 257–258.

Gariépy, G., Honkaniemi, H., Quesnel-Vallée, A., 2016. Social support and protection from depression: systematic review of current findings in Western countries. Br. J. Psychiatry 209 (4), 284–293. https://doi.org/10.1192/bjp.bp.115.169094.
Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. 81 (2), 629–683. https://doi.org/10.1152/physrev.2001.81.2.629.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (1), 56–62. https://doi.org/10.1136/jnnp.23.1.56.
Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54 (12), 1389–1398. https://doi.org/10.1016/S0006-3223(03)00465-7.
Heinrichs, M., Dawans, B., von, Domes, G., 2009. Oxytocin, vasopressin, and human social behavior. Front. Neuroendocrinol. 30 (4), 548–557. https://doi.org/10.1016/j.yfrne.2009.05.005.
Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558. https://doi.org/10.1002/sim.1186.
Hirschfeld, R.M., Montgomery, S.A., Keller, M.B., Kasper, S., Schatzberg, A.F., Moller, H.J., Healy, D., Baldwin, D., Humble, M., Versiani, M., Montenegro, R., Bourgeois, M., 2000. Social functioning in depression: a review. J. Clin. Psychiatry 61 (4), 268–275.
Ioannidis, J.P., 2005. Differentiating biases from genuine heterogeneity: distinguishing artifactual from substantive effects. In: Rothstein, H.R., Sutton, A.J., Borenstein, M. (Eds.), Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments. Wiley, Sussex, pp. 287–302.
Jobst, A., Sabaß, L., Hall, D., Brücklmeier, B., Buchheim, A., Hall, J., Sarubin, N., Zill, P., Falkai, P., Brakemeier, E.-L., Padberg, F., 2018. Oxytocin plasma levels predict the outcome of psychotherapy: a pilot study in chronic depression. J. Affect. Disord. 227, 206–213. https://doi.org/10.1016/j.jad.2017.10.037.
*Jobst, A., Sabass, L., Palagyi, A., Bauriedl-Schmidt, C., Mauer, M.C., Sarubin, N., Buchheim, A., Renneberg, B., Falkai, P., Zill, P., Padberg, F., 2015. Effects of social exclusion on emotions and oxytocin and cortisol levels in patients with chronic depression. J. Psychiatr. Res. 60, 170–177. https://doi.org/10.1016/j.jpsychires.2014.11.001.
Kendler, K.S., Gardner, C.O., Prescott, C.A., 2002. Toward a comprehensive developmental model for major depression in women. Am. J. Psychiatry 159 (7), 1133–1145. https://doi.org/10.1176/appi.ajp.159.7.1133.
Kendler, K.S., Gardner, C.O., Prescott, C.A., 2006. Toward a comprehensive developmental model for major depression in men. Am. J. Psychiatry 163 (1), 115–124. https://doi.org/10.1176/appi.ajp.163.1.115.
Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E., 2005. Oxytocin increases trust in humans. Nature 435 (7042), 673–676. https://doi.org/10.1038/nature03701.
Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocrinol. 25 (3–4), 150–176. https://doi.org/10.1016/j.yfrne.2004.05.001.
Levine, S., 2001. Primary social relationships influence the development of the hypothalamic–pituitary–adrenal axis in the rat. Physiol. Behav. 73 (3), 255–260. https://doi.org/10.1016/S0031-9384(01)00496-6.
*Lien, Y.-J., Chang, H.H., Yang, Y.K., Lu, R.-B., Chen, P.S., 2016. The serum oxytocin levels among major depressive and bipolar II disorder. Int. J. Neuropsychopharmacol. 19 (Suppl. 1), 17.
Lipsey, M.W., Wilson, D.B., 2001. Practical Meta-Analysis. Sage Publications, Thousand Oaks.
MacDonald, K., MacDonald, T.M., Brüne, M., Lamb, K., Wilson, M.P., Golshan, S., Feifel, D., 2013. Oxytocin and psychotherapy: a pilot study of its physiological, behavioral and subjective effects in males with depression. Psychoneuroendocrinology 38 (12), 2831–2843. https://doi.org/10.1016/j.psyneuen.2013.05.014.
Massey, S.H., Backes, K.A., Schuette, S.A., 2016. Plasma oxytocin concentration and depressive symptoms: a review of current evidence and directions for future research. Depress. Anxiety 33 (4), 316–322. https://doi.org/10.1002/da.22467.
McQuaid, R.J., McInnis, O.A., Abizaid, A., Anisman, H., 2014. Making room for oxytocin in understanding depression. Neurosci. Biobehav. Rev. 45, 305–322. https://doi.org/10.1016/j.neubiorev.2014.07.005.
Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci. 12 (9), 524–538. https://doi.org/10.1038/nrn3044.
Mikolajczak, M., Gross, J.J., Lane, A., Corneille, O., Timary, P., de, Luminet, O., 2010a. Oxytocin makes people trusting, not gullible. Psychol. Sci. 21 (8), 1072–1074. https://doi.org/10.1177/0956797610377343.
Mikolajczak, M., Pinon, N., Lane, A., Timary, P., de, Luminet, O., 2010b. Oxytocin not only increases trust when money is at stake, but also when confi dential information is in the balance. Biol. Psychol. 85 (1), 182–184. https://doi.org/10.1016/j.biopsycho.2010.05.010.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (4), 264–269. https://doi.org/10.1371/journal.pmed.1000097.g001.
Neumann, I.D., 2008. Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. J. Neuroendocrinol. 20 (6), 858–865. https://doi.org/10.1111/j.1365-2826.2008.01726.x.
Olff, M., Frijling, J.L., Kubzansky, L.D., Bradley, B., Ellenbogen, M.A., Cardoso, C., Bartz, J.A., Yee, J.R., van Zuiden, M., 2013. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology 38 (9), 1883–1894. https://doi.org/10.1016/j.psyneuen.2013.06.019.
*Ozsoy, S., Esel, E., Kula, M., 2009. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. Psychiatry Res. 169 (3), 249–252. https://doi.org/10.1016/j.psychres.2008.06.034.
*Parker, K.J., Kenna, H.A., Zeitzer, J.M., Keller, J., Blasey, C.M., Amico, J.A., Schatzberg, A.F., 2010. Preliminary evidence that plasma oxytocin levels are elevated in major depression. Psychiatry Res. 178 (2), 359–362. https://doi.org/10.1016/j.psychres.2009.09.017.
Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R., Rushton, L., 2007. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat. Med. 26 (25), 4544–4562. https://doi.org/10.1002/sim.2889.
*Pitts, A.F., Samuelson, S.D., Meller, W.H., Bissette, G., Nemeroff, C.B., Kathol, R.G., 1995. Cerebrospinal fluid corticotropin-releasing hormone, vasopressin, and oxytocin concentrations in treated patients with major depression and controls. Biol. Psychiatry 38 (5), 330–335. https://doi.org/10.1016/0006-3223(95)00229-A.
Renner, F., Cuijpers, P., Huibers, M.J.H., 2014. The effect of psychotherapy for depression on improvements in social functioning: a meta-analysis. Psychol. Med. 44 (14), 2913–2926. https://doi.org/10.1017/S0033291713003152.
Rohatgi, A., 2015. WebPlotDigitizer. https://automeris.io/WebPlotDigitizer/.
Ros-Simó, C., Valverde, O., 2012. Early-life social experiences in mice affect emotional behaviour and hypothalamic–pituitary–adrenal axis function. Pharmacol. Biochem. Behav. 102 (3), 434–441. https://doi.org/10.1016/j.pbb.2012.06.001.
Rothstein, H.R., Bushman, B.J., 2012. Publication bias in psychological science: Comment on Ferguson and Brannick (2012). Psychol. Methods 17 (1), 129–136. https://doi.org/10.1037/a0027128.
Rutigliano, G., Rocchetti, M., Paloyelis, Y., Gilleen, J., Sardella, A., Cappucciati, M., Palombini, E., Dell'Osso, L., Caverzasi, E., Politi, P., McGuire, P., Fusar-Poli, P., 2016. Peripheral oxytocin and vasopressin: biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. Psychiatry Res. 241, 207–220. https://doi.org/10.1016/j.psychres.2016.04.117.
*Sasayama, D., Hattori, K., Teraishi, T., Hori, H., Ota, M., Yoshida, S., Arima, K., Higuchi, T., Amano, N., Kunugi, H., 2012. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. Schizophr. Res. 139 (1–3), 201–206. https://doi.org/10.1016/j.schres.2012.06.016.
Serra, M., Pisu, M.G., Floris, I., Biggio, G., 2005. Social isolation-induced changes in the hypothalamic–pituitary–adrenal axis in the rat. Stress 8 (4), 259–264. https://doi.org/10.1080/10253890500495244.
Strawbridge, R., Young, A.H., Cleare, A.J., 2017. Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatr. Dis. Treat. 13, 1245–1262.
Strunk, D.R., Adler, A.D., 2009. Cognitive biases in three prediction tasks: a test of the cognitive model of depression. Behav. Res. Ther. 47 (1), 34–40. https://doi.org/10.1016/j.brat.2008.10.008.
Terrin, N., Schmid, C.H., Lau, J., Olkin, I., 2003. Adjusting for publication bias in the presence of heterogeneity. Stat. Med. 22 (13), 2113–2126. https://doi.org/10.1002/sim.1461.
Theodoridou, A., Rowe, A.C., Penton-Voak, I.S., Rogers, P.J., 2009. Oxytocin and social perception: oxytocin increases perceived facial trustworthiness and attractiveness. Horm. Behav. 56 (1), 128–132. https://doi.org/10.1016/j.yhbeh.2009.03.019.
Thompson, R.J., Parker, K.J., Hallmayer, J.F., Waugh, C.E., Gotlib, I.H., 2011. Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. Psychoneuroendocrinology 36 (1), 144–147. https://doi.org/10.1016/j.psyneuen.2010.07.003.
Thompson, S.M., Hammen, C., Starr, L.R., Najman, J.M., 2014. Oxytocin receptor gene polymorphism (rs53576) moderates the intergenerational transmission of depression. Psychoneuroendocrinology 43, 11–19. https://doi.org/10.1016/j.psyneuen.2014.01.012.
Tse, W.S., Bond, A.J., 2004. The impact of depression on social skills. J. Nerv. Ment. Dis. 192 (4), 260–268. https://doi.org/10.1097/01.nmd.0000120884.60002.2b.
Valstad, M., Alvares, G.A., Egknud, M., Matziorinis, A.M., Andreassen, O.A., Westlye, L.T., Quintana, D.S., 2017. The correlation between central and peripheral oxytocin concentrations: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.04.017.
*van Londen, L., 1997. Plasma levels of arginine vasopressin elevated in patients with major depression. Neuropsychopharmacology 17 (4), 284–292. https://doi.org/10.1016/S0893-133X(97)00054-7.
*van Londen, L., Kerkhof, G.A., van den Berg, F., Goekoop, J.G., Zwinderman, K.H., Frankhuijzen-Sierevogel, A.C., Wiegant, V.M., de Wied, D., 1998. Plasma arginine vasopressin and motor activity in major depression. Biol. Psychiatry 43 (3), 196–204. https://doi.org/10.1016/S0006-3223(97)80433-7.
Wells, G.A.Shea, B.O'Connell, D.Peterson, J.Welch, V.Losos, M.Tugwell, P. The Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies (Accessed 4 March 2018). http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
*Yuen, K.W., Garner, J.P., Carson, D.S., Keller, J., Lembke, A., Hyde, S.A., Kenna, H.A., Tennakoon, L., Schatzberg, A.F., Parker, K.J., 2014. Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. J. Psychiatr. Res. 51, 30–36. https://doi.org/10.1016/j.jpsychires.2013.12.012.
*Zetzsche, T., Frasch, A., Jirikowski, G.F., Murck, H., Steiger, A., 1995. Nocturnal plasma concentrations of oxytocin are reduced in patients with depression compared with age-matched controls. Pharmacopsychiatry 28, 231.
*Zetzsche, T., Frasch, A., Jirikowski, G.F., Murck, H., Steiger, A., 1996. Nocturnal Oxytocin Secretion Is Reduced in Major Depression.