Neuroscience and Biobehavioral Reviews 167 (2024) 105935

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Is the "social hormone" oxytocin relevant to psychotherapy treatment outcomes? A systematic review of observational and experimental studies☆

Caio Hummel Hohl [a], Sigal Zilcha-Mano [b], Jaime Delgadillo [a,*]

[a] Department of Psychology, University of Sheffield, United Kingdom
[b] Department of Psychology, University of Haifa, Israel

ARTICLE INFO

Keywords:
Oxytocin
Psychotherapy
Predictor
Moderator
Mediator

ABSTRACT

Background: Oxytocin, popularly known as the "social hormone", has wide implications for the regulation of socially relevant cognitions, emotions and behaviors. Individual differences in oxytocin may be relevant to mental health treatment outcomes, given the centrality of the therapeutic relationship in psychotherapy.
Methods: This systematic review aimed to synthesize findings from psychotherapy studies that examined oxytocin measurement and augmentation methods and their association with treatment outcomes. The methodology was preregistered in the Open Science Framework (https://osf.io/xtyvc/?view_only=2bc37dc0b2cd41f8939e2964bd8b884f). Five databases were searched on 30th of March 2023 (PubMed, SCOPUS, Web of Science, Medline, PsycINFO). Eligible studies were assessed for risk of bias and findings were summarized using narrative synthesis and vote counting methods.
Results: Overall, 24 studies (n=881 participants) including experimental and observational designs and covering various diagnostic groups were reviewed. Findings from 9 studies (n=406) indicate that oxytocin measures were associated with psychotherapy treatment outcomes for depression, and oxytocin-augmentation improved depression outcomes. Results regarding other mental disorders were mixed and inconclusive.
Discussion: Current evidence indicates that oxytocin-augmented psychotherapy for depression warrants further research. Currently there is not sufficient evidence to draw firm conclusions regarding the clinical relevance of oxytocin in the context of other disorders. Key limitations are the lack of meta-analytic synthesis and small sample sizes for primary studies.

1. Introduction

Oxytocin is a peptide hormone that plays a role in social bonding behaviors including reproduction, childbirth, lactation and early attachment formation (Froemke and Young, 2021). Oxytocin modulates attention to socially relevant cues, supporting the formation of social memories and, thus, the consolidation of attachment representations (Cochran, 2013). Higher oxytocin levels in parents are associated with greater synchrony and responsiveness in parent-infant interactions, which plays an important role in the formation of early affiliative bonds (Scatliffe et al., 2019). Oxytocin is also involved in supporting essential processes that foster empathy, such as the perception of emotions (Ellenbogen, 2018) and theory of mind (Domes et al., 2007). Moreover, it has been associated with regulating interpersonal trust, and in regulating stress to support social performance (Striepens et al., 2011). Neurologically, oxytocin inhibits the amygdala's response to social stimuli (Hurlemann, 2017), leading to decreased psychophysiological reactions by modulating the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic autonomic nervous system responses (Cardoso et al., 2013).

Given its widespread role in regulating cognitive, emotional and behavioral responses to social stimuli, there has been increasing interest in the potential relevance of oxytocin regarding psychopathology (see reviews by Cochran et al., 2013; Rutigliano et al., 2016; Engel et al., 2019; John and Jaeggi, 2021). For example, in a recent meta-analysis of studies that compared peripheral oxytocin levels between psychiatric patients and healthy controls (Ferreira and de Lima Osório, 2022), lower levels were found in patients with schizophrenia, anorexia and

☆ Registration. Preregistered on Open Science Framework (OSF) on 28th of March 2023, prior to conducting any searches (https://osf.io/xtyvc/?view_only=2bc37dc0b2cd41f8939e2964bd8b884f).

* Correspondence to: Clinical and Applied Psychology Unit, University of Sheffield, Cathedral Court, 1 Vicar Lane, Sheffield S1 2LT, United Kingdom.
E-mail address: j.delgadillo@sheffield.ac.uk (J. Delgadillo).

https://doi.org/10.1016/j.neubiorev.2024.105935
Received 24 January 2024; Received in revised form 27 October 2024; Accepted 29 October 2024
Available online 30 October 2024

borderline personality disorder. However, higher levels of oxytocin were found in patients with bipolar disorder and obsessive-compulsive disorder. Furthermore, no significant differences in oxytocin levels were found when comparing healthy controls to patients with bulimia, autism, depression, or social anxiety. According to such evidence, altered endogenous oxytocin concentrations are observed in some conditions but not others.

In another line of research, several studies have examined the potential clinical effects of intranasal oxytocin administration, with mixed results. For example, according to meta-analytic evidence, oxytocin administration had no significant effects on emotional theory of mind or emotion expression among healthy or clinical adult populations with various diagnoses (Leppanen et al., 2017), but it did significantly increase the physiological startle response to threat in healthy people (Leppanen et al., 2018). A meta-analysis by Zhang et al. (2021) found that oxytocin administration significantly reduced behaviors of attachment insecurity (e.g., social avoidance) in interpersonal situations with ambiguous social cues. Meta-analyses specifically focusing on studies involving participants with autism spectrum disorders found that oxytocin administration had significant beneficial effects on social functioning (Huang et al., 2021) but no significant effects on other outcomes such as anxiety or repetitive behaviors (Kiani et al., 2023). Other recent meta-analyses of oxytocin administration found no significant effects on positive or negative symptoms of schizophrenia (e.g., Sabe et al., 2021), no significant effects on depression or anxiety symptoms (e.g., De Cagna et al., 2019), mixed and inconclusive effects on post-traumatic stress disorder (e.g., Giovanna et al., 2020) and on food and substance-related craving and addictive behaviors (Houghton et al., 2021). Overall, observational and interventional studies indicate that oxytocin is relevant for social functioning and attachment-related behaviors, but its clinical relevance for conditions other than autism spectrum disorders is as yet unclear.

Wider research outside of the field of psychopathology indicates that the influence of oxytocin on social and emotional functioning is context dependent. For example, oxytocin administration significantly increases trust and cooperative behaviors specifically in an in-group social context (Van IJzendoorn and Bakermans-Kranenburg, 2012; Yang et al., 2021), and it therefore contributes not only to affiliative behaviors with in-group members but also to aggression toward outgroups (De Dreu et al., 2011). Furthermore, studies indicate that the pro-social effects of oxytocin administration may be attenuated or absent in individuals who experienced unfavorable or adverse early caregiving experiences, and who may have negatively biased reactions toward social cues (see review by Bakermans-Kranenburg and Van Ijzendoorn, 2013). Related to the above, Bartz et al. (2010) found that the effects of oxytocin administration were moderated by attachment style, with less anxiously attached participants remembering their mother as more caring and close after oxytocin (vs. placebo) and more anxiously attached participants remembering their mother as less caring and close after oxytocin. Furthermore, oxytocin administration diminishes interpersonal trust in individuals with borderline personality disorder, conditional on childhood adversity (Brüne, 2016), suggesting that oxytocin has opposing effects depending on past experiences.

The context dependencies described above raise important questions for the practice of psychotherapy, which places great emphasis on the establishment of a therapeutic relationship characterized by mutual trust and collaboration toward agreed goals and tasks. Meta-analytic evidence indicates that psychotherapy outcomes are associated with patient-reported measures of the therapeutic alliance (Flückiger et al., 2018), empathy (Elliott et al., 2018), positive regard (Farber et al., 2018) and collaboration (Tryon et al., 2018). Furthermore, patients with a more secure attachment style measured pre-treatment have more favorable psychotherapy outcomes compared to insecurely attached patients, and improvements in attachment security during therapy are associated with better psychotherapy outcomes (Levy et al., 2018). It is plausible that oxytocin may be implicated in regulating many of the social-cognitive processes outlined above, and hence individual differences in oxytocin levels may be associated with psychotherapy outcomes. Oxytocin may exert its effects in psychotherapy through additional mechanisms (Sippel et al., 2017), including modulation of reward pathways (Clark-Elford et al., 2014; Groppe et al., 2013) and anxiolytic effects mediated by its influence on the limbic system (Kou et al., 2022; Mottolese et al., 2014). There has been a growing interest in the theoretical relevance of oxytocin in the context of psychotherapy (Shamay-Tsoory and Abu-Akel, 2016). In recent years, several empirical studies have examined the prognostic value of oxytocin reactivity to the therapeutic encounter (e.g., Atzil-Slonim et al., 2022), oxytocin synchrony between therapist and patient (Zilcha-Mano et al., 2021), the effects of oxytocin augmentation during psychotherapy for various mental disorders (e.g., Ellenbogen et al., 2018; Flanagan et al., 2018; Guastella et al., 2009; Azadbakht et al., 2022), and moderators of the effect of oxytocin (e.g., Bitan et al., 2023). Reviews of this literature have mostly focused on oxytocin augmentation in the context of pharmacotherapy (e.g., Guastella and Hickie, 2016; Oya et al., 2016; Zheng et al., 2019). Reviews considering psychotherapy outcomes have been limited to specific conditions such as post-traumatic stress disorder (e.g., Giovanna et al., 2020; Preckel et al., 2021). Hence, the clinical relevance of oxytocin in the context of psychotherapy remains unclear. The present study aimed to fill this gap in the literature, integrating findings across a broad range of mental disorders. To achieve this, we conducted a systematic review of observational and experimental studies that investigated the role of oxytocin in the context of psychotherapy. Given that the relevance of oxytocin may differ across mental disorders, this review included studies where psychotherapy was offered to patients with a variety of mental health problems, and where both measurement and augmentation methods were applied.

2. Methods

2.1. Protocol and registration

A study protocol outlining the search strategy and review methodology was preregistered in the Open Science Framework (OSF) database on the 28th of March 2023, prior to conducting any searches (https://osf.io/xtyvc/?view_only=2bc37dc0b2cd41f8939e2964bd8b884f).

2.2. Eligibility criteria

To be included in the review, studies had to have included adult participants (age $\geq$18) accessing some form of psychotherapy for a mental disorder, which either examined associations between measures of oxytocin (independent variable of interest) with psychotherapy outcomes (dependent variable) or examined the effects of oxytocin augmentation on psychotherapy outcomes. Studies investigating oxytocin-related predictor, moderator or mediator hypotheses were eligible for inclusion. Quantitative experimental (e.g., randomized controlled trials) and observational (e.g., cross-sectional or longitudinal) studies were eligible, except for case reports or single case experimental designs, and except for studies where oxytocin was the dependent variable. The full study inclusion and exclusion criteria are outlined in Table 1.

2.3. Search strategy

The search was applied on 30th of March 2023 (after registering the protocol) across five databases: PubMed, SCOPUS, Web of Science, Medline, and PsycINFO. It was peer-reviewed by an independent librarian and consisted of a combination of Boolean operators and relevant search terms in the following format: ["oxytocin"] AND ["correlat*" OR "associat*"] AND ["psychotherap*" OR "counselling" OR "counseling"]. The terms "correlated" and "associated" were included for searches to yield studies that reported any statistical

Table 1
Inclusion and Exclusion Criteria.

Research question: is oxytocin a predictor of psychological treatment response?		
PICO Framework	**Inclusion Criteria**	**Exclusion Criteria**
Population	Studies in which adult participants accessed psychological interventions for any mental health problems for which psychotherapy is indicated as a treatment	Children (less than 18 years old) Animal studies Healthy participants Participants with neurological disorders who did not access psychotherapy targetting other comorbid mental disorders
Intervention (s)	Any type of psychotherapy Studies comparing psychological and pharmacological interventions Oxytocin-enhanced psychotherapy	Studies that did not include a psychological intervention Studies with only pharmacological interventions Oxytocin administration as the only intervention, without psychotherapy
Comparison	Statistical association between oxytocin measures and treatment outcomes Comparison of oxytocin augmentation versus placebo	Studies that did not include a quantitative measurement of oxytocin Any studies that are not randomized controlled trials (RCTs) or observational studies (OBSs) Studies that looked at genes associated to oxytocin receptores rather than oxytocin levels
Outcome	Mental health symptoms measured by psychometrically reliable and validated questionnaires	Studies that did not include any kind of treatment outcome measurement Oxytocin levels as the only outcome

relationships between oxytocin and interventions. See Tables S1 and S2 in the Supplemental Materials for further details.

The search included peer-reviewed articles and grey literature. No restrictions were specified on publication date or language. Backward and forward citation searches were also conducted after the initial selection of eligible studies were retrieved through database searches. References cited in systematic reviews on similar topics (cited in the introduction) were screened.

2.4. Study selection

The study selection process was conducted by the first author following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), and validated by a second reviewer. The non-eligible reports and their exclusion reasons are reported in the Supplemental Materials (S3).

2.5. Data extraction

The data extraction was carried out by two reviewers, following the Cochrane Collaboration data extraction form (Higgins et al., 2019), with few modifications relevant to the research question. The extracted data included: study design, participants' demographics (self-reported gender, age, ethnicity, and diagnoses), treatment setting, sample size, intervention type, oxytocin measurement, outcome measures, number of sessions (and duration of psychotherapy), and key findings. The study characteristics and results tables were organized into oxytocin augmentation and oxytocin measurement studies, with each section divided into randomized controlled trials (RCTs) of oxytocin augmentation and observational studies (OBSs).

The primary outcome of interest was psychotherapy response measured by psychometrically validated questionnaires of mental disorders/symptoms. Data for relevant secondary outcomes (e.g., treatment adherence, therapeutic alliance, etc.), where available, were also extracted and synthesized. For oxytocin augmentation studies, the outcome effect measure was group mean differences, while for oxytocin measurement studies it was regression coefficients.

2.6. Quality and risk of bias assessment

Risk of bias was assessed using the Critical Appraisal Skills Programme (CASP) checklists for RCTs and OBSs (Long et al., 2020). Due to the subjective nature of this task, studies were rated by two independent reviewers. The inter-rater reliability was reported using percent agreement and Kappa statistics. Any discrepancies were discussed until arriving at a consensus. Risk of bias ratings were used to achieve a weighted synthesis of findings, giving more importance to findings that came from methodologically sound studies.

2.7. Data synthesis

The synthesis was conducted qualitatively, informed by ESRC guidelines (Economic and Social Research Council, 2015). It focused on the overall theory and how it relates to the findings, including relevant relationships within and between studies, followed by an assessment of the robustness of the evidence. In the results, the synthesis was divided into disorders, with sub-divisions between oxytocin-augmentation and oxytocin measurement studies. A quantitative synthesis (meta-analysis) was not appropriate due to the extensive methodological heterogeneity in relation to study design (RCTs, OBSs), measures of oxytocin, measures of psychotherapy outcomes, and types of psychotherapy (different theoretical models, some of which were augmented with oxytocin). A comprehensive summary of quantitative results across all studies is reported in Supplemental Materials (S6). Based on these results, a vote-count table supported the narrative synthesis; it was divided into negative, positive, and no effects for primary outcomes, and positive or negative effects from exploratory analyses.

3. Results

3.1. Study characteristics

The study selection process is summarized in the PRISMA flow-diagram in Fig. 1. Overall, k=24 eligible studies included n=881 participants, using experimental (k=19) and observational designs (k=5). Detailed study characteristics are reported in Table 2. The number of participants per study ranged from 5 to 87, with a mean of 36.7, and 25 % of the studies had samples smaller than 20. Most were mixed-gender studies, although some only included males (k=7), while others only included females (k=2) or other gender identities (k=1). The mean age ranged from 21.92 to 59, with an overall mean of 38.34 years. Across studies that reported ethnicity, the proportion of Caucasians ranged from 25 % to 100 %.

Most studies (k=16) were RCTs of oxytocin augmentation in the context of psychotherapy. Treatment settings included outpatient (k=20) and inpatient (k=4) care across various countries (USA, Iran, Israel, Australia, Italy, Canada, and Germany). Interventions included various types of therapy such as cognitive behavior therapy (CBT) (k=10); psychodynamic therapy (k=6); interpersonal therapy (IPT) (k=2); and motivational interviewing (MI) (k=2). Interventions were delivered in individual (k=13) and group formats (k=5), a combination of modalities (k=5), or as couples therapy (k=1), or online (k=3). The number of therapy sessions varied from 1 to 60, with a mean of 15.46 sessions. Duration of psychotherapy ranged from 1 day to 24 weeks.

Most studies focused on specific clinical populations: depressive disorders (k=7), including postpartum depression, dysthymia, and major depression (MDD); post-traumatic stress disorder (PTSD) (k=5); schizophrenia spectrum disorders (k=3); anxiety disorders (k=3), including social anxiety (SAD), specific phobia, and adult separation

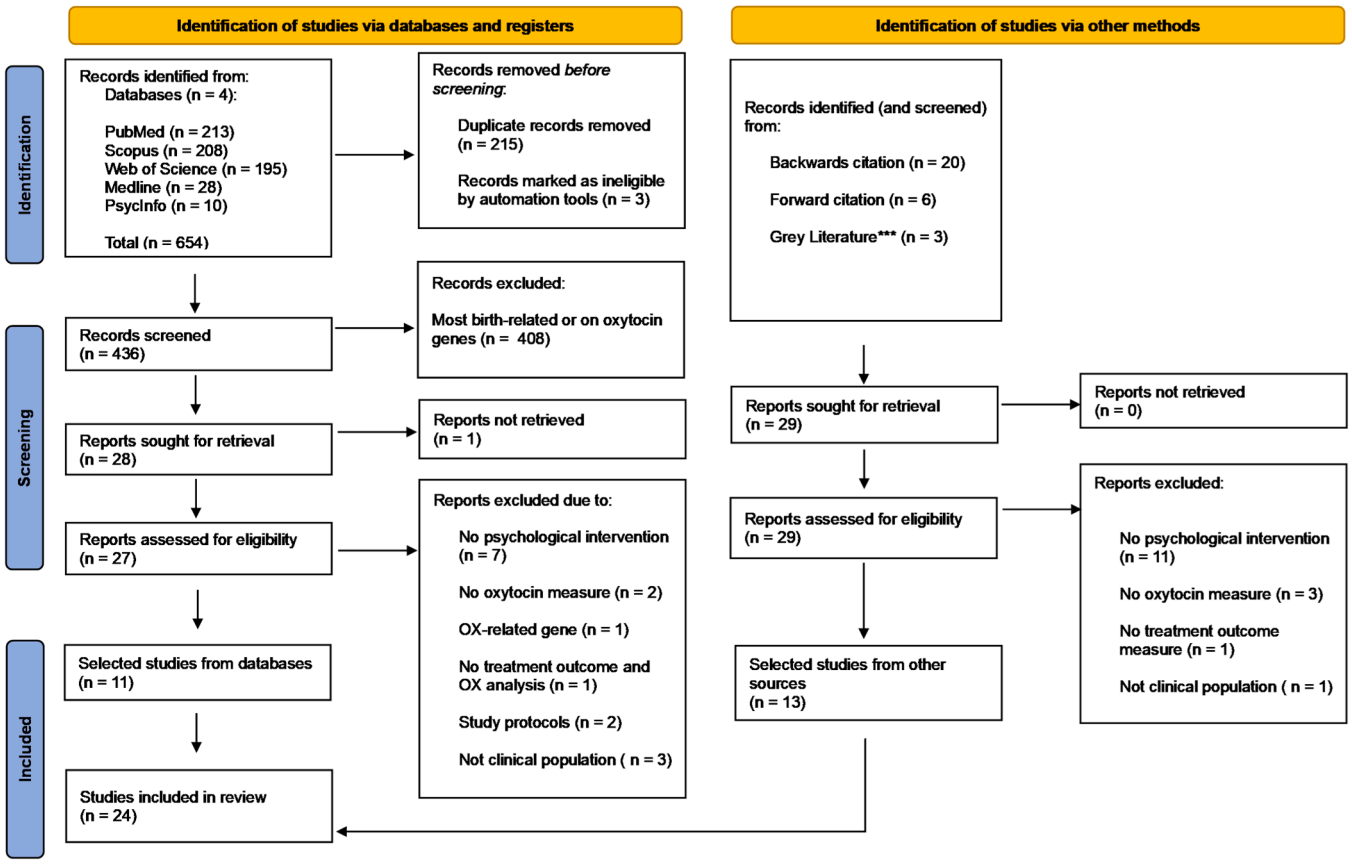

Fig. 1. PRISMA flow diagram. *** Some studies included are published academic posters, thus categorized as grey literature.

anxiety; and substance use disorders (k=4), including opioid and stimulant use. Some studies included a variety of diagnoses simultaneously (k=2). Psychotherapy outcomes for these conditions were measured using a variety of clinician-rated and patient-reported measures listed in Table 2.

Oxytocin measurement studies measured oxytocin through saliva, urine, or blood concentrations. Within those studies, one measured oxytocin synchrony between patients and therapists, and two measured oxytocin reactivity to a social exclusion paradigm or the therapeutic encounter. Oxytocin-augmentation studies measured its administration in international units (IU), which varied from 16 to 40 IU. All studies administered oxytocin intranasally (30–45 minutes before sessions, with some including daily administration), assuming an optimal route of administration for rapid absorption, acknowledging the olfactory nerve proximity to the brain.

3.2. Risk of bias assessment

The proportion of agreement between raters was 83.3 %, with Kappa=0.52 (p=0.004), 95 % confidence intervals (0.13–0.90), suggesting moderate to substantial agreement. Tables S4 and S5 in the supplemental materials report the risk of bias ratings for all studies. Most studies had a moderate risk (k=15), some had a low risk (k=9), and no studies were rated as having a high risk of bias. While most studies had very small samples, it did not affect their rating, since they explicitly reported being pilot studies with preliminary findings. The main source of bias was the inclusion of several outcome measures and multiple testing in small samples.

3.3. Narrative synthesis within disorders

3.3.1. Depressive disorders

3.3.1.1. Oxytocin augmentation. Three studies investigated oxytocin augmentation effects on psychotherapy outcome for depression. Ellenbogen et al. (2018) found that the oxytocin group showed greater decreases in symptoms during interpersonal therapy. Similarly, Ellenbogen et al. (2019) indicated that, for the first two sessions of interpersonal therapy, the oxytocin group showed greater therapeutic alliance, which in turn led to significant symptom reductions. Conversely, Clarici et al. (2015) did not find such effects in psychodynamic therapy. In secondary analyses, they found significant decreases in narcissistic traits for the oxytocin group. However, reductions in dysphoric traits were only found in the placebo condition. Nonetheless, the latter had a very small sample size (N=16), and all studies had a moderate risk of bias.

3.3.1.2. Oxytocin measures. Four studies investigated whether oxytocin measures predict treatment outcome for depression across a diverse range of psychotherapies. Zilcha-Mano et al. (2021) found that higher oxytocin synchrony between patients and therapists correlated to significantly better responses. Similarly, Atzil-Slonim et al. (2022) indicated that greater (but not directional) oxytocin reactivity to the therapeutic encounter predicted better symptom improvements, despite also finding that higher baseline oxytocin predicted worse outcomes. Conversely, Jobst et al. (2018) found that higher baseline predicted better responses. When investigating oxytocin reactivity to a social exclusion paradigm, they found that slower recovery predicted worse psychotherapy response. While Reiner et al. (2022) found no effects of oxytocin on psychotherapy outcomes, when differentiating depressed patients between remitters and non-remitters, they found that non-remitters had significantly lower oxytocin levels compared to

Table 2
Study characteristics.

First author and year	Study design	Demographic information: sex (M/F), age (M), ethnicity (White %), diagnosis Augmentation	Treatment setting	Analysed N	Intervention	Oxytocin measurement	Outcome measures	Number of sessions, duration of treatment
Oxytocin RCTs								
Acheson et al. (2015)	RCT	4/19, 30.04, 53.1 %, Specific Phobia	Outpatient, lab-based (CA, USA)	23	ET + OX vs ET + placebo	Intranasal augmentation (24IU prior to session)	TSPQ, FSQ, BAT, CGI, m-WAI	1
Azadbakht et al. (2022)	RCT	42/0, 33.6, NA, MUD	Outpatient, substance abuse center in Isfahan, Iran	42	MTM + OX vs MTM + placebo	Intranasal augmentation (40IU daily)	BDI, BAI, CCQ-b, ACTH and Cortisol levels	22, 4 weeks
Bitan et al. (2023)	RCT	71.3 % F, 36.44, NA, affective disorders (55.2 %), anxiety disorders (17.2 %), and other diagnoses (27 %)	Two inpatient adult psychiatric wards at the Shalvata Mental Health Center (MHC)	87	Psychodynamic + OX vs psychodynamic + placebo	Intranasal augmentation (32IU daily)	STAI, HRSD, SSI, OQ−45, HSCL−11, SAI, ECR, BFI	8–12, 4 weeks
Cacciotti-Saija et al. (2015)	RCT	36/16, 21.92, NA, early psychosis	Brain & Mind Research Institute, University of Sydney	52	GSCT + OX vs GSCT + placebo	Intranasal augmentation (24 IU daily + additional 24IU before each session)	RMET, (SAPS + SANS), SFS Secondary: FEEST, The Movie Stills Task, The False Belief Picture Sequencing Task, The Faux Pas Task, The Empathy Quotient, The Ambiguous Intentions Hostility Questionnaire, The Repeatable Battery for the Assessment of Neuropsychological Status, DASS−21, K−10, SIAS, CGI-S, SSPA, ICQ, SDS	12, 6 weeks
Clarici et al. (2015)	RCT	0/16, 36.5, NA, postpartum depression	Outpatient, Italy	16	Psychodynamic + OX vs psychodynamic + placebo	Intranasal augmentation (16 IU daily)	ANPS, EPDS, HDRS, SWAP	12, 12 weeks
Davis et al. (2014)	RCT	27/0, 39.9, 33 %, Schizophrenia	Outpatients, USA	27	SCT + Oxytocin vs SCT + placebo	Intranasal augmentation (40 IU prior to sessions)	MCCB, BPRS, CAINS, C-SSRS, Facial affect recognition, EAT, PONS, MSCEIT, TASIT	12, 6 weeks
Ellenbogen (2018)	RCT	12/12, NA, NA, MDD	Outpatient, Canada	24	IPT + OX vs IPT + placebo	Intranasal augmentation (24 IU prior to therapy)	IDS	16, NA
Ellenbogen et al. (2019)	RCT	12/12, NA, NA, MDD	Outpatient, Canada	24	IPT + OX vs IPT + placebo	Intranasal augmentation (24 IU prior to therapy)	IDS, WAI.	16, NA
Flanagan et al. (2018) *	RCT	14/3, 43.82, 35.3 %, PTSD	Research setting, USA	17	PE + OX vs PE + placebo	Intranasal augmentation (40 IU prior to sessions 2–9)	CAPS−5, PCL−5, BDI-II, HAQ-II, CSQ	10, 10 weeks
Guastella et al. (2009)	RCT	25/0, 42.28, 83 %, SAD	University of New South Wales Psychology Clinic	25	GET + OX vs GET + placebo	Intranasal augmentation (24 IU before sessions 2–5)	SPAI, LSAS, BFNE, LIS, informal fear/anxiety self-report (1–100 scale) during speech, Appearance Scale, SPQ, CEQ	5, 5 weeks
Grossman-Giron et al. (2023)	RCT	71.3 % F, 36.44, NA, Affective disorders (55.2 %), anxiety disorders (17.2 %) or with other disorders (27.6 %)	3 inpatient wards of the Shalvata MHC, Israel	87	Psychodynamic (group and individual sessions) + OX vs Psychodynamic + placebo	Intranasal augmentation (32IU daily)	HRSD, STAI, OQ−45, HSCL−11, SAI, ECR	8, 4 weeks

(*continued on next page*)

Table 2 (*continued*)

Sippel et al. (2020) *	RCT	3/10, 42.77, NA, PTSD	Research lab, USA	13	PE + OX vs PE + placebo	Intranasal augmentation (40 IU prior to sessions 2–9) - blood samples	CAPS−5, PCL−5	10, 10 weeks
Stauffer et al. (2018)	RCT	Men who have sex with men, NA, NA, MUD	NA	27	MIGT+ Oxytocin vs MIGT + placebo	Intranasal augmentation (40 IU before sessions)	Urine toxicology, attendance	6, 6 weeks
Stauffer et al. (2020)	RCT	(45 M, 1TM, 2 genderqueer), 43.35, 45.83 %, MUD	Research clinic at UCSF, USA	48	MIGT + OX vs MIGT + placebo	Intranasal augmentation (40 IU before sessions)	Attendance, GQ, STAI−6, MCQ-Br, Urine toxicology, ECG	6, 6 weeks
Stauffer et al. (2022)	RCT	40/0, 59, 25 %, MUD	Outpatient, San Francisco Veterans Affairs (VA) Health Care System, San Francisco VA Medical Center, and Oakland Behavioral Health Clinic	40	OTP (opioid agonist medication + counselling) + OX vs OTP + placebo	Intranasal augmentation (40IU daily)	Self-Reported Stimulant Use, Urine Toxicology, STCQ-Br, WAI-SR, WAI-SR-T, Attendance	NA, 6 weeks
Strauss et al. (2019)	RCT	38/24, 41.75, 51.6 %, Schizophrenia or schizoaffective disorder	Outpatients, CA, USA	62	GCBTSST + OX vs GCBTSST + placebo	Intranasal augmentation (36 IU prior to sessions)	RMET, EAT, TG, FERT	48, 24 weeks
OBS								
Sippel et al. (2023)	OBS	10/10, 33.95, 58.5 %, PTSD (only one in each dyads)	Online – VA telehealth platform	10 couples (n = 20)	bCBCT + OX	Intranasal augmentation (40IU prior to each session)	PCL−5, collateral-report PCL−5, CSI−32, CSI−4	8, NA
Oxytocin Levels RCT								
Engel et al. (2021)	Stepped wedge RCT	39/0, 37.74, NA, PTSD	Online, Germany	39	Internet-based TF-CBT vs waitlist	Blood concentration	CAPS−5	10, 5 weeks
Engel et al. (2022)	Stepped wedge RCT	35/0, 37.91, NA, PTSD	Online, Germany	35	Internet-based TF-CBT vs waitlist	Blood concentration	CAPS−5, SACiP, PQTEE	10, 5 weeks
Zilcha-Mano et al. (2021)	RCT	15/22, 31.54, NA, MDD	Outpatient, Israel	37	Supportive vs SE psychodynamic therapies	Saliva sample (Synchrony between patient and therapist)	HRSD, SRF from the OQ−45	16, NA
OBSs								
Atzil-Slonim et al. (2022)	OBS	19/11, 34.63, NA, MDD	Outpatient, Israel	30	SE Psychodynamic	Saliva samples (OT reactivity)	BDI-II	16, NA
Jobst et al. (2018)	OBS	7/9, 41, NA, chronic depression	Inpatient, Germany	16	CBASP program (2 sessions of group + 2 sessions of individual therapy + 2 sessions of mindfulness per week)	Blood samples before and after a social exclusion (ostracism) paradigm	HRSD−24, BDI-II	60, 10 weeks
Milrod et al. (2016)	OBS	59 % F, 50.5, 62 %, Separation anxiety	USA	5	PFPP-XR	Saliva samples	SCI-SAS, CGI-S, HARS, HRSD, ADIS-IV-L, HRV	21–24, 12 weeks
Reiner et al. (2022)	OBS (quasi-experimental design, case-control)	0/85, 30.1, 100 %, MDD and/ or dysthymia	Inpatient unit of a Department of Psychosomatic Medicine and Psychotherapy in Mainz, Germany.	85 Depressed (n=43) [remitting (n= 16) + non-remitting (n=26)] Control/ healthy (n=42)	Multimodal Mainz Model: individual and group therapy (Psychodynamic)	Blood and urinary samples	PHQ−9, HRSD−17 (score below 8 indicated remission)	20 – 48, 5 – 12 weeks

ADIS-IV-L: Anxiety Disorders Interview Schedule for DSM IV – Lifetime version**; ANPS**: Affective Neuroscience Personality Scale; **BAT**: Behavioral Approach Task; **BAI**: Beck's Anxiety Inventory; **bCBCT**: Brief Cognitive-Behavioral Conjoint Therapy; **BDI**: Beck's Depression Inventory; **BDI-II**: Beck's Depression Inventory, 2nd edition; **BFI**: The Big Five Inventory; **BFNE**: Brief Fear of Negative Evaluation Scale; **BPRS**: Brief Psychiatric-Rating Scale**; CAINS**: Clinical-Assessment Interview for Negative Symptoms; **CAPS-5**: Clinician Administered PTSD Scale for DSM-5; **CBASP**: Cognitive Behavioral Analysis System of Psychotherapy; **CBT**: Cognitive Behavioural Therapy; **CCQ-b**: Cocaine Craving Questionnaire – brief; **CEQ**: Credibility/Expectancy Questionnaire; **CGI**: Clinician-rated Clinical Global Impressions scale; **CGI-S**: Clinicians' Global Index of Severity; **CSI**: Couples Satisfaction Index; **CSQ**: Client Satisfaction Questionnaire**; C-SSRS**: Columbia Suicide Severity Rating Scale; **DASS-21**: Depression, Anxiety, and Stress Scale; **EAT**: Empathic Accuracy Test; **ECR:** Experiences in Close Relationships scale; **EPDS**: Edinburgh Postnatal Depression Scale; **ET:** Exposure therapy; **FEEST**: The Facial Expressions of Emotions Task; **FERT**: Facial Expression Recognition Test; **FSQ**: Fear of Spiders Questionnaire; **GCBTSST**: Group CBT Social skills training; **GET**: Group exposure therapy**; GQ**: Group Questionnaire; **GSCT**: Group social cognition training; **HAQ-II**: Helping Alliance

Questionnaire; **HARS**: Hamilton Anxiety Rating Scale; **HRSD**: Hamilton Rating Scale for Depression; **HRV**: Heart Rate Variability; **HSCL-11**: The Hopkins Symptom Checklist – short form; **ICQ**: Interpersonal Competence Questionnaire; **IDS**: Inventory of Depressive Symptomatology; **IPT**: Interpersonal therapy; **K-10**: Kessler Psychological Distress Scale; **LIS**: Life Interference Scale; **LSAS**: Liebowitz Social Anxiety Scale; **MCCB**: MATRICS Consensus Cognitive Battery; **MCQ-Br**: Methamphetamine Craving Questionnaire-Brief; **MDD**: Major Depressive Disorder; **MIGT**: Motivational Interviewing group therapy; **MSCEIT**: Managing emotions component of Mayer–Salovey–Caruso emotional intelligence test; **MTM**: Matrix treatment model; **MUD**: Meth Use Disorder; **m-WAI**: modified Working Alliance Inventory; **OQ-45**: The Outcome Questionnaire-45; **OTP**: Opioid treatment program; **OX**: Oxytocin; **PCL-5**: PTSD Checklist for DSM-5; **PE**: Prolonged Exposure; **PFPP-XR**: Panic Focused (and attachment-based) Psychodynamic Psychotherapy eXtended Range; **PHQ-9:** Patient Health Questionnaire; **PONS**: Profile of Nonverbal Sensitivity; **PQTEE**: Patient Questionnaire on Therapy Expectation and Evaluation; **RMET**: the Reading the Mind in the Eyes Test; **SACiP**: Multiperspective Assessment of General Change Mechanisms in Psychotherapy; **SAD**: Social Anxiety Disorder; **SAI:** The Session Alliance Inventory; **SANS/SAPS**: the Scale for the Assessment of Negative and Positive Symptoms; **SCI-SAS**: Structured Clinical Interview for Separation Anxiety Symptoms; **SCT**: Social cognition training; **SDS**: Sheehan Disability Scale; **SE**: Supportive-Expressive Psychodynamic therapy; **SFS**: the Social Functioning Scale; **SIAS**: Social Interaction Anxiety Scale; **SPAI**: Social Phobia and Anxiety Inventory; **SPQ**: Speech Performance Questionnaire; **SRF**: Social Role Functioning subscale; **SSI**: Scale for Suicidal Ideation; **SSPA**: Social Skills Performance Assessment; **STAI**: State-Trait Anxiety Inventory; **STAI-6:** State-Trait Anxiety Inventory - Short Form; **STCQ-Br**: Stimulant Craving Questionnaire-Brief; **SWAP**: Shedler-Westen Assessment Procedure; **TASIT**: The Awareness of Social Inference Test; **TF-CBT**: Trauma-focused CBT; **TG**: Trust Game; **TSPQ**: The Spider Phobia Questionnaire; **WAI**: Working Alliance Inventory; **WAI-SR**: Working alliance inventory-short revised; **WAI-SR-T**: therapist WAI version; * note that the studies by Flanagan et al. (2018) and Sippel et al. (2020) were drawn from the same sample.

healthy controls, while remitters showed no differences. Most of these studies had low risks of bias, except Jobst et al. (2018), which had a very small sample size (N=16).

3.3.1.3. Synthesis. Findings for the effect of oxytocin on depression psychotherapy outcomes were mostly consistent across different types of psychotherapies. According to the vote-count method reported in Fig. 2 (additional data available in Supplementary Materials S7), two studies did not find any statistically significant effects of oxytocin on primary outcomes, and five found statistically significant positive effects. There is also consistent evidence indicating that oxytocin reactivity and synchrony are associated with depression psychotherapy outcomes.

3.3.2. Post-traumatic stress disorder (PTSD)

3.3.2.1. Oxytocin augmentation. Three studies investigated oxytocin augmentation effects on psychotherapy outcome for PTSD treatment. Two studies drawn from the sample of patients receiving prolonged exposure found no differences in symptoms between conditions (Flanagan et al., 2018; Sippel et al., 2020). In exploratory analyses, they consistently found significant symptom reductions after the third session only. Conversely, in a study of Brief Cognitive-Behavioral Conjoint Therapy, Sippel et al. (2023) found significant symptom improvements after treatment. All of these studies had a moderate risk of bias and very small sample sizes (Flanagan et al., 2018: N=17; Sippel et al., 2020: N=13; Sippel et al., 2023: N=10 dyads).

3.3.2.2. Oxytocin measures. Two studies investigated if oxytocin measures predict PTSD psychotherapy outcomes in internet based trauma-focused CBT. Engel et al. (2021) found that baseline oxytocin did not predict changes in symptoms. Similarly, Engel et al. (2022) suggested that, while the therapeutic alliance predicted improvements in symptomology, oxytocin levels did not correlate with either of them. While the latter suggested positive effects on secondary outcomes, such conclusions were based on descriptive statistics, with no inferential analyses. Moreover, both studies had a moderate risk of bias.

3.3.2.3. Synthesis. According to the vote-count method, four studies did not find any statistically significant effects of oxytocin on psychotherapy outcomes, and only one found positive effects. Since this study was not controlled, it is unknown if such effects were due to oxytocin administration or simply due to therapy. In exploratory analyses only, two studies found short-lived effects after specific sessions. In summary, oxytocin augmentation or baseline levels are not associated with PTSD psychotherapy outcomes in cognitive and exposure-based interventions, especially when considering risk of bias across these studies.

3.3.3. Schizophrenia spectrum disorders

3.3.3.1. Oxytocin augmentation. Three studies investigated oxytocin augmentation effects on psychotherapy outcomes for schizophrenia. In a study of group social cognition training, Cacciotti-Saija et al. (2015) indicated that the oxytocin group showed less improvements in positive symptoms, with no differences in negative symptoms. Similarly, Davis et al. (2014) found no effects of oxytocin on any outcome measures, except increasing empathy in social cognition training. Likewise, Strauss et al. (2019) also did not find any significant effects in group cognitive behavioral therapy social skills training.

3.3.3.2. Synthesis. According to the vote-count method, two studies did not find any statistically significant effects of oxytocin on psychotherapy outcome, and one found a negative effect. In exploratory analyses only, two of them found positive effects. However, studies that eventually found such effects had a moderate risk of bias, while the study that did not, had a low risk. Overall, oxytocin augmentation or baseline measures are not associated with psychotherapy outcomes in schizophrenia as part of social skills training oriented interventions, especially when considering risk of bias across these studies.

3.3.4. Anxiety disorders

3.3.4.1. Oxytocin augmentation. Two studies investigated oxytocin augmentation effects on outcome for exposure-based treatments for anxiety. Guastella et al. (2009) found no significant effect of oxytocin in the adjunct treatment of social anxiety. Exploratory analyses indicated positive effects on self-rated appearance after exposure sessions. However, this study had a moderate risk of bias. Conversely, Acheson et al. (2015) had a low risk of bias and found that the oxytocin group actually had significantly less improvements after psychotherapy for specific phobia.

3.3.4.2. Oxytocin measures. Milrod et al. (2016) found no prognostic value of oxytocin in predicting symptomology change in panic focused (and attachment-based) psychodynamic psychotherapy. However, it had a moderate risk of bias and very small sample size (N=5).

3.3.4.3. Synthesis. According to the vote-count method, two studies did not find any statistically significant effects, and one study actually found negative effects. In exploratory analyses only, one study found positive effects on secondary outcomes after specific sessions. Overall, oxytocin augmentation or baseline measures are not associated with anxiety psychotherapy outcomes in exposure or psychodynamic interventions, especially when considering risk of bias across these studies.

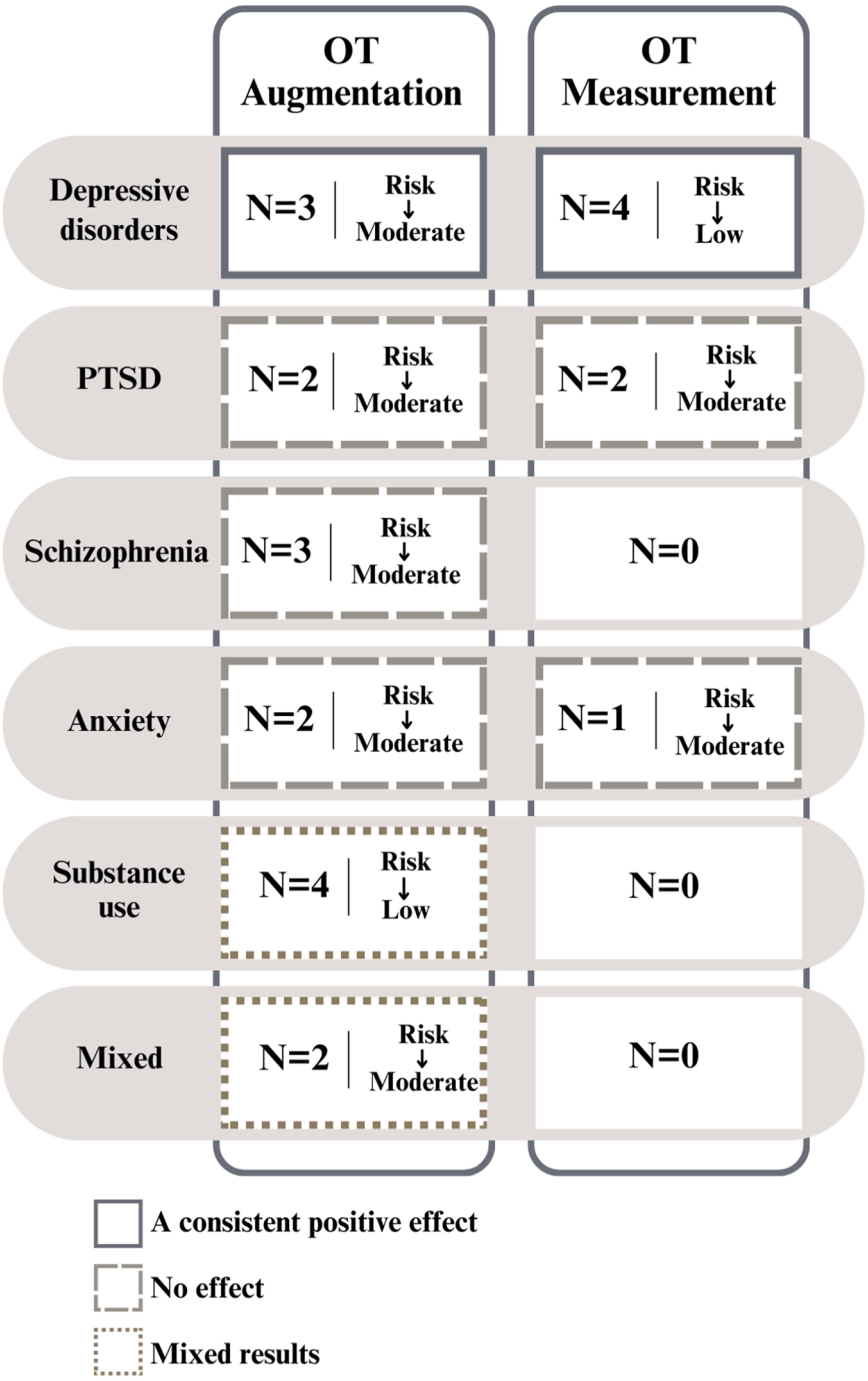

Fig. 2. Associations between psychotherapy treatment outcomes with oxytocin (OT) augmentation or measurement.

3.3.5. *Substance use disorders*

3.3.5.1. Oxytocin augmentation. Four studies investigated oxytocin augmentation effects on psychotherapy outcomes for addictions. In a study of the matrix treatment model, Azadbakht et al. (2022) found that the oxytocin group had fewer cravings and depressive symptoms, but no differences in anxiety. Similarly, in a study of motivational interviewing, Stauffer et al. (2018) suggested that the oxytocin group showed greater reductions in drug use. Conversely, two studies applying motivational or counselling interventions found no significant differences in symptom reduction between groups (Stauffer et al., 2020, 2022). However, secondary analyses indicated significant improvements in interpersonal problems and attendance for the oxytocin group. Within this category, most studies had a low risk of bias, with the exception of Stauffer et al. (2018).

3.3.5.2. Synthesis. According to the vote-count method, two studies did not find any statistically significant effects of oxytocin, and two found positive effects. In exploratory analyses, the studies that did not find any effect of oxytocin on primary symptoms still found positive effects on other outcomes (treatment adherence and relationship improvements). Despite being methodologically sound, many of these studies had the same authors, which may introduce allegiance bias. Overall, the mixed evidence precludes drawing any firm conclusions about the clinical role of oxytocin in the context of motivational and counseling interventions for substance use disorders.

3.3.6. Samples including several diagnoses

3.3.6.1. Oxytocin augmentation. Two studies investigated oxytocin administration effects as an adjunct to psychodynamic psychotherapy for different diagnoses. With a moderate risk of bias, Bitan et al. (2023) found that, depending on personality traits, those who were administered oxytocin had lower depression and suicidal symptoms. Exploratory analyses, however, found interactions between oxytocin and personality traits in deteriorating the therapeutic alliance. Similarly, but with a low risk of bias, Grossman-Giron et al. (2023) also found evidence for decreased depression among the oxytocin group. Furthermore, they found decreases in trait (but not state) anxiety, anxious (but not avoidant) attachment, and general symptomatic distress, as well as increased relationship satisfaction. Conversely, they also found that the placebo group only showed improvements in the working alliance.

3.3.6.2. Synthesis. According to the vote-count method, both studies found positive effects of oxytocin augmentation on outcomes of psychodynamic interventions, consistently indicating decreases in depressive symptoms. In exploratory analyses, they both found negative effects on the therapeutic alliance. Whereas these findings suggest evidence of oxytocin administration improving psychotherapy outcome across disorders, they also suggest that oxytocin acts differently on different people, and could even be harmful for some, in line with two studies that found adverse effects in anxious and schizophrenic samples.

4. Discussion

4.1. Summary of main findings

This systematic review synthesized available findings across two dozen experimental and observational studies where psychotherapy was offered to patients with a variety of mental disorders. Overall, there is consistent evidence from disorder-specific samples and samples with mixed diagnosis, indicating that oxytocin measures are associated with depression psychotherapy outcomes, despite the diverse types of theoretical orientations of psychotherapies featured across studies. Baseline measures of oxytocin, reactivity and synchrony predicted depression psychotherapy outcomes, with few contradictory findings. In experimental studies, patients with oxytocin-augmented psychotherapy tended to have significantly better depression treatment outcomes relative to controls. However, there was no consistent evidence to draw any firm conclusions about the relevance of oxytocin measures or augmentation in the context of psychotherapies for PTSD, schizophrenia spectrum disorders, anxiety disorders, or substance use disorders.

The specificity of associations in the context of depression is of clinical and theoretical interest. Various types of psychotherapies for depression have been found to be equally efficacious (e.g., Cuijpers et al., 2008). This has led some authors to propose that this effect may be mostly driven by common factors that are present across interventions, rather than specific technical differences between therapies of different theoretical orientations (Wampold, 2015). One such common factor is the therapeutic alliance, which has been well-documented to be associated with psychotherapy response across a wide range of therapies, even after adjusting for other potential confounders (Flückiger et al., 2020). Given the centrality of the alliance in psychotherapies for depression, and the role of oxytocin in the regulation of social-cognitive processes such as attachment formation and interpersonal trust, it is plausible that interpersonal differences in oxytocin levels may influence treatment response indirectly via its intermediate effect on the therapeutic alliance. However, this association may be complex, and influenced by other associated factors such as personality and attachment styles, which are discussed below.

4.2. Moderators of oxytocin effects on psychotherapy outcomes

Individual differences in personality traits and attachment styles have been found to interact with oxytocin and to modify its effects (Bitan et al., 2023). Oxytocin effects in decreasing depressive symptoms and suicidal ideation were only present for individuals low in the personality traits of “openness” and “extraversion”, although this is based on few studies. Conceptually, these findings suggest that people low in such social traits might benefit more from oxytocin effects than people that are already highly sociable or motivated to have different experiences. For patients high in “extraversion”, and low in “agreeableness” and “neuroticism”, oxytocin was actually associated with deteriorations in the therapeutic alliance. Conceptually, these findings suggest that oxytocin effects interact with people’s dispositional inclinations in yielding different behaviors. This argument is consistent with conceptual models and research outside of psychotherapy (e.g., Shamay-Tsoory and Abu-Akel, 2016). That said, oxytocin might reinforce pre-established attachment representations, making individuals that are already highly sociable less likely to form new bonds. Similarly, oxytocin effects in promoting social approaching behaviors might be manifested as increased defiance (e.g., aggression or disagreeableness) for people low in agreeableness. Likewise, since people low in neuroticism tend to experience lower levels of social anxiety, such effects might also lead to more defiance, acknowledging the diminished preoccupation to others’ perceptions of them.

Regarding attachment representations, oxytocin augmentation was found to be effective in reducing attachment insecurity for those with anxious attachment, but not for those with avoidant attachment (Grossman-Giron et al., 2023). This suggests that, while oxytocin enhances pre-established attachments in dispositionally dependent individuals, it may not promote its formation in highly independent people.

Future psychotherapy studies should explore additional potential moderators of oxytocin response, including patient and therapist interpersonal and intrapersonal characteristics (Shamay-Tsoory and Abu-Akel, 2016), as well as the role of sex differences. Despite evidence suggesting sex-specific roles of oxytocin (Domes et al., 2010; Lieberz et al., 2020), most human research has not accounted for potential sex differences in their analyses (Dumais and Veenema, 2016). This gap in the literature is also apparent in psychotherapy research.

4.3. Mediators of oxytocin effects on psychotherapy outcomes

Current evidence indicates that the significant changes in symptoms for the oxytocin augmentation groups (relative to controls) were explained by changes in the therapeutic alliance. Similarly, the finding that higher oxytocin synchrony, conceptualized as a biological measure of the therapeutic alliance, led to more symptom improvements further suggests that oxytocin is closely related to the working alliance, which in turn influences psychotherapy outcomes. Seemingly contradictory findings may be explained by the observation that increased oxytocin levels are sometimes associated with more ruptures in the working alliance (Zilcha-Mano et al., 2018), which actually offer the opportunity to apply rupture-repair strategies that are associated with improved psychotherapy outcomes (Eubanks et al., 2018).

4.4. Adverse effects

Oxytocin augmentation was generally found to be safe in all dosages, with minor side effects. However, some studies found evidence for negative effects of oxytocin on psychotherapy outcomes for specific phobias and schizophrenia. Other studies found that oxytocin augmentation was associated with less improvements in the working alliance, which could be harmful to psychological treatment, and which may be plausibly related to the moderating effects of personality and attachment variables discussed above.

4.5. Methodological considerations

A major source of heterogeneity in this area of research concerns the measurement of oxytocin. Whether oxytocin is measured in extracted on unextracted samples, using radioimmunoassay (RIA) or an in-vitro enzyme-linked immunosorbent assay (ELISA), in plasma, saliva or urine samples are all important decisions that can influence the interpretation, reliability and validity of what was measured and therefore the interpretation, reliability and validity of reported associations (Tabak et al., 2023). In current psychological research on oxytocin, there is a notable focus on measuring its peripheral levels. However, the validity of these measures in reflecting oxytocin levels in the brain remains uncertain. While some studies, like Lefevre et al. (2017), have found correlations between peripheral measurements and oxytocin levels in the cerebrospinal fluid, others, such as Reiner et al. (2022), found no correlation between urinary and plasma oxytocin levels. The fact that plasma and urinary measures may not correlate does not make them invalid - plasma and urinary oxytocin reflect different things, as does plasma oxytocin at baseline and after stimulation or treatment. Quintana et al. (2018) and Sippel et al. (2020) observed no change in oxytocin levels after augmentation, further questioning the reliability of peripheral measurements. However, studies like Weisman et al. (2012) have reported meaningful correlations between administered oxytocin and its peripheral levels. Moreover, since baseline levels of plasma oxytocin show considerable intra-individual variability, studies comparing levels of central and peripheral oxytocin in humans should require numerous assessments over a 24-hour period to account for diurnal variation (Amico et al., 1983). The use of single measurements of baseline oxytocin concentrations in saliva and plasma has been questioned as valid trait markers of the physiology of the oxytocin system in humans (Martins et al., 2020), and this is a major source of uncertainty, undermining the replicability of results from several studies in this area.

Following intranasal administration, it is assumed that oxytocin could penetrate directly into the brain or affect its activity via increased peripheral concentrations that cross the blood-brain barrier or influence vagal projections. Research suggests that oxytocin may produce contrasting effects on socioemotional cues depending on the route through which it influences brain function (Kou et al., 2021). There have been debates about whether intranasally administered oxytocin enters the brain via the nose-to-brain route and whether this results in functionally relevant increases in central oxytocin levels. While some evidence from animal models (Lee et al., 2020; Smith et al., 2019) and human studies (Martins et al., 2020; Paloyelis et al., 2016) suggests that intranasal oxytocin can influence brain function, other concerns persist. Accumulating evidence indicates that intranasal oxytocin may influence brain function either through transport involving the olfactory and trigeminal nerves or via the blood-brain barrier after entering the peripheral vasculature (Yamamoto and Higashida, 2020; Yamamoto et al., 2019), or through peripherally mediated autonomic effects (Carter, 2014). It has been proposed that although only a small amount of peripherally circulating OT may cross the blood-brain barrier due to an endothelial barrier with tight junctions, this amount may still reach the brain in biologically and functionally relevant quantities (Quintana et al., 2021).

An included study suggested that oxytocin synchrony could yield better inferences about the therapeutic relationship (Zilcha-Mano et al., 2021). Likewise, other included studies indicated oxytocin variability as an alternative way of detecting its psychological effects (Atzil-Slonim et al., 2022; Jobst et al., 2018). Oxytocin reactivity/recovery might better indicate one's social ability to flexibly regulate themselves than simply basal levels, as proposed by Feldman (2020). Moreover, most research to date investigating oxytocin effects on psychotherapy are small pilot studies with limited sample sizes. This is problematic since multiple tests inflate the probability of type 1 errors, making it likely for significant findings to arise simply by chance.

Another important consideration for future research is the issue of dose effects in oxytocin augmentation. Human intranasal oxytocin studies typically employ dosages ranging from 20 to 48 IU, with a predominant use of a 24 IU dose (Quintana et al., 2021). Future research should aim to elucidate dose-response patterns of oxytocin in psychotherapy to establish guidelines for optimal dosages, taking into account potential disorder-specific and sex-specific differential effects. Mixed and non-significant effects observed may result from incorrect dosage (Quintana et al., 2021). Furthermore, higher doses may lead to the occupation of vasopressin receptors, potentially contributing to both behavioral effects and side effects (Neumann and Landgraf, 2012). Adding further complexity to the study of dose-response, studies suggest that intranasal oxytocin may not exhibit a linear dose-response curve (Guoynes et al., 2018), and sex-specific effects may also be at play (Dumais and Veenema, 2016). A related issue concerns the variable duration of psychological interventions applied across these studies – the associations observed in studies could vary depending on the follow-up measurement schedules and treatment duration, and currently available data is insufficient to draw conclusions about this source of variability.

4.6. Strengths and limitations of the review

This review followed good practice guidelines for the conduct of systematic reviews, including the preregistration of a review protocol, systematic searches across multiple databases, a comprehensive search including grey literature, backward and forward citation searches, double-rated risk of bias assessments, and a transparent reporting excluded studies and detailed statistical results from included studies.

This review also has some limitations. The review excluded genetic studies to attain greater homogeneity across studies in terms of the methods of oxytocin augmentation and measurement. However, such studies might have been relevant, acknowledging the issues surrounding the measurement of peripheral oxytocin. The search strategy may have limitations in its sensitivity to experimental studies, although a number of additional methods were employed to identify potentially eligible studies. Although we provide available information about oxytocin measurement methods, several, this information lacks detail in many reviewed studies, which makes it difficult to evaluate the extent to which measurement heterogeneity may confound the results. Lastly, due to the considerable clinical and methodological heterogeneity across studies, a quantitative synthesis using meta-analytic methods was not possible. Related to this, the risk of bias assessment could not be included as a potential moderator, given the lack of adequate data to perform a meta-analytic synthesis.

4.7. Conclusions

Current evidence indicates that oxytocin is potentially relevant to psychotherapy outcomes for depression, plausibly due to its effects on the therapeutic alliance – a well known predictor of treatment response. Oxytocin-augmented psychotherapy may be particularly effective for depressed patients with low levels of trait openness to experience, trait extraversion, and anxious attachment. Oxytocin augmentation is, however, contraindicated for depressed patients with high levels of trait extraversion, agreeableness and neuroticism. Furthermore, currently there is not sufficient evidence to draw firm conclusions regarding the clinical relevance of oxytocin in the context of other disorders, and augmentation may actually be detrimental in the context of schizophrenia and specific phobias.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

With thanks to Grace Shepherd and Joao Victor Xavier, who contributed as independent raters in the risk of bias assessment.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105935.

References

* Acheson, D.T., Feifel, D., Kamenski, M., Mckinney, R., Risbrough, V.B., 2015. Intranasal oxytocin administration prior to exposure therapy for arachnophobia impedes treatment response. Depress Anxiety 32 (6), 400–407. https://doi.org/10.1002/da.22362.

Amico, J.A., Tenicela, R., Johnston, J., Robinson, A.G., 1983. A time-dependent peak of oxytocin exists in cerebrospinal fluid but not in plasma of humans. J. Clin. Endocrinol. Metab. 57 (5), 947–951. https://doi.org/10.1210/jcem-57-5-947.

* Atzil-Slonim, D., Stolowicz-Melman, D., Bar-Kalifa, E., Gilboa-Schechtman, E., Paz, A., Wolff, M., Feldman, R., 2022. Oxytocin reactivity to the therapeutic encounter as a biomarker of change in the treatment of depression. J. Couns. Psychol. 69 (5), 755–760. https://doi.org/10.1037/cou0000617.

* Azadbakht, A., Salehi, M., Maracy, M.R., Banafshe, H.R., 2022. The effects of oxytocin on craving, mental health parameters, and stress hormones in methamphetamine-dependent patients undergoing matrix treatment model: a randomized, double-blind clinical trial. Eur. Addict. Res. 28 (5), 340–349. https://doi.org/10.1159/000525443.

Bakermans-Kranenburg, M.J., Van Ijzendoorn, M.H., 2013. Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. e258-e258 Transl. Psychiatry 3 (5). https://doi.org/10.1038/tp.2013.34.

Bartz, J.A., Zaki, J., Ochsner, K.N., Bolger, N., Kolevzon, A., Ludwig, N., Lydon, J.E., 2010. Effects of oxytocin on recollections of maternal care and closeness. Proc. Natl. Acad. Sci. 107 (50), 21371–21375. https://doi.org/10.1073/pnas.1012669107.

* Bitan, D.T., Grossman-Giron, A., Sedoff, O., Zilcha-Mano, S., Nitzan, U., Maoz, H., 2023. A double-edged hormone: the moderating role of personality and attachment on oxytocin's treatment facilitation effect. Psychoneuroendocrinology 151, 106074. https://doi.org/10.1016/j.psyneuen.2023.106074.

Brüne, M., 2016. On the role of oxytocin in borderline personality disorder. Br. J. Clin. Psychol. 55 (3), 287–304. https://doi.org/10.1111/bjc.12100.

* Cacciotti-Saija, C., Langdon, R., Ward, P.B., Hickie, I.B., Scott, E.M., Naismith, S.L., Guastella, A.J., 2015. A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. Schizophr. Bull. 41 (2), 483–493. https://doi.org/10.1093/schbul/sbu094.

Cardoso, C., Ellenbogen, M.A., Orlando, M.A., Bacon, S.L., Joober, R., 2013. Intranasal oxytocin attenuates the cortisol response to physical stress: a dose–response study. Psychoneuroendocrinology 38 (3), 399–407. https://doi.org/10.1016/j.psyneuen.2012.07.013.

Carter, C.S., 2014. Oxytocin pathways and the evolution of human behavior. Annu. Rev. Psychol. 65, 17–39. https://doi.org/10.1146/annurev-psych-010213-115110.

* Clarici, A., Pellizzoni, S., Guaschino, S., Alberico, S., Bembich, S., Giuliani, R., Panksepp, J., 2015. Intranasal administration of oxytocin in postnatal depression: implications for psychodynamic psychotherapy from a randomized double-blind pilot study. Front. Psychol. 6, 426. https://doi.org/10.3389/fpsyg.2015.00426.

Clark-Elford, R., Nathan, P.J., Auyeung, B., Voon, V., Sule, A., Müller, U., Baron-Cohen, S., 2014. The effects of oxytocin on social reward learning in humans. Int. J. Neuropsychopharmacol. 17 (2), 199–209. https://doi.org/10.1017/S1461145713001120.

Cochran, D., 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. https://doi.org/10.1097/HRP.0b013e3182a75b7d.

Cuijpers, P., van Straten, A., Andersson, G., van Oppen, P., 2008. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J. Consult. Clin. Psychol. 76 (6), 909–922. https://doi.org/10.1037/a0013075.

* Davis, M.C., Green, M.F., Lee, J., Horan, W.P., Senturk, D., Clarke, A.D., Marder, S.R., 2014. Oxytocin-augmented social cognitive skills training in schizophrenia. Neuropsychopharmacology 39 (9), 2070–2077. https://doi.org/10.1038/npp.2014.68.

De Cagna, F., Fusar-Poli, L., Damiani, S., Rocchetti, M., Giovanna, G., Mori, A., Brondino, N., 2019. The role of intranasal oxytocin in anxiety and depressive disorders: a systematic review of randomized controlled trials. Clin. Psychopharmacol. Neurosci. 17 (1), 1–11 https://doi.org/10.9758%2Fcpn.2019.17.1.1.

De Dreu, C.K., Greer, L.L., Van Kleef, G.A., Shalvi, S., Handgraaf, M.J., 2011. Oxytocin promotes human ethnocentrism. Proc. Natl. Acad. Sci. 108 (4), 1262–1266. https://doi.org/10.1073/pnas.1015316108.

Domes, G., Heinrichs, M., Michel, A., Berger, C., Herpertz, S.C., 2007. Oxytocin improves "mind-reading" in humans. Biol. Psychiatry 61 (6), 731–733. https://doi.org/10.1016/j.biopsych.2006.07.015.

Domes, G., Lischke, A., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., Herpertz, S.C., 2010. Effects of intranasal oxytocin on emotional face processing in women. Psychoneuroendocrinology 35 (1), 83–93. https://doi.org/10.1016/j.psyneuen.2009.06.016.

Dumais, K.M., Veenema, A.H., 2016. Presence and absence of sex differences in structure and function of the brain oxytocin system: implications for understanding the regulation of social behavior. In: Shansky, R.M. (Ed.), Sex Differences in the Central Nervous System. Academic Press, San Diego, pp. 247–295.

Economic and Social Research Council. 2015. ESRC Framework for research ethics. [online] Available at: ⟨https://esrc.ukri.org/files/funding/guidance-for-applicants/esrc-framework-for-research-ethics-2015/⟩.

Ellenbogen, M.A., 2018. Oxytocin and facial emotion recognition. Behav. Pharmacol. Neuropept.: oxytocin 349–374. https://doi.org/10.1007/7854_2017_20.

* Ellenbogen, M., Cardoso, C., Serravalle, L., Virginia, T., 2018. T142. Intranasal oxytocin augments the efficacy of psychotherapy for major depressive disorder. Biol. Psychiatry 83 (9), S183. https://doi.org/10.1016/j.biopsych.2018.02.479.

* Ellenbogen, M.A., Cardoso, C., Serravalle, L., Trespalacios, F., 2019. Intranasal oxytocin improves subjective ratings of the therapeutic alliance during psychotherapy for major depressive disorder. Psychoneuroendocrinology 107, 54. https://doi.org/10.1016/j.psyneuen.2019.07.154.

Elliott, R., Bohart, A.C., Watson, J.C., Murphy, D., 2018. Therapist empathy and client outcome: an updated meta-analysis. Psychotherapy 55 (4), 399–410. https://doi.org/10.1037/pst0000175.

Engel, S., Laufer, S., Knaevelsrud, C., Schumacher, S., 2019. The endogenous oxytocin system in depressive disorders: a systematic review and meta-analysis. Psychoneuroendocrinology 101, 138–149. https://doi.org/10.1016/j.psyneuen.2018.11.011.

* Engel, S., Schumacher, S., Niemeyer, H., Kuester, A., Burchert, S., Klusmann, H., Knaevelsrud, C., 2021. Associations between oxytocin and vasopressin concentrations, traumatic event exposure and posttraumatic stress disorder symptoms: group comparisons, correlations, and courses during an internet-based cognitive-behavioural treatment. Eur. J. Psychotraumatology 12 (1), 1886499. https://doi.org/10.1080/20008198.2021.1886499.

* Engel, S., Schumacher, S., Niemeyer, H., Küster, A., Burchert, S., Rau, H., Knaevelsrud, C., 2022. Does oxytocin impact the psychotherapeutic process? An explorative investigation of internet-based cognitive-behavioral treatment for posttraumatic stress disorder. Verhaltenstherapie 1–13. https://doi.org/10.1159/000506028.

Eubanks, C.F., Muran, J.C., Safran, J.D., 2018. Alliance rupture repair: a meta-analysis. Psychotherapy 55 (4), 508–519. https://doi.org/10.1037/pst0000185.

Farber, B.A., Suzuki, J.Y., Lynch, D.A., 2018. Positive regard and psychotherapy outcome: a meta-analytic review. Psychotherapy 55 (4), 411–423. https://doi.org/10.1037/pst0000171.

Feldman, R., 2020. What is resilience: an affiliative neuroscience approach. World Psychiatry 19 (2), 132–150. https://doi.org/10.1002/wps.20729.

Ferreira, A.C., de Lima Osório, F., 2022. Peripheral oxytocin concentrations in psychiatric disorders–a systematic review and methanalysis: further evidence. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 117, 110561. https://doi.org/10.1016/j.pnpbp.2022.110561.

* Flanagan, J.C., Sippel, L.M., Wahlquist, A., Moran-Santa Maria, M.M., Back, S.E., 2018. Augmenting Prolonged Exposure therapy for PTSD with intranasal oxytocin: a randomized, placebo-controlled pilot trial. J. Psychiatr. Res. 98, 64–69. https://doi.org/10.1016/j.jpsychires.2017.12.014.

Flückiger, C., Del Re, A.C., Wampold, B.E., Horvath, A.O., 2018. The alliance in adult psychotherapy: a meta-analytic synthesis. Psychotherapy 55 (4), 316–340. https://doi.org/10.1037/pst0000172.

Flückiger, C., Del Re, A.C., Wlodasch, D., Horvath, A.O., Solomonov, N., Wampold, B.E., 2020. Assessing the alliance–outcome association adjusted for patient characteristics and treatment processes: A meta-analytic summary of direct comparisons. J. Couns. Psychol. 67 (6), 706–711. https://doi.org/10.1037/cou0000424.

Froemke, R.C., Young, L.J., 2021. Oxytocin, neural plasticity, and social behavior. Annu. Rev. Neurosci. 44, 359–381. https://doi.org/10.1146/annurev-neuro-102320-102847.

Giovanna, G., Damiani, S., Fusar-Poli, L., Rocchetti, M., Brondino, N., de Cagna, F., Politi, P., 2020. Intranasal oxytocin as a potential therapeutic strategy in post-traumatic stress disorder: a systematic review. Psychoneuroendocrinology 115, 104605. https://doi.org/10.1016/j.psyneuen.2020.104605.

Groppe, S.E., Gossen, A., Rademacher, L., Hahn, A., Westphal, L., Gründer, G., Spreckelmeyer, K.N., 2013. Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. Biol. Psychiatry 74 (3), 172–179. https://doi.org/10.1016/j.biopsych.2012.12.023.

* Grossman-Giron, A., Maoz, H., Nitzan, U., Kivity, Y., Zilcha-Mano, S., Bloch, Y., Tzur Bitan, D., 2023. Intranasal oxytocin as add-on treatment for inpatients with severe mental illness: a randomized clinical trial. Neuropsychobiology 82 (1), 14–23. https://doi.org/10.1159/000528314.

Guastella, A.J., Hickie, I.B., 2016. 'Oxytocin treatment, circuitry, and autism: a critical review of the literature placing oxytocin into the autism context'. Biol. Psychiatry (1969) 79 (3), 234–242. https://doi.org/10.1016/j.biopsych.2015.06.028.

* Guastella, A.J., Howard, A.L., Dadds, M.R., Mitchell, P., Carson, D.S., 2009. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure

therapy for social anxiety disorder. Psychoneuroendocrinology 34 (6), 917–923. https://doi.org/10.1016/j.psyneuen.2009.01.005.
Guoynes, C.D., Simmons, T.C., Downing, G.M., Jacob, S., Solomon, M., Bales, K.L., 2018. Chronic intranasal oxytocin has dose-dependent effects on central oxytocin and vasopressin systems in prairie voles (Microtus ochrogaster. Neuroscience 369, 292–302. https://doi.org/10.1016/j.neuroscience.2017.11.037.
Houghton, B., Kouimtsidis, C., Duka, T., Paloyelis, Y., Bailey, A., 2021. Can intranasal oxytocin reduce craving in automated addictive behaviours? A systematic review. Br. J. Pharmacol. 178 (21), 4316–4334. https://doi.org/10.1111/bph.15617.
Huang, Y., Huang, X., Ebstein, R.P., Yu, R., 2021. Intranasal oxytocin in the treatment of autism spectrum disorders: a multilevel meta-analysis. Neurosci. Biobehav. Rev. 122, 18–27. https://doi.org/10.1016/j.neubiorev.2020.12.028.
Hurlemann, R., 2017. Oxytocin-augmented psychotherapy: beware of context. Neuropsychopharmacology 42 (1), 377. https://doi.org/10.1038/2Fnpp.2016.188.
* Jobst, A., Sabass, L., Hall, D., Brücklmeier, B., Buchheim, A., Hall, J., 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.
John, S., Jaeggi, A.V., 2021. Oxytocin levels tend to be lower in autistic children: a meta-analysis of 31 studies. Autism 25 (8), 2152–2161. https://doi.org/10.1177/13623613211034375.
Kiani, Z., Farkhondeh, T., Aramjoo, H., Aschner, M., Beydokhti, H., Esmaeili, A., Samarghandian, S., 2023. Oxytocin effect in adult patients with autism: an updated systematic review and meta-analysis of randomized controlled trials. CNS Neurol. Disord. Drug Targets 22 (6), 906–915. https://doi.org/10.2174/1871527321666220517112612.
Kou, J., Lan, C., Zhang, Y., Wang, Q., Zhou, F., Zhao, Z., Kendrick, K.M., 2021. In the nose or on the tongue? Contrasting motivational effects of oral and intranasal oxytocin on arousal and reward during social processing. Transl. Psychiatry 11 (1), 94. https://doi.org/10.1038/s41398-021-01241-w.
Kou, J., Zhang, Y., Zhou, F., Gao, Z., Yao, S., Zhao, W., Becker, B., 2022. Anxiolytic effects of chronic intranasal oxytocin on neural responses to threat are dose-frequency dependent. Psychother. Psychosom. 91 (4), 253–264. https://doi.org/10.1159/000521348.
Lee, M.R., Shnitko, T.A., Blue, S.W., Kaucher, A.V., Winchell, A.J., Erikson, D.W., Leggio, L., 2020. Labeled oxytocin administered via the intranasal route reaches the brain in rhesus macaques. Nat. Commun. 11 (1), 2783. https://doi.org/10.1038/s41467-020-15942-1.
Lefevre, A., Mottolese, R., Dirheimer, M., Mottolese, C., Duhamel, J.R., Sirigu, A., 2017. A comparison of methods to measure central and peripheral oxytocin concentrations in human and non-human primates. Sci. Rep. 7 (1), 1–10. https://doi.org/10.1038/s41598-017-17674-7.
Leppanen, J., Ng, K.W., Kim, Y.R., Tchanturia, K., Treasure, J., 2018. Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans. J. Affect. Disord. 225, 167–179. https://doi.org/10.1016/j.jad.2017.08.041.
Leppanen, J., Ng, K.W., Tchanturia, K., Treasure, J., 2017. Meta-analysis of the effects of intranasal oxytocin on interpretation and expression of emotions. Neurosci. Biobehav. Rev. 78, 125–144. https://doi.org/10.1016/j.neubiorev.2017.04.010.
Higgins, J.P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A. (Eds.), 2019. Cochrane Handbook For Systematic Reviews Of Interventions. John Wiley & Sons.
Levy, K.N., Kivity, Y., Johnson, B.N., Gooch, C.V., 2018. Adult attachment as a predictor and moderator of psychotherapy outcome: a meta-analysis. J. Clin. Psychol. 74 (11), 1996–2013. https://doi.org/10.1002/jclp.22685.
Lieberz, J., Scheele, D., Spengler, F.B., Matheisen, T., Schneider, L., Stoffel-Wagner, B., Hurlemann, R., 2020. Kinetics of oxytocin effects on amygdala and striatal reactivity vary between women and men. Neuropsychopharmacology 45 (7), 1134–1140. https://doi.org/10.1038/s41386-019-0582-6.
Long, H.A., French, D.P., Brooks, J.M., 2020. Optimising the value of the critical appraisal skills programme (CASP) tool for quality appraisal in qualitative evidence synthesis. Res. Methods Med. Health Sci. 1 (1), 31–42. https://doi.org/10.1177/263208432094755.
Martins, D.A., Mazibuko, N., Zelaya, F., Vasilakopoulou, S., Loveridge, J., Oates, A., Paloyelis, Y., 2020. Effects of route of administration on oxytocin-induced changes in regional cerebral blood flow in humans. Nat. Commun. 11 (1), 1160. https://doi.org/10.1038/s41467-020-14845-5.
* Milrod, B., Altemus, M., Gross, C., Busch, F., Silver, G., Christos, P., Schneier, F., 2016. Adult separation anxiety in treatment nonresponders with anxiety disorders: delineation of the syndrome and exploration of attachment-based psychotherapy and biomarkers. Compr. Psychiatry 66, 139–145. https://doi.org/10.1016/j.comppsych.2016.01.004.
Mottolese, R., Redouté, J., Costes, N., Le Bars, D., Sirigu, A., 2014. Switching brain serotonin with oxytocin. *Proc. Natl. Acad. Sci*ences 111 (23), 8637–8642. https://doi.org/10.1073/pnas.1319810111.
Neumann, I.D., Landgraf, R., 2012. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci. 35 (11), 649–659. https://doi.org/10.1016/j.tins.2012.08.004.
Oya, K., Matsuda, Y., Matsunaga, S., Kishi, T., Iwata, N., 2016. Efficacy and safety of oxytocin augmentation therapy for schizophrenia: an updated systematic review and meta-analysis of randomized, placebo-controlled trials. Eur. Arch. Psychiatry Clin. Neurosci. 266, 439–450. https://doi.org/10.1007/s00406-015-0634-9.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int. J. Surg. 88, 105906. https://doi.org/10.1016/j.ijsu.2021.105906.
Paloyelis, Y., Doyle, O.M., Zelaya, F.O., Maltezos, S., Williams, S.C., Fotopoulou, A., Howard, M.A., 2016. A spatiotemporal profile of in vivo cerebral blood flow changes following intranasal oxytocin in humans. Biol. Psychiatry 79 (8), 693–705. https://doi.org/10.1016/j.biopsych.2014.10.005.
Preckel, K., Trautmann, S., Kanske, P., 2021. Medication-enhanced psychotherapy for posttraumatic stress disorder: recent findings on oxytocin's involvement in the neurobiology and treatment of posttraumatic stress disorder. Clin. Psychol. Eur. 3 (4) e3645–e3645. https://doi.org/10.32872%2Fcpe.3645.
Quintana, D.S., Lischke, A., Grace, S., Scheele, D., Ma, Y., Becker, B., 2021. Advances in the field of intranasal oxytocin research: lessons learned and future directions for clinical research. Mol. Psychiatry 26 (1), 80–91. https://doi.org/10.1038/s41380-020-00864-7.
Quintana, D.S., Westlye, L.T., Smerud, K.T., Mahmoud, R.A., Andreassen, O.A., Djupesland, P.G., 2018. Saliva oxytocin measures do not reflect peripheral plasma concentrations after intranasal oxytocin administration in men. Horm. Behav. 102, 85–92. https://doi.org/10.1016/j.yhbeh.2018.05.004.
* Reiner, I.C., Gimpl, G., Beutel, M.E., Bakermans-Kranenburg, M.J., Frieling, H., 2022. OXTR-related markers in clinical depression: a longitudinal case–control psychotherapy study. J. Mol. Neurosci. 1–13. https://doi.org/10.1007/s12031-021-01930-7.
Rutigliano, G., Rocchetti, M., Paloyelis, Y., Gilleen, J., Sardella, A., Cappucciati, M., 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.
Sabe, M., Zhao, N., Crippa, A., Strauss, G.P., Kaiser, S., 2021. Intranasal oxytocin for negative symptoms of schizophrenia: systematic review, meta-analysis, and dose-response meta-analysis of randomized controlled trials. Int. J. Neuropsychopharmacol. 24 (8), 601–614. https://doi.org/10.1093/ijnp/pyab020.
Scatliffe, N., Casavant, S., Vittner, D., Cong, X., 2019. Oxytocin and early parent-infant interactions: A systematic review. Int. J. Nurs. Sci. 6 (4), 445–453. https://doi.org/10.1016/j.ijnss.2019.09.009.
Shamay-Tsoory, S.G., Abu-Akel, A., 2016. The social salience hypothesis of oxytocin. Biol. Psychiatry 79 (3), 194–202. https://doi.org/10.1016/j.biopsych.2015.07.020.
Sippel, L.M., Allington, C.E., Pietrzak, R.H., Harpaz-Rotem, I., Mayes, L.C., Olff, M., 2017. Oxytocin and stress-related disorders: neurobiological mechanisms and treatment opportunities, 2470547016687996 Chronic Stress 1. https://doi.org/10.1177/2470547016687996.
* Sippel, L.M., Khalifian, C.E., Knopp, K.C., Webster, K., Maglione, J., Holcomb, J., Morland, L.A., 2023. Pilot test of intranasal oxytocin as an enhancer of brief couples therapy for posttraumatic stress disorder. J. Psychiatr. Res. 161, 165–169. https://doi.org/10.1016/j.jpsychires.2023.03.001.
* Sippel, L.M., King, C.E., Wahlquist, A.E., Flanagan, J.C., 2020. A preliminary examination of endogenous peripheral oxytocin in a pilot randomized clinical trial of oxytocin-enhanced psychotherapy for posttraumatic stress disorder. J. Clin. Psychopharmacol. 40 (4), 401. https://doi.org/10.1097/JCP.0000000000001226.
Smith, A.S., Korgan, A.C., Young, W.S., 2019. Oxytocin delivered nasally or intraperitoneally reaches the brain and plasma of normal and oxytocin knockout mice. Pharmacol. Res. 146, 104324. https://doi.org/10.1016/j.phrs.2019.104324.
* Stauffer, C., Moschetto, J., McKernan, S., Hsiang, E., Woolley, J., 2018. T260. oxytocin-enhanced motivational interviewing group therapy for methamphetamine use disorder in men who have sex with men: preliminary results from a randomized controlled trial. Biol. Psychiatry 83 (9), S230–S231. https://doi.org/10.1016/j.biopsych.2018.02.597.
* Stauffer, C.S., Moschetto, J.M., McKernan, S., Meinzer, N., Chiang, C., Rapier, R., Woolley, J.D., 2020. Oxytocin-enhanced group therapy for methamphetamine use disorder: randomized controlled trial. J. Subst. Abus. Treat. 116, 108059. https://doi.org/10.1016/j.jsat.2020.108059.
* Stauffer, C.S., Samson, S., Hickok, A., Hoffman, W.F., Batki, S.L., 2022. Intranasal oxytocin for stimulant use disorder among male veterans enrolled in an opioid treatment program: a randomized controlled trial. Front. Psychiatry 12, 2542. https://doi.org/10.3389/fpsyt.2021.804997.
* Strauss, G.P., Granholm, E., Holden, J.L., Ruiz, I., Gold, J.M., Kelly, D.L., Buchanan, R. W., 2019. The effects of combined oxytocin and cognitive behavioral social skills training on social cognition in schizophrenia. Psychol. Med. 49 (10), 1731–1739. https://doi.org/10.1017/S0033291718002465.
Striepens, N., Kendrick, K.M., Maier, W., Hurlemann, R., 2011. Prosocial effects of oxytocin and clinical evidence for its therapeutic potential. Front. Neuroendocrinol. 32 (4), 426–450. https://doi.org/10.1016/j.yfrne.2011.07.001.
Tabak, B.A., Leng, G., Szeto, A., Parker, K.J., Verbalis, J.G., Ziegler, T.E., Mendez, A.J., 2023. Advances in human oxytocin measurement: challenges and proposed solutions. Mol. Psychiatry 28 (1), 127–140. https://doi.org/10.1038/s41380-022-01719-z.
Tryon, G.S., Birch, S.E., Verkuilen, J., 2018. Meta-analyses of the relation of goal consensus and collaboration to psychotherapy outcome. Psychotherapy 55 (4), 372–383. https://doi.org/10.1037/pst0000170.
Van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., 2012. A sniff of trust: meta-analysis of the effects of intranasal oxytocin administration on face recognition, trust to in-group, and trust to out-group. Psychoneuroendocrinology 37 (3), 438–443. https://doi.org/10.1016/j.psyneuen.2011.07.008.
Wampold, B.E., 2015. How important are the common factors in psychotherapy? An update. World Psychiatry 14 (3), 270–277. https://doi.org/10.1002/wps.20238.
Weisman, O., Zagoory-Sharon, O., Feldman, R., 2012. Intranasal oxytocin administration is reflected in human saliva. Psychoneuroendocrinology 37 (9), 1582–1586. https://doi.org/10.1016/j.psyneuen.2012.02.014.
Yamamoto, Y., Higashida, H., 2020. RAGE regulates oxytocin transport into the brain. Commun. Biol. 3 (1), 70. https://doi.org/10.1038/s42003-020-0799-2.

Yamamoto, Y., Liang, M., Munesue, S., Deguchi, K., Harashima, A., Furuhara, K., Higashida, H., 2019. Vascular RAGE transports oxytocin into the brain to elicit its maternal bonding behaviour in mice. Commun. Biol. 2 (1), 76. https://doi.org/10.1038/s42003-019-0325-6.

Yang, X., Wang, W., Wang, X.T., Wang, Y.W., 2021. A meta-analysis of hormone administration effects on cooperative behaviours: oxytocin, vasopressin, and testosterone. Neurosci. Biobehav. Rev. 126, 430–443. https://doi.org/10.1016/j.neubiorev.2021.03.033.

Zhang, K., Fan, Y., Yu, R., Tian, Y., Liu, J., Gong, P., 2021. Intranasal oxytocin administration but not peripheral oxytocin regulates behaviors of attachment insecurity: a meta-analysis. Psychoneuroendocrinology 132, 105369. https://doi.org/10.1016/j.psyneuen.2021.105369.

Zheng, W., Zhu, X.M., Zhang, Q.E., Yang, X.H., Cai, D.B., Li, L., Xiang, Y.T., 2019. Adjunctive intranasal oxytocin for schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials. Schizophr. Res. 206, 13–20. https://doi.org/10.1016/j.schres.2018.12.007.

* Zilcha-Mano, S., Goldstein, P., Dolev-Amit, T., Shamay-Tsoory, S., 2021. Oxytocin synchrony between patients and therapists as a mechanism underlying effective psychotherapy for depression. J. Consult. Clin. Psychol. 89 (1), 49. https://doi.org/10.1037/ccp0000619.

Zilcha-Mano, S., Porat, Y., Dolev, T., Shamay-Tsoory, S., 2018. Oxytocin as a neurobiological marker of ruptures in the working alliance. Psychother. Psychosom. 87 (2), 126–127. https://doi.org/10.1159/000487190.