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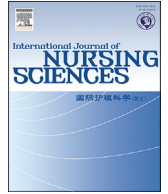
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Review

Oxytocin and early parent-infant interactions: A systematic review

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ABSTRACT

Objectives: Social relationships throughout lifespan are critical for health and wellbeing. Oxytocin, often called the 'hormone of attachment' has been suggested as playing an important role in early-life nurturing and resulting social bonding. The objective of this paper is to synthesize the associations between oxytocin levels and interactions between infants and parents that may trigger oxytocin release, and in turn facilitate attachments.

Methods: A comprehensive cross-disciplinary systematic search was completed using electronic databases. The inclusion criteria included studies that focused on mother-infant and father-infant interaction and measured both baseline and post-interaction oxytocin levels.

Results: Seventeen studies were included in the final systematic review. The reviewed studies used mother-infant and/or father-infant play and skin-to-skin contact between maternal-infant and paternal-infant dyads to examine the oxytocin role in early life bonding and parenting processes. Studies showed a positive correlation between parent-infant contact and oxytocin levels in infancy period. Increased maternal oxytocin levels were significantly related to more affectionate contact behaviors in mothers following mother-infant contact, synchrony, and engagement. Meanwhile, increased paternal oxytocin levels were found to be related to more stimulatory contact behaviors in fathers following father-infant contact. Oxytocin levels significantly increased in infants, mothers and fathers during skin-to-skin contact and parents with higher oxytocin levels exhibited more synchrony and responsiveness in their infant interactions.

Conclusion: The review suggests that oxytocin plays an important role in the development of attachment between infants and parents through early contact and interaction. The complexities of oxytocinergic mechanisms are rooted in neurobiological, genetic, and social factors.

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What is known?

Parent-Infant contact positively influences attachment.

What is new?

The interaction between parent-infant contact, social factors and oxytocin are based in neurobiological factors.

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1. Introduction

From Bowlby's [1] seminal work on attachment, parent-infant bonding has been widely accepted as the foundation for the infant's social attachment. The parent-infant bond is thought to be the evolutionary and the neurobiological foundation for our capacity to form social bonds which ensure physical and mental health and wellbeing through adulthood [2,3]. As parents interact with their infant, bio-behavioral provisions assist in organizing the infant's physiological systems, stress response and social orientation [4,5]. Thus, as researchers become increasingly interested in biomarkers that promote bonding, caregiving and synchrony, oxytocin (OT) has become a major focus as it has been found to play an essential role in the developing nervous system and in the expression of sociality that is pivotal to developing relationships [2].

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Oxytocin is a nine-amino-acid neuropeptide that is synthesized in the hypothalamus, it then travels to and is stored in the posterior pituitary gland and has been shown to enhance activation in brain areas related to bonding and empathy and functional connectivity between those areas [6]. The organization of oxytocin availability is critical to the limbic and neocortical systems – those structures related to emotion and depends on early caregiving experiences. Neurobiologically oxytocin directs the young infant to preferentially select species-specific social stimuli to form dyadic attachments and is considered critical in the experience-dependent plasticity to feed forward auto-regulated functioning during sensitive periods of development [7]. Oxytocin helps to regulate the autonomic nervous system, with consequences for sensory, visceral, metabolic, and smooth motor systems.

Oxytocin increases social sensitivity and modulates reactivity to stressors via the hypothalamic pituitary adrenal (HPA) axis. The HPA axis is an eloquent and dynamic intertwining of the central nervous system and endocrine system. The main determinants of HPA function or dysfunction are genetic, early-life environments and current life stress. In response to stress, cortisol can be released for several hours. With repeated exposure to stressors organisms habituate with sustained HPA axis activation. Oxytocin is within a subset of neurons that responds with major adaptive or stress hormones, that regulate the HPA axis and have been implicated in some of the detrimental effects of chronic stress [8]. Oxytocin may be co-released as an adaptive response to an assortment of challenges, both positive and negative [9,10]. Oxytocin can encourage emotional states that allow optimal development and enhance social competence. Oxytocin may protect and heal tissues and has therapeutic benefits of containing antioxidant and anti-inflammatory properties which help buffer the consequences of stress and adversity.

Numerous animal and human studies have investigated parent infant interaction. Prairie voles have been used to explore how early infant-parent interactions influence the ability to develop social bonds later in life. Voles that experienced bi-parental licking and grooming compared to those raised only by the mother displayed greater ability to bond socially [11]. Another rodent study found oxytocin influenced behavior such that maternal rats that exhibited high levels of Licking, Grooming and Arch-Backed Nursing behaviors (LG-ABN) had higher oxytocin receptor densities in brain structures associated with oxytocin release as compared to maternal rats with low LG-ABN levels [12,13]. It appears that oxytocin is pivotal in creating a cohesive parent-infant bond that stems from the soothing and comforting interactions infants experience during their early life care. This has helped inform the concept that parent-infant contact is critical for establishing affiliative bonds. These bonds are formed through synchronous (or reciprocal) social interactions. Synchronous interactions are those in which a parent or infant respond to one another, the actions and responses are not predetermined, and serve as self-organizing processes from the social inputs found in the interaction [14]. Parental contact is not only critical to social interaction but also to an infant's developmental trajectory. The presence or absence of these early life experiences influence infant neurodevelopmental outcomes [15,16].

Weber and colleagues identified social context as critical to the infant's developing brain [17]. The neurobiological processes including genetic and or epigenetic regulation influence the infant's brain structure and functioning which is dependent on experiences to enhance the infant's emotional and self-regulation. The purpose of this review was to synthesize the findings of oxytocin research in regards to the association between oxytocin levels and interactions between infants and their parents.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) standards were used to guide this review [18]. A literature search was performed in October 2018 using CINAHL, PsycInfo, PubMed, and Scopus electronic databases to identify primary research articles published between 2010 and 2018 that focused on the primary outcome measure of oxytocin and parent-infant bonding. An example of the search strategy in PubMed was the use of the key words “oxytocin” AND “infant” OR “parent-infant bonding”. Additional keywords included: ‘parent-infant interaction’, ‘neuropsychological tests’, ‘infant-newborn,’ ‘parent-infant relations’, and ‘attachment behavior’. Key words were combined using “and”, “or” as well as “and/or”. Manual searches were also completed using references from previously published studies and literature reviews.

Publications selected met the following inclusion criteria for this review: 1) measured both baseline oxytocin and post-interaction oxytocin levels, 2) articles focused on mother-infant and father-infant interaction, including skin-to-skin contact (SSC), 3) infant age was limited from birth to ≤ 1 year of age, and 4) written in English. Studies were rejected based on the following exclusion criteria: 1) studies not published in English; 2) studies that did not focus on the population of interest and effects of oxytocin and parent-infant interaction; and, 3) review articles or case-study publications. Database searches were conducted by two authors (First and Third authors) and also verified by the corresponding author. Articles retrieved via these search methods were reviewed for duplication. The two authors, independently reviewed database search results, read titles and abstracts to determine inclusion. Of the 214 articles selected, five were found through manual reference searches, 167 were excluded due to duplication, and another 35 were excluded given their focus was not on infants, resulting in 17 articles that are included in this review.

To evaluate the quality of selected articles, the first and fourth authors used a scale based on The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [19]. The STROBE instrument contains 22 items and each article was assessed and received either one point if the item was present or zero if it was not. Disagreements were resolved by discussion between three authors. Authors agreed that articles scoring < 20 be excluded. The process used to screen and select articles for the review are shown in Fig. 1.

Review data were reviewed and studies analyzed using qualitative description and then divided into groups of topics that would allow for ease of understanding. Qualitative description was used to gather richness of data related to the effects of oxytocin and early contact.

3. Results

The 17 studies included in this review were conducted in Israel ($n = 11$), the United States ($n = 2$), the United Kingdom ($n = 1$), Canada ($n = 1$), Israel/USA ($n = 1$), and Israel/Germany ($n = 1$). Ten of the studies used an observational study design without follow-ups (Table 1), five studies used prospective observational-longitudinal design (Table 2), and two used randomized cross-over design (Table 3). The review results were summarized into the following groups of topics.

3.1. Parent-infant contact examined in the studies

In the observational studies without follow-ups (Table 1), many of them used timed mother-infant and/or father-infant play and touch as the parent-infant interaction mode to examine the

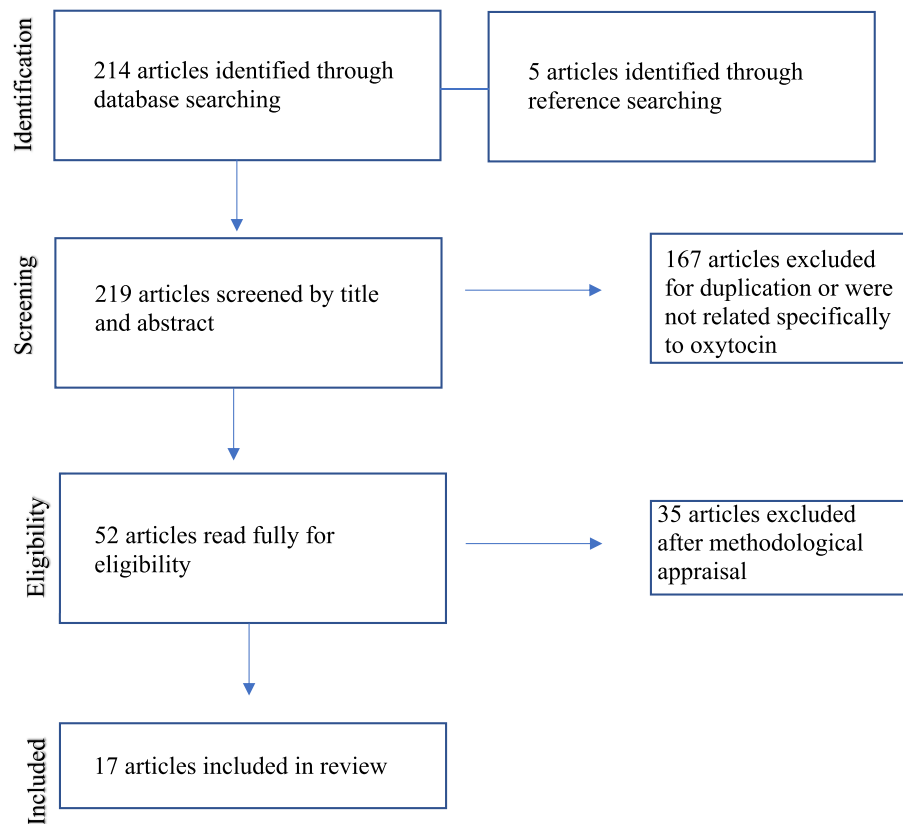


Fig. 1. Diagram of study selection for the integrative review.

oxytocin role in the bonding and parenting process [13,20–23]. Additional methods included video recording of parent-infant interaction and then observing parents' responses upon reviewing the recordings [23–25]. In the observational-longitudinal studies (Table 2), video of 10–15 min of parent-infant free-play and triadic interactions were conducted [12,26]. Interactions between child and his/her best friend were also observed during the structured play [27]. In the cross-over design studies (Table 3), 30–60 min of SSC (Kangaroo Care) were conducted in the mother with her preterm infant as well as the father with his preterm infant [28,29].

3.2. Oxytocin measurements

In the reviewed studies, oxytocin measurements were conducted using plasma, salivary and/or urinary samples before and after parent-infant interactive contacts. Plasma samples to measure oxytocin measure were used in most of the studies by Feldman and other researchers (Tables 1 and 2). Salivary oxytocin levels were measured in several studies [20,21,25,27–29] and one study also examined urinary oxytocin levels [21]. Enzyme immunoassay (ELISA) method was utilized by researchers to determine the oxytocin levels using various commercial oxytocin kits, which were similar to one specifically developed and validated for oxytocin analysis by Carter, Pournajafi-Nazarloo [30]. Plasma and salivary oxytocin levels were found to be significantly inter-related [20,21], but were not correlated with oxytocin levels in urine samples [21].

3.3. The relationship of parent-infant contacts and oxytocin

Most studies in this review found a positive correlation

between parent-infant contact and oxytocin levels in infancy period. The positive parent-infant interaction and engagement encompassed behaviors in social gaze, social synchrony, social salience (being able to draw the attention of another), vocalizations, and proprioceptive stimulation between parent and infant (Table 1). Increased maternal oxytocin levels were significantly related to more affectionate contact behaviors in mothers following mother-infant contact, synchrony, and engagement [13,20,24,25]. Mothers with high oxytocin levels at baseline were shown as high sensitivity mothers in contact with their children, while, mothers with low oxytocin levels were those mothers who showed low sensitivity in the mother-infant interaction [22]. Meanwhile, increased paternal oxytocin levels were found to be related to more stimulatory contact behaviors in fathers following father-infant contact [13,20,21].

In observational-longitudinal studies (Table 2), individual stability of maternal and paternal oxytocin levels were found overtime in study participants [7,27]. Mother and father dyads showed similar and related levels of oxytocin across time, at 1 month and 6 months [12,27]. Infant oxytocin levels were also found to be correlated with maternal oxytocin, showing a cross-generation transfer of oxytocin through caregiving in early life [27].

Two studies showed that maternal-infant and paternal-infant oxytocin levels increased in during SSC (Table 3). SSC, also known as Kangaroo Care, is when the infant is clothed only in a diaper and placed in between the mother or father's breasts, chest-to-chest. This was also shown to reduce stress and anxiety in parents after interaction, indicating an inverse relationship in oxytocin's role as a modulator of depressive disorders [28,29].

Table 1
Studies pertaining to oxytocin with parents and infants using observational study design without follow-ups.

Authors Year/Country	Study design/Purpose	Subjects	Parent-Infant contact method/ Theoretical construct	Outcome Measures/Time Points	Primary Results
Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010 Israel	Observational design Compared salivary and plasma M-OT and P-OT at baseline and after parent-infant interaction at 4–6 months after term birth.	Parents: $n = 112$ (not couples; 71 mothers, 41 fathers) Infants: $n = 112$ 4–6 months age	15-min play-and- touch interaction Theoretical construct of study not described Affectionate contact is central determinant of maternal care, integrates discrete maternal behaviors in gaze, affect, and vocal modalities into maternal style consistent across time and context.	Plasma & salivary M-OT & P-OT before and after play interaction; Parental touch behaviors categorized (micro-coded) into affectionate touch, proprioceptive touch, and stimulatory touch. Time Points: Before and after interaction	Plasma & salivary M-OT & P-OT similar at baseline and inter-related $P < 0.001$. M-OT \uparrow in affectionate contact mothers following mother- infant contact. P-OT \uparrow in stimulatory contact fathers following parent-infant contact.
Atzil, Hendler, & Feldman, 2011 Israel	Observational design Examined neurobiological basis of human parenting. Synchronous & intrusive maternal behaviors correlated to specific brain responses. Infant cues activate networks related to reward circuitry related to M-OT.	Mothers: $n = 23$ (screened for depression and anxiety) Infants: $n = 23$ 4–6 month age	1st session: home visit, mother-infant interaction and infant solitary videotaped; 2nd session: fMRI (observing movies: own infant solitary play & mother-own-infant interactions, compared with unfamiliar infants & unfamiliar mother-infant interactions). Theoretical construct of study not described.	Plasma M-OT; Behavioral coding: Gaze, affect, vocalization, touch; fMRI responses of synchronous vs intrusive mothers (amygdala and left nucleus accumbens - NAcc). Time Points: Two sessions – home visit and fMRI	\uparrow M-OT correlated mother-infant synchrony, $P < 0.05$; 3 functional neural networks activated in response to infant stimuli. Limbic networks via amygdala & NAcc attentional network, and emotional networks. Intrusive mothers \uparrow right amygdala response, $P < 0.01$; In synchronous mothers, OT correlated with left NAcc and right amygdala activations, $P < 0.01$.
Feldman, Gordon, & Zagoory-Sharon, 2011 Israel	Observational design Compared plasma, salivary, and urinary OT in parents before, during and after free-play interaction; relationship between OT and synchronous parent-infant interactions.	Parents: $n = 112$ (not couples; 71 mothers, 41 fathers) Infants: $n = 112$ 4–6 months age	15-min parents infant free-play interaction Theoretical Construct: Parent-infant synchrony, describes temporal coordination between parents' & infant's affective behavior, is component of sensitive parenting that contributes to infant's development	Plasma, salivary & urinary M-OT & P-OT before and after play; Coding of parent-infant interaction (micro-coded). Parents' stress and affiliation (YIPTA, Adult Attachment Style Scale, PBI, & PSI) Time points: Before and after play	Correlation between plasma OT and salivary OT more significant than compared to urinary OT, $P < 0.001$. Plasma OT and salivary OT related to positive parent-infant engagement, positive affect synchrony & communication.
Atzil, Hendler, Zagoory-Sharon, Winetraub, & Feldman, 2012 Israel	Exploratory design Examined whether mothers and fathers would synchronize their brain responses to own-infant cues. The degree of coordination in parents' brain reactivity was assessed.	Parents: $n = 30$ (15 couples) Infants: $n = 15$ 4–6 months age	1st session: Home visit and video typed infant play; 2nd session: Parents' brain fMRI (observing mother-infant, father-infant interactions, infant solitary play, compared with standard infant videos); 3rd session: Plasma OT and AVP samples	Plasma M-OT, P-OT, & AVP; Brain fMRI Paradigm between mothers and fathers Time Points: Two sessions – home visit and fMRI	Mothers \uparrow amygdala activation correlated with M-OT, $P < 0.05$; Fathers \uparrow activations in social-cognitive circuits, correlated with AVP, $P < 0.01$. Human attachment may develop within the matrix of biological attunement of brain-to-brain synchrony between attachment partners.
Feldman, Zagoory-Sharon, Weisman, Schneiderman, Gordon, Maoz, Shalev, & Ebstein, 2012 Israel	Observational design Investigated cross-generational transfer of OT through selected OXTR & CD38 SNPs; relationship to parental behaviors, parent touch & synchrony; examined the whether the selected risk alleles are associated with poor social behaviors and a decreased parental touch and synchrony.	Total: $n = 352$ Parents: $n = 272$ (151 mothers, 121 fathers) Non-parents: $n = 80$ Infants: $n = 192$ 4–6 month age	Interactive play between each parent and their infant was conducted. Duration of play was not described. Theoretical construct of study not described.	Plasma OT; Genotyping of OXTR & CD38; Coded behaviors of parent and infant interaction. Researchers focused on parent and infant gaze, affect, vocalization, and touch. Time Points: During the interaction	M-OT & P-OT stable overtime, \uparrow touch, \uparrow gaze synchrony for parents with \uparrow OT levels, $P < 0.003$. Overall interaction linked between plasma OT and CD38 SNP. Parents with \downarrow risk CD38 allele had longer gaze synchrony, \uparrow interaction infants. Parents homozygous for OXTR TT risk allele had \downarrow touch with infants with GG homozygous parents, $P < 0.003$.
Abraham, Hendler, Shapira-Lichter, Kanat-Maymon,	Observational design Examined brain basis of fatherhood and parenting behavior; specifically	Parents: $n = 89$ couples (41 heterosexual couples; 48 homosexual couples)	Video of parent-infant interaction 2-min parent-infant solitary activity interaction	Salivary OT at baseline and after parent-infant interaction; fMRI; Parent-infant interaction coded for	Primary caregiver mothers and fathers have \uparrow synchrony $P < 0.001$ compared with secondary caregiver

Zagoory-Sharon, & Feldman, 2014 Israel/German	parental brain responses to infant stimuli.	1st born infant: n not reported 11 month age	Theoretical construct of study not described.	CIB Time Points: Before and after interaction	fathers. No differences in OT or fMRI with biological or adoptive fathers. No inherent differences parental network function based on sexual orientation & parental brain. Mothers provided ↑ affectionate contact, fathers provided ↑ stimulatory contact. OT and AVP levels in mothers and fathers interrelated, $P < 0.05$. Parents with ↑ OT had ↑ affectionate and ↑ social gaze. Parents with ↑ AVP levels had ↑ stimulatory contact. Highlights involvement of OT in adaptive human parental bonding. Individual stability of OT for participants. ↑ baseline M-OT ↑ sensitivity mothers ↓ M-OT in ↓ sensitivity mothers implies ↑ stress responses to demands of caring for infant; or past deficiencies in own parenting relationships. OT may ↓ stress and anxiety in low sensitivity mothers. OT levels positively correlated with nonintrusive scores and non depressive scores $P < 0.01$. Mothers with ↑ OT levels exhibited less intrusive behavior. Significant interaction effect of mental health and OT; ↑ OT linked to less depressive behavior only in mothers with anxiety or mood disorders.
Apter-Levi, Zagoory-Sharon, & Feldman, 2014 Israel	Observational design To compare the hormonal effects of OT and AVP on maternal and paternal parenting behaviors and to the processes of parent-infant interaction as they synchronize with hormonal activity.	Parents: $n = 119$ (not couples; 71 mothers, 48 fathers) Infants: $n = 119$ 4–6 month age	Parent-infant 10-min contact and interaction. Theoretical Construct: Bio-behavioral synchrony The coordination of parental behavior with the infant's social signals describes a distinct and stable constellation uniquely expressed in mothers and fathers.	Plasma M-OT, P-OT, & AVP at baseline; Parent-child interaction micro-coded (Gaze, Affect, Vocalization, & Touch) and coded systematically for Affectionate and Stimulatory Contact, Joint Attention, and Gaze Synchrony. Time Points: Baseline and during interaction	OT levels positively correlated with nonintrusive scores and non depressive scores $P < 0.01$. Mothers with ↑ OT levels exhibited less intrusive behavior. Significant interaction effect of mental health and OT; ↑ OT linked to less depressive behavior only in mothers with anxiety or mood disorders.
Elmadhi, Wan, Numan, Elliott, Downey, & Abel, 2014 United Kingdom	Observational design Examined how opposite extremes of the distribution in maternal sensitivity to infant cues are related to maternal plasma OT levels in a community sample of healthy new mothers.	Mothers: $n = 30$ (15 ↑ sensitivity mothers, 15 ↓ sensitivity mothers; selected from 105 expectant mothers; 80 were blind-rated for maternal sensitivity at 4–6 months) Infants: $n = 30$ 7–9 months age	Mother-infant 10-min play interaction Theoretical construct of study not described.	Plasma M-OT pre and post mother-infant play between mothers with ↑ & ↓ extremes maternal sensitivity (via MACI). Time Points: Before and after interaction	OT levels positively correlated with nonintrusive scores and non depressive scores $P < 0.01$. Mothers with ↑ OT levels exhibited less intrusive behavior. Significant interaction effect of mental health and OT; ↑ OT linked to less depressive behavior only in mothers with anxiety or mood disorders.
Samuel, Hayton, Gold, Feeley, Carter, & Zerkowitz, 2015 Canada	Observational design Examined whether maternal mental health moderated the relationship between OT levels and (tense, remote, self-conscious, withdrawn, lethargic) interactive behaviors	Mothers: $n = 110$ (20 Clinical, 90 Community) Infants: $n = 110$ 2 months age (Clinical: 6 male, 14 female; Community: 53 male, 37 female)	5 min of mother-infant interaction videotaped to assess interactive behaviors Theoretical construct of study not described.	Plasma M-OT in both clinical and community sample; 4 maternal scales: Global Rating Scales, Maternal Sensitivity, Maternal Intrusiveness, and Maternal Non-remote Scale, Mother-infant interactive behaviors coded with Global Rating Scale. Time Points: Two sessions - clinical and community	OT levels positively correlated with nonintrusive scores and non depressive scores $P < 0.01$. Mothers with ↑ OT levels exhibited less intrusive behavior. Significant interaction effect of mental health and OT; ↑ OT linked to less depressive behavior only in mothers with anxiety or mood disorders.
Ulmer-Yaniv, Avitsur, Kanat-Maymon, Schneiderman, Zagoory-Sharon, & Feldman, 2016 Israel	Observational design Assessed the neurobiological synergetic role of OT, beta-endorphin, and interleukin-6 in bond formation between parents and infants, lovers, and singles.	Total: $n = 200$ Singles: $n = 35$ (17 male, 18 female) Couples: $n = 25$ Parents: $n = 115$ (71 mothers, 44 fathers) Firstborn infants: $n = 115$ 4–6 month age	10 min of Parent-Infant play; 10 min of positive interaction between lovers. Theoretical construct of study not described.	Plasma OT; beta-endorphin, IL-6; Videotaped interactions were micro-coded based on touch, gaze, vocalization and affect. Time Points: Before and after interaction	Significant difference in OT levels between the 3 groups, $P < 0.01$; New lovers having ↑ OT levels. β-End & IL-6 levels ↑ among parents. Positive correlation between all 3 biomarkers among parents than new lovers and singles.

Note: OT= Oxytocin, SC = salivary cortisol, M-OT = maternal oxytocin, P-OT = paternal oxytocin, AVP = vasopressin, MACI = Manchester Assessment of Caregiver-Infant Interaction; YIPTA= Yale Inventory of Parent and Action; PBI= The Parental Bonding Instrument; PSI= The Parental Stress Index.

Table 2
Studies pertaining to oxytocin with parents and infants using prospective observational-longitudinal study design.

Authors Year/ Country	Study design/Purpose	Subjects	Parent-Infant contact method/ Theoretical construct	Outcome Measures/ Time Points	Primary Results
Feldman, Weller, Zagoory-Sharon, & Levine, 2007 Israel	Prospective longitudinal design Compared OT levels in mothers during pregnancy and postpartum months, and examine whether OT levels are indicative of what maternal behaviors are expressed during postpartum.	Pregnant women: $n = 62$	15 min of mother-infant interaction. Theoretical construct of study not described.	Plasma M-OT; Maternal screening of anxiety and depression done through questionnaires before giving birth; Coded behaviors included: Maternal gaze, affect, touch, and vocalization. Follow-up: 1st trimester, 3rd trimester, & infant at 1 month of age	Individual OT levels showed stability over time. Certain maternal behaviors were found to be related to OT, the strongest correlation being a mother constantly checking on their infant, $P < 0.01$.
Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010 Israel	Prospective longitudinal design Compared plasma M-OT & P-OT across first 6 months after birth and interrelatedness OT with cohabitating partners; examined M-OT & P-OT related to maternal/paternal behavioral characteristics.	Parents: $n = 128$ (66 mothers, 62 fathers) First born infants: $n = 80$ (37 males, 43 females)	Video of 10-min parents infant free-play interaction Theoretical construct of study not described.	Plasma M-OT and P-OT; Composite scores of parents-infant behaviors for gaze, affect, proximity position, and touch created categories. Follow-up: 1st postpartum weeks & 6 months	Provided normative data for OT in mothers & fathers. Peripheral OT in cohabitating parents are interrelated. Mothers & fathers show similar levels of OT across time, first 6 months $P < 0.01$. Mothers ↑ affectionate parenting touch behaviors $P < 0.05$. Fathers had more stimulatory parenting touch behaviors $P < 0.05$.
Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010 Israel	Prospective longitudinal design Examined the relationship between M-OT and P-OT with patterns of touch and contact in the family unit during triadic interactions.	Parents: $n = 74$ (37 couples) First-born infants: $n = 37$ (22 female, 15 male)	Video of 10-min parent-infant free play triadic interaction Theoretical Construct: Family system's approach; focused on M-OT & P-OT in shaping parents' engagement in synchronous & coherent triadic interactions.	Plasma M-OT & P-OT; salivary cortisol; Composite score of behavioral triadic synchrony. Follow-up: 2 months & 6 months age	Plasma M-OT, P-OT and salivary cortisol levels are stable over time $P < 0.001$. Parents' triadic synchrony scores were correlated $P < 0.001$. Mothers with ↑ OT & ↓ SC predict triadic synchrony. For fathers, only OT independently predicted triadic synchrony.
Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013 Israel	Prospective longitudinal design Examined the possible cross-generational transfer of human attachment through hormonal systems, genetics, and observed interactions.	Parents: $n = 160$ (80 couples) Firstborn infants $n = 80$ Baseline: 1 month age; 6 months: (66 mothers, 62 fathers) 3 years: (50 mothers, 48 fathers, 50 friends of infant)	1 month: videotaped parent and infant freely interacting. 6 months: videotaped parent and infant freely interacting. 3 years: each parent-infant interaction for 7-min. Then, a 10-min interaction between child and best friend was videotaped during structured play. Theoretical construct of study not described.	Plasma & salivary M-OT & P-OT; Genotyping; At 1 month visit categories of parenting behavior. Early Parental Care composite score given. A cumulative OT risk' score was computed. At 3 yrs Coding Interactive Behavior composite score for social interactions. Follow-up: 1 month, 6 month, & 3 years of age	Demonstrated individual stability in parental peripheral OT $P < 0.001$ and behavior with genetic variability over several years. Child OT correlated with M-OT $P < 0.01$. Early maternal care was associated with mother-child reciprocity at 3 years $P < 0.05$. Bio-behavioral experiences within parent-infant bond shapes child's affiliative biology and social behavior across multiple attachments. Children's social reciprocity with best friend was associated with mother-child reciprocity $P < 0.01$.
Gordon, Pratt, Bergunde, Zagoory-Sharon, & Feldman, 2017 Israel/USA	Prospective longitudinal design Examined the interaction of OT and testosterone implicated in parental care, and its effect on synchrony and gender-specific behaviors	Parents: $n = 160$ (80 couples) Firstborn Infants: $n = 80$ (37 female, 43 male)	5 min of play between infant and both parents. Theoretical Construct: Bio-behavioral Synchrony Model such that ↑ parental OT stimulates human specific parental repertoire of synchronous parent-infant interactions.	Plasma OT & testosterone; Parental behaviors coded for vocalizations, affect, touch, synchrony, and gaze. Follow-up: 1 month & 6 month of age	Parental OT levels were stable overtime. M-OT coupled with a ↑ testosterone was associated with ↑ affectionate touch, $P < 0.01$. An ↑ testosterone in fathers was negatively correlated with lower OT and affectionate touch, $P < 0.05$.

Note: OT = Oxytocin, SC = salivary cortisol, M-OT = maternal oxytocin, P-OT = paternal oxytocin.

3.4. Other outcome measures of parent-infant interaction and oxytocin

3.4.1. Behavioral coding and maternal sensitivity

Higher maternal oxytocin levels were found to be related to more positive interactive behaviors [31]. Elamdih and colleagues [22] found that oxytocin levels were high in low sensitivity mothers at baseline and post-interaction than high sensitivity mothers and researchers suggested that higher baseline oxytocin levels in

healthy low sensitivity mothers may indicate greater stress responses to the demands of caring for their infants.

3.4.2. Parent anxiety

Levels of anxiety in mothers and fathers were measured before, during, and after SSC between mother-infant and father-infant dyads using an 8-item visual analogue scale [28,29]. Parents who participated in SSC with their infant activated oxytocin in both mothers and fathers and showed a negative correlation between

Table 3
Studies pertaining to oxytocin with parents and infants using cross-over study design.

Authors/Year/Country	Study design/Purpose	Subjects/Time points	Parent-Infant contact method/Theoretical construct	Outcome Measures/Time Points	Major Results
Cong, Ludington-Hoe, Hussain, Cusson, Walsh, Vazquez, Briere, & Vittner, 2015	Randomized cross-over design Examined parental salivary OT and SC levels before, during, and after parental skin-to-skin contact with premature infants.	Parents: n = 45 (26 mothers, 19 fathers) Premature infants: n = 28 3–14 days old Time points: Before, during and after SSC	30 min of maternal-infant SSC (M-SSC) & 30 min paternal infant SSC (P-SSC) Theoretical construct of study not described. 60 min of maternal-infant SSC (M-SSC) & 60 min paternal infant SSC	Salivary M-OT & P-OT, SC, Parent stress and anxiety were measured before, during and after 30 min of SSC Time Points: Before, during & after SSC	Salivary M-OT & P-OT ↑ during SSC (P < 0.05). Mother and father dyads showed correlated or synchronized stress and anxiety responses (P < 0.05), before, during and after SSC. M-SSC and P-SSC activated M-OT & P-OT and reduced stress and anxiety responses P-OT remained ↑ post SSC while M-OT dropped post SSC Salivary OT for infant, mothers, fathers ↑ during SSC (P < 0.001). Mother/father dyads had correlated stress and anxiety responses (P < 0.05).
USA Vittner, McGrath, Robinson, Lawhohn, Cusson, Eisenfeld, Walsh, Young, & Cong, 2018	Randomized cross-over design Examined changes in infant & parent salivary OT and SC levels before, during, and after skin-to-skin contact with preterm infants.	Parents: n = 56 (28 couples) Premature infants: n = 28 3–10 days old Time points: Before, during and after SSC	Theoretical construct: Roy Adaptation Model	Salivary infant OT, M-OT, P-OT, and SC, Parent stress and anxiety were measured before, during and after 60 min of SSC. Time Points: 5 min parent-infant interaction (dyadic mutuality coding) Before, during & after SSC	SC ↓ infants during SSC with mother or father. ↑ OT had ↑ synchronous and responsive interactions Mother-infants (P < 0.01)

Note: SSC = skin-to-skin contact, OT = Oxytocin, SC = salivary cortisol, M-OT = maternal oxytocin, P-OT = paternal oxytocin.

oxytocin and anxiety levels. Moreover, mother-father dyads showed correlated or synchronized anxiety responses, before, during and after SSC [28,29].

3.4.3. Cortisol

Cortisol, released from the HPA-axis in response to stress was used as an indicator of stress in the studies. Similar to oxytocin, cortisol was found to be stable among mothers and fathers. After 6 months postpartum, mothers had higher cortisol levels than fathers [26]. Salivary cortisol was higher before and after skin-to-skin contact, but lower during the parent-infant interaction, showing a negative correlation with oxytocin levels [28,29].

3.4.4. Arginine vasopressin (AVP)

AVP is another neuropeptide that also oversees social-emotional functioning of humans. Under early high stress AVP has been found to promote threat-detection capabilities while oxytocin motivates non-selective proximity seeking to others. Under low early life stress AVP promotes preservation of energy and oxytocin increases detection of interpersonal flaws [32]. In one study, AVP levels were related to stimulatory contact and social salience in both mothers and fathers and oxytocin and AVP levels were correlated [13]. Brain activity in social-cognitive areas in the brain were associated with AVP in fathers [23].

3.4.5. Interleukin 6 (IL-6) and beta-endorphin (β -end)

Interestingly, IL-6, a biomarker for inflammatory and stress response was found to be higher in co-parenting couples and lower among single parents [33]. β -End, a biomarker of the reinforcement and award system was also highest in couples who co-parent than in single parents [33]. A positive correlation among OT, IL-6, and β -End was found in co-parenting couples [33].

3.4.6. Testosterone

Testosterone levels were predictably higher in fathers than in mothers. Interaction between testosterone and oxytocin could predict parent synchrony and affectionate touch. Paternal synchrony and affectionate touch were predicted by testosterone levels. Maternal synchrony and affectionate touch were positively correlated with higher levels of oxytocin and testosterone [34].

3.4.7. Genotyping of OXTR CD38 single nucleotide polymorphisms (SNPs)

OXTR are oxytocin receptors in the brain. Female rats exposed to greater maternal care in infancy exhibited more widespread expression of OXTR. CD38 is a multifunctional molecule that combines enzymatic and receptor properties. Lack of CD38 resulted in marked deficits in social behavior and reduced plasma oxytocin [35]. Mothers who were homozygous for the TT, CC, and GG allele on OXTR risk alleles showed lower parental oxytocin levels and reduced early parental care. When compared to homozygotes, mothers that were carriers of G and A alleles were found to have higher parental oxytocin levels and demonstrated early parental care [35]. Parents with the high-risk CD38 allele and lower plasma oxytocin levels showed less sensitive parenting to their infants [27].

3.4.8. Functional magnetic resonance imaging (fMRI)

Mothers and fathers showed synchrony in motivational-emotional limbic structures in the brain while viewing a video of their own infant. Parents showed higher activations in the brain in response to their own infant than a video of a standard infant. Activations differed in the areas of the brain for mothers and fathers that mothers had increased amygdala activations, while fathers showed activations in social cognitive circuits [23].

4. Discussion

The studies in this review explored the role of oxytocin in the context of establishing social affiliative bonds during early parental care. The framework for an individuals' behavioral repertoire is shaped largely by the synchronous and salient connections modulated by oxytocin during infancy. Thus, the research that will be discussed here serves to underscore and affirm the importance of oxytocinergic mechanisms in a bio-behavioral sphere. These mechanisms can impact bond attachments and relationships formed during the course of ones' life.

Overall, the studies in this review found that maternal and paternal oxytocin levels are stable overtime. This stability ensures cross-generational transfer of oxytocin to children, and is established during the neonatal period [27]. As a child develops, the social and behavioral connections made between a child and their parents later influences the social reciprocity they exhibit towards friends and partners [27].

As a result of the stability of oxytocin, the type of behavior to be expressed by parents towards their infants can be predicted, including the nature in which they are expressed are different [26]. Studies found that maternal care tended to be highly affectionate in touch, vocalizations and gaze [20]. Paternal care differed in that behavior was more stimulatory and playful [13,20,22]. Neither maternal nor paternal care is superior to the other, however interactive behaviors whether by affectionate or stimulatory means promotes social synchrony between parent and child [13]. As found in many studies, baseline oxytocin levels did not differ between mothers or fathers, however, there was an association between oxytocin release and social synchrony [13]. Likewise, an increase in parental oxytocin during interaction with their infant reinforces the importance of oxytocin's role in social bonding and attachment. Through cognitive mechanisms, oxytocin release relies on behavioral cues, and positive reinforcement of these behaviors allows for stronger connections in the limbic structures of the brain that control emotions and behavior [13]. Social micro-behaviors such as gaze, vocalization, touch, and affect provide information of social synchrony and social reciprocity. A positive correlation in social synchrony & reciprocity results in increased oxytocin levels in parents. Thus, while methods of interaction may differ between mothers and fathers, these studies suggest it is the social synchrony and oxytocin that lead to stronger parent-infant bonds.

In addition to analyzing behavioral outcomes as a result of oxytocin, some studies have looked more closely at the genetic composition and mechanisms of oxytocin and other behavioral hormone release. Oxytocin receptors have been found to be susceptible to epigenetic programming (changes in gene expression rather than actual DNA), as they are malleable and can be altered depending on the nature of the infant's care [36]. Genotypic research such as the study done by Feldman et al. [35] have recognized several risk alleles on the OXTR gene that are associated with lower oxytocin receptors and thus lower oxytocin levels in parents and during early parental care. This suggests that parents who are heterozygous for the risk allele may have greater numbers of oxytocin receptors and thus have greater ability to engage in parent-infant synchrony. The degree in which genetics plays a role in oxytocin transmission is still debated, more research needs to be conducted to reach any firm conclusions regarding oxytocin's allelic variations.

In this review, not all results from the studies selected were distinguishable. The studies conducted by Elmadih et al. [22] and Samuel et al. [31] did not find a positive correlation between interactive behaviors and oxytocin levels. After parent-infant interaction, oxytocin levels of high-sensitivity mothers decreased

while, oxytocin levels in the lower sensitivity mother group did not show a significant change [22]. Although low-sensitivity mothers had higher baseline and post infant interaction oxytocin levels, those low-sensitivity mothers were also associated with a lower quality of parenting [22]. In the study by Samuel et al. [31], oxytocin levels of the community group exhibited a range rather than being high after infant interaction. These results may provoke questions regarding oxytocin's role in a stress response system. In instances where mothers regard interaction or affiliation with their infants as stressful, one would expect oxytocin may show a greater effect in mothers who are more affiliative [22].

While there are many studies demonstrating positive correlations between parent-infant interaction and oxytocin levels, it is clear that there are many confounding variables that may influence oxytocin release. These variables range from maternal sensitivity to risk alleles related to lower numbers of oxytocin receptors. Each of these variables has the potential to either enhance or negatively influence not only parent-child relationships but the child's neurodevelopment. There are many more studies that need to be conducted and many more variables that need to be assessed including the maternal exposome, or the sum total of environmental exposures and effects on the mother throughout her lifetime. It is possible that her own interactions with her parents have influenced the number of her oxytocin receptors or levels. This is simply one variable that needs to be investigated in order to gain greater insight into the mechanisms of oxytocin release.

Limitations for this review include that many of the studies reviewed did not work with diverse set of populations. Furthermore, many of the study designs did not allow for clear definition of causality and did not determine whether hormonal change resulted from behavioral changes or vice versa. Another limitation of oxytocin studies in human beings is the inability to measure central oxytocin levels, which is a truer indication of what is going in the brain than peripheral (plasma, salivary, or urinary) oxytocin measurements. Lastly, the majority of studies examined in this review are observational and thus may be lower quality of evidence.

5. Conclusion and implications for practice

Oxytocin is widely accepted as a major biomarker involved in attachment and bonding as well as mental and physical health. This review focused on early life stress and adaption via parent interaction. Future research may benefit from investigating the effects of maternal and paternal stress exposures in the context of parent-infant interactions as well as following family interactions and adaptability longitudinally. This review has the potential to inform the evolution of current parent-infant models of care to better support infant development. Ultimately, this study lends credence to the hypothesis that increased parent-child contact facilitates the establishment of attachment from the perspective of biological mechanisms thus providing a scientific basis for encouraging health institutions to provide increased opportunities for parent-child contact.

Conflicts of interest

There are no declared conflicts of interest or commercial interest for any of this study's authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijnss.2019.09.009>.

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