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A systematic review of human paternal oxytocin: Insights into the methodology and what we know so far

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ABSTRACT

Background. With the consolidation of fathers' engagement in caregiving, understanding the neuroendocrine and hormonal mechanisms underlying fatherhood becomes a relevant topic. Oxytocin (OT) has been linked with maternal bonding and caregiving, but less is known about the role of OT in human fatherhood and paternal caregiving.

Methods. A systematic review of methods and findings of previous OT research in human fathers was carried. The literature search on PubMed and Scopus yielded 133 records. Twenty-four studies were included and analyzed.

Results. Significant variability emerged in OT methodology, including laboratory tasks, assessment methods, and outcome measures. Fathers' OT levels appear to increase after childbirth. OT was significantly correlated with less hostility and with the quality of paternal physical stimulation in play interactions, but not with paternal sensitivity. Fathers' and children's OT levels were significantly correlated in a limited subset of studies, intriguingly suggesting that cross-generational OT regulation may occur during the early years of life.

Discussion. This study highlights relevant issues and limitations of peripheral OT assessment in human subjects, especially in fathers. Although the study of paternal neuroendocrinology appears promising, coping with these issues requires dedicated efforts and methodological suggestions are provided to guide future advances in this field.

Keywords: caregiving, fathers, fatherhood, hormones, oxytocin, parenting

1. INTRODUCTION

The family role of fathers has changed radically in contemporary Western societies during the last two decades (Parke, 2014; Pleck, 2010). These societal changes require a re-examination of traditional conceptualizations of what it means to be a father, the characteristics and behaviors defining the paternal role, and fathers' involvement in caregiving activities (Kaźmierczak & Karasiewicz, 2019). There is substantial variation in the relative involvement of fathers in caregiving (Murphy, Gallegos, Jacobvitz, & Hazen, 2017). Notwithstanding, increases in employment rates of women (Sigurdardottir & Garðarsdóttir, 2018), vast economic changes in the early years of the 21st century (Berik & Kongar, 2013) resulted in a shift in what defines the core elements of fatherhood in humans (Gettler, 2016). Evidence of this change is observable in the greater amount of time spent by fathers in direct (e.g., feeding and playing) and indirect (e.g., providing economic well-being and protection) caregiving (Brown et al., 2018; Lee & Lee, 2018). For example, U.S. fathers have nearly tripled the time they spend with their children, from 2.5 hours in 1965 to 7.3 hours per week in the early 2000s (Bianchi, 2011). Given the extensive change in men's roles in the family, and particularly in their role as fathers, researchers started to examine both the determinants of fathering behavior as well as the consequences of fathering on children's development. At the same time, even though societal changes have resulted in greater scientific interest in human fatherhood, more research is needed that tackles the wide cultural variation in what it means to be a father and what constitutes fathering behavior in Western and non-Western societies (Volling & Cabrera, 2019).

Extensive literature suggests that specific neuroendocrine modifications that have their roots in pregnancy underlie maternal caregiving in the early years of infancy and further facilitate immediate post-natal mother-infant bonding (Bridges, 2020). Oxytocin (OT) is a nine-amino-acid neuropeptide hormone that is produced in the paraventricular nucleus and supraoptic nucleus of the hypothalamus (Uvnäs-Moberg, Arn, & Magnusson, 2005). OT plays a key role in enhancing maternal caregiving, which is essential for early relational attunement and bonding between the mother and the newborn baby (Feldman & Bakermans-Kranenburg, 2017). Previous research indicated that increased OT was associated with the transition to motherhood (Kendrick, 2000) and with the quality of maternal behaviors in mother-child interaction (Galbally, Lewis, IJzendoorn, & Permezel, 2011; Markova & Siposova, 2019).

The study of the neuroendocrinology of paternal behavior has received far less attention in the scientific literature compared to maternal neuroendocrinology. This may partially reflect the fact that – contrary to mothers – fathers do not undergo the same prenatal biological and hormonal changes that are inherent with maternal pregnancy. Nonetheless, exactly for this reason, studying OT in fathers represents a unique opportunity to understand how biological and social processes interact and contribute to set the behavioral phenotype of fatherhood. Changes in fathers' OT regulation may reflect environmental exposures to their offspring and/or to the pregnant partner (Abraham et al., 2014) and, in turn, these hormonal adjustments may contribute to the emergence of caregiving-related attitudes and parenting behavioral patterns (Bartz et al., 2010). Noteworthy, previous studies reported that basal OT

levels are not significantly different between men and women (Amico et al., 1981; Grewen et al., 2005), suggesting that significant changes in fathers' endogenous OT concentrations may reflect different psychosocial adaptation to parenting.

In this scenario, the role played by OT in fathering behavior is intriguing. Animal model studies – especially those investigating fatherhood neuroendocrinology in biparental species – are showing that OT may be involved in promoting paternal caregiving. Findings showed that in mammals the oxytocinergic system plays a role in facilitating bonding and parenting in both females and males (Ross & Young, 2009). For instance, in mandarin vole mating pairs new fathers showed higher levels of OT expression compared to non-fathers; moreover, those with higher responsivity to the pups also displayed higher OT levels when contrasted to low-responsive fathers (Wang et al., 2015). Additionally, not only endogenous concentrations, but also experimental manipulation through OT administration appears to enhance behaviors such as guarding, feeding, and physical contact with the offspring in meerkats (Madden & Clutton-Brock, 2011) and marmosets (Finkerwirth, Martins, Deschner, & Burkart, 2016; Saito & Nakamura, 2011; Woller, Sosa, Chiang, Prudom, Keelty, Moore, & Ziegler, 2011). Notably, multiple and bi-directional effects may be observed among paternal caregiving, OT levels, and developmental outcomes in the offspring (Bales, Pfeifer, & Carter, 2004; Bales & Saltzman, 2016). More specifically, in biparental animals (e.g., meadow voles), fathers were found to have significant increases in OT receptor binding in brain regions that included the lateral amygdala compared to inexperienced counterparts (Parker et al., 2001). At the same time, in virgin male prairie voles not previously exposed to females, exposure to pups elicited a rise in plasma OT levels and immunoreactivity staining in the paraventricular nucleus of the hypothalamus (Kenkel, Suboc, & Carter, 2014). Altogether, these findings highlight the presence of a strong link between OT and paternal caregiving in several mammalian species.

The translation of these findings from bi-parental mammals to human fathers is not immediate as several methodological issues need to be considered when examining OT in human fathers. Central OT assessment in the brain is not possible in human studies and researchers must rely on peripheral assays from blood, saliva, and urine. On the one hand, central and peripheral circulations of OT are separated anatomically by the blood-brain barrier and so there has been considerable discussion as to whether there is consistency across measures of OT from central and peripheral tissues in human studies. On the other hand, the supposed role played by OT in affecting human parenting behavior often relies on the effects that this neuropeptide provokes in the central nervous system (Kenkel et al., 2014; Valstad, Alvares, Egknud, Matziorinis, Andreassen et al., 2017). Additionally, it is still relatively unknown whether peripheral OT concentrations – secreted endogenously or in response to experimental administration – are indicative of central secretion patterns. Further issues emerge on what the specific methods for sampling OT from peripheral tissues should be. Indeed, different estimation measures (e.g., radioimmunoassay, RIA; enzyme immunoassay, EIA) may lead to very different OT values, which vary up to two orders of magnitude (McCullough et al., 2013). Moreover, RIA and EIA – but especially EIA

unextracted samples – may be sensitive to molecules other than OT, which may further bias the estimations. Finally, several factors inherent to the study design (e.g., laboratory task) and to environmental conditions (e.g., temperature and time of day) may also add to the variability of findings and ultimately limit the interpretations and replicability of findings, as well as the comparisons across different studies. For example, recent meta-analytic evidence suggested that cross-correlations in OT concentrations from different tissues (e.g., plasma and central nervous system) were found under stressful conditions, but not during resting state or at baseline (Valstad et al., 2017).

In the light of both the intriguing paternal OT findings from animal model research and the number of methodological issues that apply to human OT research, a systematic review of OT research with human fathers is needed. The present systematic review had two main goals. First, we systematically reviewed the methodology of previous research conducted on human fathers and OT to highlight the reliability and robustness of this research to date and then underscore future directions for increasing the quality of methods used in OT studies and their potential for both theoretical and translational implications. Second, we reviewed the findings accumulated to date, by focusing on the role of OT in (a) fatherhood, (b) paternal caregiving behaviors, and (c) intergenerational attunement in oxytocin levels between fathers and infants. As the regulation of OT concentrations may be especially relevant for fatherhood during the first years of life (Bakermans-Kranenburg et al., 2019) and fatherhood behaviors largely change throughout children's development (Hosokawa & Katsura, 2018; Petts et al., 2020; Rothbaum & Weisz, 1994), the focus of the present review is limited to early development, including fathers of infants and preschool children.

2. METHODS

2.1. Literature search

This systematic review was performed under the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009) and the protocol is available on PROSPERO[1]. A comprehensive literature search was first performed in February 2020 – and then updated to include potential new publications in May 2020 – using PubMed and Scopus to identify primary research articles with a focus on OT and fathers. In particular, the following keywords were used: *"Oxytocin"[Mesh] AND "Fathers"[Mesh]*; *father* AND oxytocin*. Restrictions about the publication period were not set, and only documents published in peer-reviewed English journals were selected.

2.2. Study selection

Only quantitative studies that measured OT levels in human fathers were included. As anticipated, the eligible studies were restricted to those that included fathers of infants or children up to 6 years of age. This narrow developmental focus allowed us to reduce – at least partially – the variability in study designs, as paternal caregiving changes significantly as children grow through middle childhood

[1] https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020173360

and adolescence. No exclusion criteria were set for fathers' or infants' health conditions. All abstracts were reviewed first to determine inclusion or exclusion of the retrieved records. Then the full text of each paper was assessed according to the goals of the present review. The PRISMA flow diagram (Figure 1) maps out the number of records identified, included, and excluded during this process.

---------- Figure 1 about here ----------

2.3. Data extraction and analysis

For each of the 24 studies included in the final review, the following data were abstracted: paternal characteristics (sample size, age, number of kids, health status), child characteristics (age, health status), methodological variables (study design, main goals, setting, tissue, assay method, management of outliers and drop-outs, task description, category of outcomes) and findings. Data were analyzed using qualitative descriptions.

2.4. Quality Appraisal

The methodological quality was assessed according to the Quality Assessment Tool for Quantitative Studies. Sections A through F of that tool (A, selection bias; B, study design; C, confounders; D, blinding; E, data collection methods; F, withdrawal, and dropouts) were coded by two independent coders (SG and AS) and each section was scored as 3 (weak), 2 (moderate) or 1 (strong). Then, an overall 3-to-1 score was assigned to each paper according to the presence of 2 or more weak section scores (3 = weak), only 1 weak section score (2 = moderate), no weak section scores (1 = strong). A 95% agreement was obtained for each of the section scores. Any disagreement was resolved by conference under the supervision of a senior author.

3. RESULTS

3.1. Sample characteristics

Table 1 presents a schematic overview of the twenty-four included studies. Quality appraisal for each of the selected records is reported in Table 2. All selected studies included healthy fathers. Sample sizes for the various studies ranged from 16 (Gettler et al., 2019) to 121 (Feldman et al., 2012). Fathers' ages ranged from 28 to 37 years. Five studies enrolled only fathers with firstborn children (Abraham et al., 2014; Gordon et al., 2010a,b,c; Gordon et al., 2017), while others also included fathers with more than one child. Only one study engaged fathers-to-be during the third trimester of their partner's pregnancy (Cohen-Bendahan et al., 2015).

---------- Table 1 and 2 about here ----------

Twenty of the 24 studies included healthy children, whereas three studies enrolled preterm infants (Cong et al., 2015; Vittner et al. 2018; 2019), and one included children with autism spectrum disorders (Naber et al., 2013). Figure 2 displays the range in children's ages for each of the selected studies.

---------- Figure 2 about here ----------

3.2. Methodology review

3.2.1. Disentangling the interdependence of studies and labs

Fourteen papers came from the laboratory of Ruth Feldman at the Bar-Ilan University in Israel (Abraham et al., 2014; Apter-Levi et al., 2014; Feldman et al., 2010a,b; Feldman et al., 2011; Feldman et al., 2012; Gordon et al., 2010a,b,c; Gordon et al., 2017; Weisman et al., 2012, 2013, 2014, 2016). Three papers were published by Dorothy Vittner and colleagues at the University of Connecticut (Cong et al., 2015; Vittner et al., 2018, 2019). The Leiden University team led by Marian Bakermans-Kranenburg and Marinus van IJzendoorn published two papers (Naber et al., 2010, 2013). The remaining papers reported on independent samples from different research groups (Cohen-Bendahan et al., 2015; Gray et al., 2007; Gettler et al., 2019; Mascaro et al., 2014; Miura et al., 2015).

3.2.2. OT assessment

Tables 2 and 3 summarize the assessment methods used to measure OT concentrations. Paternal OT was assayed in saliva (n = 11), plasma (n = 10), or urine (n = 4). Three studies conducted cross-tissue assessment (Feldman et al., 2010a,b; Feldman et al., 2011) and showed a significant correlation between plasma and salivary OT concentrations (r = .46, n = 19 fathers, Feldman et al., 2010a; r = .41, n = 41 fathers, Feldman et al., 2010b, Feldman et al., 2011). No significant correlations emerged for urinary OT with either plasma or salivary concentrations (Feldman et al., 2011). Most of the studies (n= 18) collected hormone samples during the afternoon hours (13:00-20:00) to control for the circadian rhythm in OT secretion. EIA kits were used in 22 out of 24 records, usually citing previous validations from Carter et al (2007) as supporting the use of the EIA kits. RIA procedures were used according to Amico and colleagues (1981) validation study. EIA kits were used on extracted samples according to the manufacturer's guidelines in the majority of studies, although in some studies the information on extraction was not explicitly reported.

---------- Table 3 about here ----------

3.2.3. Interaction tasks

Half of the included studies (n=12) were conducted in a laboratory setting, whereas the remaining took place in the participant's home (n=8) or hospitals (n=4). Fourteen studies used a free or semi-structured play session ranging from 5 to 20 minutes (Abraham et al., 2014; Apter-Levi et al., 2014; Feldman et al., 2010a; Feldman et al., 2010b; Feldman et al., 2011; Feldman et al., 2012; Gordon et al., 2010a; Gordon et al., 2010b; Gordon et al., 2010c; Gordon et al., 2017; Gray et al., 2007; Miura et al., 2015; Naber et al., 2010; Naber et al., 2013). Four studies used the Face-to-Face Still-Face paradigm (Weisman et al., 2012; Weisman et al., 2013; Weisman et al., 2014; Weisman et al., 2016), whereas the three studies including preterm infants opted for sessions involving skin-to-skin contact (Cong et al., 2015; Vittner et al. 2018; 2019). Additionally, Cohen-Bendahan and colleagues (2015) used an immersive virtual reality environment to investigate associations between OT concentrations and parenting attitudes (i.e., interest in caregiving activities) in a sample of expectant fathers and single men. Two other studies did not include any interactive tasks. Mascaro et al. (2014) tested the reaction to

photographic infant stimuli using a sample of fathers and non-fathers and Gettler and colleagues (2019) only used self-report measures of fathers' parenting style.

3.3. OT in human fatherhood

3.3.1. OT in fathers and non-fathers

Three studies revealed that fathers of infants aged 4 months to 3 years had significantly higher endogenous OT levels compared to non-fathers (Abraham et al., 2014; Feldman et al., 2012; Mascaro et al., 2014). One longitudinal study (Cohen-Bendahan et al., 2015) reported that fathers-to-be (during their partner's pregnancy) did not differ in OT from non-fathers (whose partner was not pregnant). Another cross-sectional study reported similar findings for adoptive fathers, who had similar OT concentrations compared to biological fathers and higher OT levels compared to non-fathers (Abraham et al., 2014).

3.3.2. OT in fathers and mothers

No significant differences emerged in the endogenous OT concentrations between mothers and fathers of infants during the first 4 years after birth (Abraham et al., 2014; Apter-Levi et al., 2014; Feldman et al., 2010b; 2011; Gordon et al., 2010a; 2010b; Gordon et al., 2017; Miura et al., 2015; Vittner et al., 2018). Notwithstanding, seven records were from the same lab. Specifically, mothers' and fathers' OT levels were comparable and significantly correlated over time with an increase from post-partum to six months after childbirth (Gordon et al., 2010b; Gordon et al., 2017). No significant differences also emerged in another study on 19 fathers that assessed OT levels after a structured playful parent-infant interaction (Feldman et al., 2010a). Only Gettler and colleagues (2019) documented significantly higher OT levels in mothers compared to fathers, nonetheless, the sample size was limited to 16 fathers. Both Gettler et al. (2019) and Feldman et al. (2011) also investigated the presence of significant associations between the quality of the mother-father relationship and each parent's endogenous OT levels. These findings suggested that both fathers' and mothers' OT concentrations were significantly and positively correlated to romantic attachment security (Feldman et al., 2011). In another study looking at endogenous OT levels, fathers who reported high marital conflict also had lower salivary oxytocin levels, whereas fathers who reported low marital conflict had higher OT concentrations (Gettler et al., 2019).

3.4. Paternal caregiving and affect regulation

3.4.1. Endogenous OT and paternal caregiving

Eight studies focused on the association of paternal endogenous OT levels (e.g., not related to experimental administration of OT) with paternal caregiving behaviors or father-infant interactions. No significant correlations emerged between paternal OT concentrations and fathers' observed interactive behaviors (e.g., parent gaze, parent vocalization, parent touch, parent-infant synchrony, respect for autonomy) during 5-minute play interactions in 1- to 6-month-old infants (Gordon et al., 2017) and 18- to 48-month-old infants (Miura et al., 2015). In line with these results, Gettler et al. (2019) found that OT concentrations were not significantly linked with self-reported paternal direct caregiving of children up to five years of age in a remote region of the Republic of Congo. In contrast, several studies from the

lab of Ruth Feldman reported significant correlations of OT levels with frequency and quality of paternal affectionate touch (Apter-Levi et al., 2014; Feldman et al., 2012), as well as with father-infant gaze and affect synchrony (Feldman et al., 2012, Feldman et al., 2010a, Gordon et al., 2010a) during free play interactions with their 1- to 6-month-old infants. The OT levels were associated with specific caregiving behaviors in fathers. Higher OT concentrations before (Apter-Levi et al., 2014; Gordon et al., 2010b) and after (Feldman et al., 2010b) a playful interaction with 4- to 6-month-old infants were linked with more frequent use of facilitating physical stimulation (e.g., changing infants' position in space) and more functional presentations of objects to the infant.

3.4.2. OT administration and paternal caregiving

A subset of studies examined the effects of OT administration on paternal behavior during experimental studies using a within-subject design. On the one hand, OT and placebo conditions did not result in significant differences in ratings of paternal sensitivity and intrusiveness in a sample of 17 fathers (Naber et al., 2010) as well as vocal turn-taking in a slightly larger sample of 35 subjects (Weisman et al., 2013, Weisman et al., 2016). On the other hand, fathers of 2- to 3-year-old children provided more attuned physical stimulation as well as less hostility when administered OT versus the placebo (Naber et al., 2010, 2013). Fathers who received OT administration exhibited more infant-directed touch, positive vocalizations, and encouragement of infants' social initiative compared to fathers in the placebo condition (Weisman et al., 2012; Weisman et al., 2014). As only expectant fathers were included in the study by Cohen-Bendahan and collaborators (2015), the paternal caregiving behaviors were assessed only in a virtual reality environment, where they were interacting with a baby or a non-baby avatar. Nonetheless, the time spent directly engaged in interactions with the baby avatar was greater when the men were administered intranasal OT compared to the placebo condition.

3.4.3 OT and paternal caregiving in at-risk and atypical developmental conditions

Four studies examined paternal caregiving behaviors with samples of at-risk, preterm infants or infants with atypical development (i.e., autism spectrum disorder). Cong and colleagues (2015) investigated the role of OT in modulating paternal anxiety and stress during skin-to-skin contact in 19 dyads of fathers and their preterm infants. They reported that fathers who engaged in skin-to-skin contact with their newborn showed evidence of increased OT levels and reduced anxiety. A similar significant association between skin-to-skin contact and paternal OT levels was reported by Vittner and colleagues (2018; 2019). However, in this same study, paternal OT levels were negatively correlated with fathers' self-reported engagement in parenting at hospital discharge (Vittner et al., 2019). The only study that included fathers of children with a diagnosis of autism spectrum disorders tested within-subject effects of OT *vs.* placebo administration on paternal caregiving behavior. The results showed that – when compared to the placebo condition – fathers benefited from intranasal oxytocin administration by exhibiting less hostility and more appropriate physical stimulation during 15-minute free play interactions with their 4-year-old children (Naber et al., 2013).

3.4.4. Father-child OT attunement

Only two studies focused on the attunement between fathers' and children's baseline and/or post-interaction OT concentrations. One study explored father-infant OT attunement between 19 fathers and their 4- to 6-month-old infants and reported a significant positive correlation in OT levels both before and after a 15-minute playful interaction (Feldman et al., 2010a). Moreover, dyads with higher ratings of affect synchrony during interaction also showed greater dyadic OT co-regulation and attunement, suggesting that early parenting experiences may play a significant role in OT attunement in humans. Feldman and colleagues (2012) also showed that fathers who experienced higher quality parental care during their own childhood also had higher plasma OT concentrations and provided more frequent physical contact to their infants during face-to-face interaction.

4. DISCUSSION

4.1. Methodology

In the present review, OT concentrations were assessed from different peripheral samples (i.e., plasma, salivary, or urinary) and only three studies have conducted a cross-tissue assessment to determine if concentrations from one peripheral assessment (e.g., saliva) are correlated with concentrations in another (e.g., urine). Peripheral OT measurements showed high variability and there was only partial support for significant cross-sample correlations. Specifically, there was stronger concordance between salivary and plasma OT concentrations and limited support for cross-sample concordance in the case of urinary OT. The major limitation of OT studies in humans – and in fathers - is partly due to the inability to measure OT levels in brain tissue (MacLean et al., 2019; McCullough et al., 2013, Scatliffe, Casavant, Vittner, & Cong, 2019). Multiple techniques have been developed to measure endogenous oxytocin, however peripheral OT assessment (e.g., saliva, plasma) remains quite challenging and unfortunately, OT levels detected through different peripheral samples are poorly correlated with one another (MacLean et al, 2019). Future cross-sample studies in human fathers are needed to help bridge the gap and to allow more reliable data collection and interpretation (Beery, McEwen, MacIsaac, Francis, & Kobor, 2016). Based on the findings from the present review, when compared to urinary samples, saliva and blood appear to be more concordant and may be preferred when assessing OT in peripheral tissues in human studies.

Besides, previous research on human OT may be dependent on the availability and limited validation of existing methods of OT assessment tools. For example, both EIA and RIA methods may be sensitive to other immunoreactive products that remain to be identified and as a result, the obtained estimation of OT concentrations from peripheral samples may be biased (McCollough et al., 2013). The majority of studies included in this review relied on EIA. Nonetheless, a detailed description of extraction and assessment methodology was not always reported in the original papers. Thus, it may be speculated that the large differences in OT raw values among some of the included studies may be due more to different methodological procedures than to task-related or hypothesized mechanisms. Zhang and colleagues (2011) described a different approach to the measurement of OT in human peripheral

samples (i.e., mass spectrometry detection) which appears to be highly sensitive in detecting OT, yet it has not been used in previous studies with fathers. Moreover, the instrumentation needed to conduct these assessments may be available only in specialized laboratories, limiting access to this measurement approach to few research teams.

Consistent with this point, it should be highlighted that many of the studies included in the present review were from a limited number of research teams. For example, more than 50% of the papers were published by the same research team with multiple papers potentially reporting on the same fathers, using the same assayed tissue samples. Thus, findings are highly interdependent across multiple publications using the same data, which limits the possibility to conduct a proper meta-analytic study (Hedges, Tipton, & Johnson, 2010). This calls attention to the need for additional research from multiple research groups and/or on multiple samples of fathers to generate replicable findings and eventually increase generalizability.

The available data do not allow us to disentangle the reciprocal and joint contributions of OT concentrations and caregiving-related cultural values or practices on the observed paternal behavior patterns (Bakermans-Kranenburg et al., 2019). Most of the studies were carried out in western societies, and only the Gettler et al. (2019) study (i.e., Congo Republic) and the publication from Miura and colleagues (2015) (i.e., Japan) were conducted in non-western societies. Previous research is suggestive of a potential interaction between cultural-informed behaviors and neuroendocrine regulation (Sasaki, Kim & Xu, 2011). Because cultural values and norms often shape parenting and fathering behaviors (Domenech Rodriguez, Donovick et al., 2009; Marsiglio, Amato, Day & Lamb, 2000; Porter, Hart, Yang et al., 2010), we would recommend that future research explore the ways different cultural contexts may shape fathering behaviors and the role played by OT regulation. More cross-cultural research is clearly needed before we can deepen our knowledge about bio-cultural interactions that underpin fatherhood and paternal parenting in humans. This may be more relevant for research on fathering compared to mothering, as the lack of intrinsic hormonal changes that occur during maternal pregnancy are less prominent in men and may contribute to the greater variations reported for paternal caregiving phenotypes (Feldman & Masahla, 2010).

4.2. Main findings

The reviewed evidence suggests a role for OT regulation in fatherhood and paternal caregiving in infancy and early childhood. Fathers' OT concentrations significantly differed from those of non-fathers (Feldman et al 2012; Mascaro et al., 2014). Moreover, fathers exhibited similar OT levels when compared to mothers (Apter-Levi et al., 2014; Feldman et al., 2010a; 2010b; 2011; Gordon et al., 2010a; Miura et al., 2015), for whom OT is typically linked to birth, lactation and post-natal bonding (Crowley, 2011; Galbally et al., 2011). Also, fathers-to-be did not differ from non-expecting men in OT levels (Cohen-Bendahan et al., 2015). Taken together these findings suggest that the role of OT regulation in men might be more relevant after the infant's birth, rather than already during pregnancy as previously reported for women (Crowley, 2011; Galbally et al., 2011). In other words, whereas psychological

adaptation to parenthood may be observed in men (Lindstedt et al., 2020), the neuroendocrine adaptation occurs only after the transition to fatherhood (Bakermans-Kranenburg et al., 2019). As such, it is quite likely that OT levels are modulated after the birth of the child and that the active engagement in fathering further modulates the regulation of endogenous OT secretion in men. Notwithstanding, it should be highlighted that the correlational nature of the studies included in this review do not allow us to disentangle the reciprocal and causal influences between changes in OT concentrations and the observed or self-reported paternal caregiving measures.

Mixed findings emerged regarding the link between fathers' OT and paternal behaviors. Such conflicting results emerged regardless of infants' age and the type of observational task used, suggesting that wide individual variability and heterogeneity may be expected in the association of OT with paternal caregiving behaviors. Moreover, it should also be highlighted that when significant links between OT concentrations and fathers' behavior emerged, they were related to specific caregiving behaviors. Higher OT concentrations before (Apter-Levi et al., 2014; Gordon et al., 2010b) and after (Feldman et al., 2010b) parent-child interaction were linked with increased stimulatory physical activities and better object presentation to the child. This was also supported by studies using controlled intranasal OT administration, which resulted in increased attuned physical stimulation by fathers during father-child interaction (Naber et al., 2010; Weisman et al., 2012; 2014). It should be highlighted that previous research reported that high levels of OT concentrations in mothers may favor the emergence of other type of caregiving behaviors, such as affectionate or gentle touch and synchronous responses to infants' communicative bids (Scatliffe et al., 2019). Taken together, these findings are suggestive of a potential role played by OT in facilitating specific paternal behaviors that are different from those observed in mothers. Nonetheless, these conclusions require further validation in larger samples from different laboratories.

Notably, the association of OT with specific fathering behaviors was also found in the few studies conducted with fathers of at-risk infants and children with atypical developmental conditions. For example, fathers of children with a diagnosis of autism spectrum disorder showed less hostility and more appropriate physical stimulation after intranasal OT administration. Also, OT reactivity was reported for fathers of preterm infants during skin-to-skin contact (Cong et al., 2015). These findings suggest that OT may serve as a neuroendocrine protective factor that facilitates paternal bonding even with more vulnerable and at-risk children. The one counterintuitive effect indicated that higher OT concentrations were associated with less engagement for fathers of preterm infants (Vittner et al., 2018; 2019) which may be due, in part, to the high levels of stress and anxiety experienced by these fathers (Caporali et al., 2020) and the challenges they face bonding with their preterm infants during hospitalization in the neonatal intensive care unit (Provenzi & Santoro, 2015).

Finally, only two papers from Feldman and colleagues (2010b; 2012) investigated the intergenerational transmission and attunement of OT regulation between fathers and children. The quality of parenting experienced by fathers during their own childhood was associated with paternal OT

levels measured after a face-to-face interaction task with their own 4-to-6-month-old infants (Feldman et al., 2012) and higher OT attunement between fathers and infants was reported in dyads also rated as highly synchronous on the behavioral level (Feldman et al., 2010b). While these findings are intriguing, they should be considered as opening new hypotheses rather than confirming the presence of intergenerational or dyadic co-regulation of OT. More research is clearly needed before we can understand whether and how OT is co-regulated within the father-infant dyad (Bakermans-Kranenburg et al., 2019; Welch & Ludwig, 2017).

4.3. Limitations

There is substantial variability among the included studies in terms of sample size (i.e., 16 to 121), the observational tasks used, the age of the infants and children studied, and the peripheral markers used to assess OT. To at least partly reduce such variability, we focused only on fathers of infants and preschool children to reduce the heterogeneity in tasks and fathering behaviors. Of course, this may prevent the generalizability of our findings to fathers of older children and adolescents. Research with larger samples is needed to assure adequate power for experimental studies on fathers' OT and to allow longitudinal studies that may provide evidence of OT regulation in fathers from infants' birth to later childhood.

Specific limitations apply also to OT administration tasks. Previous research suggested that changes in peripheral OT secretion can be observed between 10 and 80 minutes after experimental administration (MacDonald & MacDonald, 2010) and that only small amounts of peripherally administered OT may cross the blood-brain barrier after single doses (Mens et al., 1983; Quintana et al., 2018). Therefore, it is necessary that OT administration studies also report pre- and post-administration descriptive statistics for the endogenous OT levels. Unfortunately, among the OT administration studies included in our review, only four out of seven provide complete information on pre- and post-administration values (Weisman et al., 2012, 2013, 2014, 2016) and these publications were from the same lab and sample. As the lack of appropriate quantification of the change in OT concentrations limits the interpretation of findings from OT administration studies, future research using OT administration should consistently report pre- and post-task values.

Finally, some of the results reported here are based on a limited number of studies (e.g., the inter-generational regulation of OT in father-child dyads). Future research is clearly needed not only to augment and replicate the findings reported here but also to generate additional research questions to be pursued. These studies should be directed at unveiling the association of OT concentrations with fathering behaviors as well as the role of this hormone in the establishment of early dyadic co-regulation processes that may favor long-lasting child development and the inter-generational transmission of emotional well-being (Welch & Ludwig, 2017).

4.4. Future directions

Because research on human fathers' OT holds promises for developmental psychobiology, we offer recommendations for future directions (see Figure 3). First, we need to understand better the

biological interactions between different hormones that may shape and contribute to emerging paternal caregiving behaviors. Interactions among hormones and neurotransmitters (e.g., cortisol, vasopressin, serotonin, and oxytocin) have been previously documented in parents (Bakermans-Kranenburg et al., 2008; Okabe, Kitano, Nagasawa, Mogi, & Kikusui, 2013; Rajhans, Goin-Kochel, Strathearn, & Kim, 2019), but specific investigations are needed as it pertains to fathers. Additionally, as recent research suggested that the regulation of endogenous OT may also be affected by DNA methylation changes occurring at the level of the oxytocin receptor gene (*OXTR*; Cataldo, Azhari, Lepri, & Esposito, 2018), the role of epigenetic mechanisms related to the OT system in fathers may be intriguing. A recent study reported that the quality of maternal care experienced during childhood and self-reported retrospectively by adults was associated with DNA methylation of the *OXTR* gene in men and women (Unternaehrer et al., 2015), but less is known about the role of paternal caregiving. Second, the studies reviewed here mainly focused on the first two years of life and most of them were cross-sectional. Although this is consistent with the notion that the first thousand days represent a sensitive period for human parenting effects on infants' developmental trajectories, longitudinal designs are needed to assess changes in paternal OT throughout infancy, childhood, and even adolescence. Third, it cannot be ruled out that socio-cultural values and practices may further shape fathering and, in turn, OT levels (Seward & Stanely-Stevens, 2014). Although it may be obvious that cultural values differ among societies, we also believe it would be interesting to explore directly how different fathering phenotypes may be associated with diverse patterns of OT regulation. Finally, research efforts should be dedicated to understanding how early parenting interventions may be effective in promoting more positive paternal caregiving and how OT may be involved in contributing to the protective effects of fathering. This would be especially interesting in conditions where the immediate postnatal closeness and bonding between parents and infants is partially challenged or postponed, for example in the case of preterm birth (Provenzi, Fumagalli, Bernasconi et al., 2016). As early interventions for parents of preterm infants appear to be differently beneficial for mothers and fathers (Matricardi et al., 2013), the potential role of OT regulation in supporting adaptation to parenting in such at-risk conditions may deserve specific attention.

5. CONCLUSIONS

Research on paternal OT has rapidly accumulated during the last two decades. While it is intriguing and may hold potentials for both scientific advances and clinical applications, due to the many methodological challenges highlighted in this review, there is still much to be learned. Further interdisciplinary collaborations among researchers with psychological, behavioral, and biological backgrounds will promote a more profound understanding of the reciprocal influences among human fathering, hormonal regulation, and their effects on child development. This continuing venture can provide the missing pieces needed to conclude with more certainty how OT is linked to human fatherhood, which may be used in clinical applications, and ultimately, to provide the evidence base needed to inform early parenting interventions in at-risk developmental conditions.

Data availability statement: Data are available upon reasonable request to the corresponding author.

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FIGURE LEGEND

Figure 1. Study selection flow chart.

Figure 2. Overview of the age range of infants and children whose fathers were enrolled in previous research on paternal oxytocin. Note: Black bars are obtained from min and max age values reported in original papers. White bars are obtained by adding and subtracting two standard deviations from the mean age obtained from studies that did not report min and max age for infants/children.

Figure 3. Schematic overview of potential future directions in human paternal oxytocin research.

Table 1. Characteristics of included studies.

Study	Study location	Fathers N	Comparison group	Child status	OT baseline	OT reactivity	OT administration	Setting	Interaction task	Main finding
Abraham et al. (2014)	Israel	69	mothers (n=20); homosexual fathers (n= 48)	healthy	X	X	NA	home	free play	↑ OT ↔ ↑ paternal STS response to infant visual stimuli
Apter-Levi et al. (2014)	Israel	119	mothers (n= 71)	healthy	X	NA	NA	laboratory	free play	↑ affectionate contact and gaze synchrony → ↑ parental OT
Cohen-Bendahan et al. (2015)	The Netherlands	46	non-fathers (n=20)	healthy	NA	NA	X	laboratory	virtual reality	ns association between OT and paternal interest in caregiving and parenting behavior
Cong et al. (2015)	USA	19		preterm	X	X	NA	hospital	skin-to-skin contact	skin-to-skin contact → ↑ paternal OT
Feldman et al. (2010a)	Israel	19	mothers (n=36) of other infants	healthy	X	X	NA	laboratory	structured play	↑ dyadic synchrony ↔ ↑ correlation between parents and infants OT
Feldman et al. (2010b)	Israel	41	mothers (n=71)	healthy	X	X	NA	laboratory	structured play	↑ paternal physical stimulations ↔ ↑ paternal OT
Feldman et al. (2011)	Israel	41	mothers (n=71)	healthy	X	X	NA	laboratory	free play	↑ dyadic synchrony ↔ ↑ paternal OT
Feldman et al. (2012)	Israel	121	non-parents (n=80; 40 males)	healthy	X	NA	NA	laboratory	free play	↑ investment in parental care ↔ ↑ parental OT
Gettler et al. (2019)	Republic of Congo	16	mothers (n=19)	healthy	X	NA	NA	laboratory	NA	↓ marital conflict ↔ ↑ paternal OT
Gordon et al. (2010a)	Israel	37	mothers (n=37)	healthy	X	NA	NA	home	free play	↑ paternal OT ↔ ↑ triadic interactive synchrony
Gordon et al. (2010b)	Israel	62	mothers (n=66)	healthy	X	NA	NA	home	free play	↑ paternal OT ↔ ↑ physical stimulation and object presentations
Gordon et al. (2010c)	Israel	43	NA	healthy	X	NA	NA	home	structured play	↑ paternal OT ↔ ↑ dyadic synchrony

Gordon et al. (2017)	Israel	80	mothers (n=80)	healthy	X	X	NA	home	free play	↓ OT ↔ ↑ affectionate touch (only with high testosterone)
Gray et al. (2007)	USA	16	singles; non biological fathers (n= 15)	healthy	X	X	NA	hospital	free play	ns difference in OT concentrations between primary and secondary fathers
Mascaro et al. (2014)	USA	88	non-fathers (n=50)	healthy	X	NA	NA	laboratory	NA	↑ OT in fathers compared to non-fathers
Miura et al. (2015)	Japan	30	mothers (n=50)	healthy	X	NA	NA	home	structured play	ns association between OT and father-infant interaction measures
Naber et al. (2010)	The Netherlands	17	NA	healthy	NA	NA	X	home	free play	OT administration → fathers more encouragement and less hostility
Naber et al. (2013)	The Netherlands	32	fathers of healthy children (n=14)	autism spectrum	NA	NA	X	home	free play	OT administration → fathers optimal physical stimulation
Vittner et al. (2018)	USA	28	mothers (n=28)	preterm	X	X	NA	hospital	skin-to-skin contact; free play	skin-to-skin contact → ↑ paternal OT
Vittner et al. (2019)	USA	28	mothers (n=28)	preterm	X	X	NA	hospital	skin-to-skin contact	↓ OT ↔ ↑ paternal engagement
Weisman et al. (2012)	Israel	35	NA	healthy	X	X	X	laboratory	still-face paradigm	OT administration → ↑ paternal sensitive caregiving and bonding
Weisman et al. (2013)	Israel	35	NA	healthy	X	X	X	laboratory	still-face paradigm	OT administration → ↑ paternal physical proximity
Weisman et al. (2014)	Israel	35	NA	healthy	X	X	X	laboratory	still-face paradigm	OT administration → ↑ infant social gaze to fathers (in high-synchrony dyads)
Weisman et al. (2016)	Israel	35	NA	healthy	X	X	X	laboratory	still-face paradigm	ns association between OT administration and paternal fatherese and speech turn-taking

Note. OT: oxytocin; NA: not applicable; Child age, months: mean (standard deviation) [min-max]; X: yes; ↓: lower; ↑: higher; ↔: correlation; →: prediction.

Table 2. Quality appraisal of included studies.

Study	A	B	C	D	E	F	FINAL
Abraham et al. (2014)	3	2	1	1	1	NA	2
Apter-Levi et al. (2014)	3	2	1	1	1	NA	2
Cohen-Bendahan et al. (2015)	2	2	1	1	1	1	1
Cong et al. (2015)	3	1	1	1	1	1	2
Feldman et al. (2010a)	3	2	1	1	1	NA	2
Feldman et al. (2010b)	3	2	1	1	1	2	2
Feldman et al. (2011)	3	2	1	3	1	NA	3
Feldman et al. (2012)	3	2	1	3	1	NA	3
Gettler et al. (2019)	3	2	2	2	1	NA	2
Gordon et al. (2010a)	3	1	1	1	1	NA	2
Gordon et al. (2010b)	3	2	2	1	2	NA	2
Gordon et al. (2010c)	3	2	1	1	1	1	2
Gordon et al. (2017)	3	2	1	3	2	2	3
Gray et al. (2007)	2	1	1	1	1	NA	1
Mascaro et al. (2014)	3	2	1	1	1	2	2
Miura et al. (2015)	2	2	1	1	1	NA	1
Naber et al. (2010)	3	1	1	1	1	1	2
Naber et al. (2013)	3	2	1	1	1	NA	2
Vittner et al. (2018)	3	2	1	1	2	NA	2
Vittner et al. (2019)	3	1	1	1	1	NA	2
Weisman et al. (2012)	3	1	1	1	2	1	2
Weisman et al. (2013)	3	1	1	1	1	1	2
Weisman et al. (2014)	3	1	1	1	2	1	2
Weisman et al. (2016)	3	1	1	1	1	NA	2

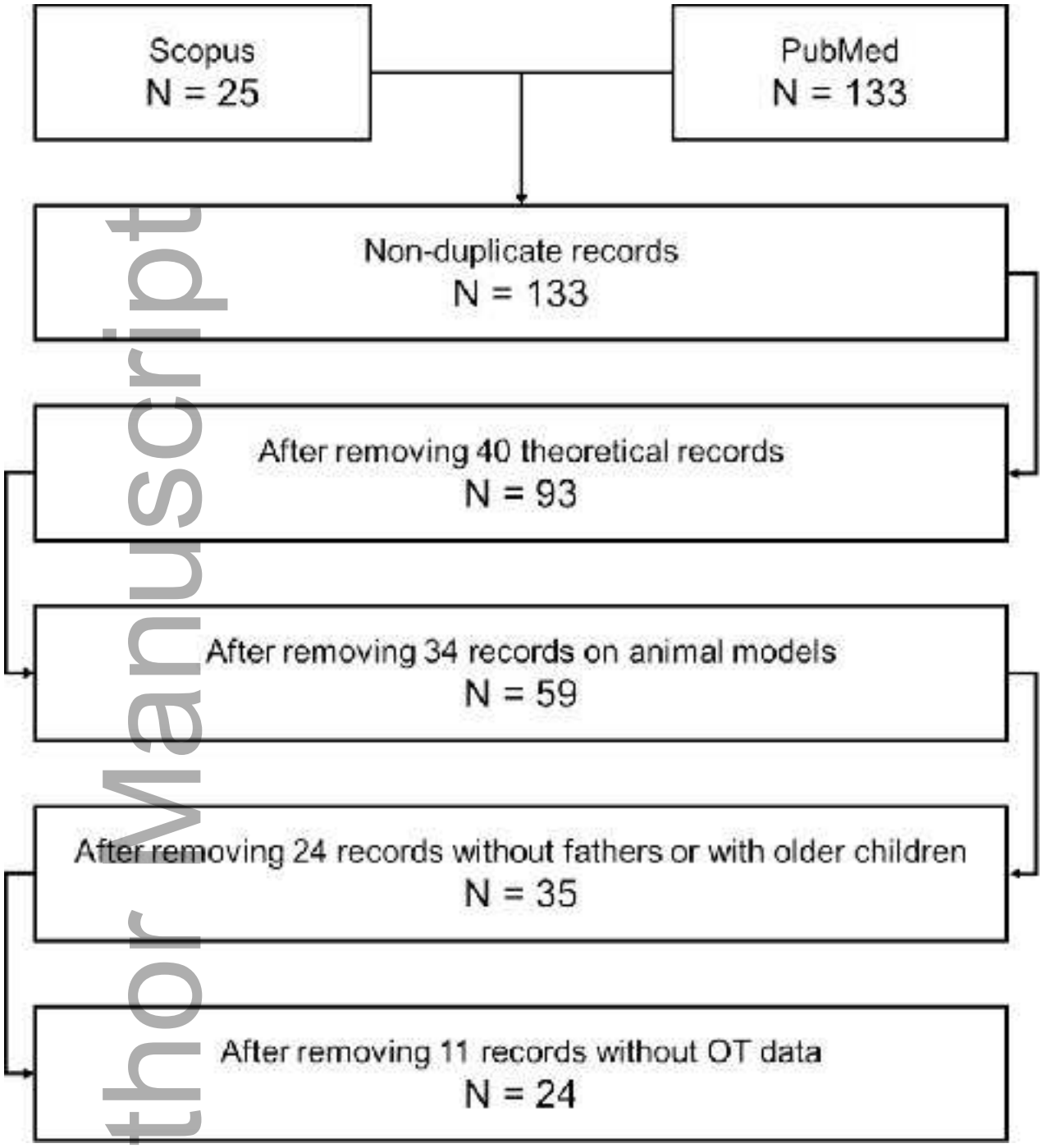
Note. A, Selection bias; B, Study design; C, Confounders; D, Blinding; E, Data collection methods; F, withdrawals and drop-outs. Quality codes: 1, strong; 2, moderate; 3, weak; NA, not applicable.

Table 3. Oxytocin (OT) assessment and concentrations.

Study	Hormone tissue	Study timing	Estimation method	Salivary OT	Plasma OT	Urinary OT
Abraham et al. (2014)	saliva	16:00 - 20:00	EIA	6.33 pg/mL	NA	NA
Apter-Levi et al. (2014)	plasma	13.00 - 16.00	EIA	NA	391.18 pg/mL	NA
Cohen-Bendahan et al. (2015)	urine	16:00 - 19:00	EIA	NA	NA	4.14 ng/mmol (ratio to creatinine)
Cong et al. (2015)	saliva	13:00 – 15:00	EIA	41.25 pg/mL	NA	NA
Feldman et al. (2010a)	saliva; plasma	13.00 – 16.00	EIA	10.46 pg/mL	356.13 pg/mL	NA
Feldman et al. (2010b)	saliva; plasma	13.00 – 16.00	EIA	7.09 pg/ml	405.10 pg/mL	NA
Feldman et al. (2011)	plasma, saliva, urine	13.00 – 16.00	EIA	7.09 pg/mL	405.10 pg/mL	9.81 pg/mL
Feldman et al. (2012)	plasma	16:00 – 19:00	EIA	NA	377.69 pg/mL	NA
Gettler et al. (2019)	saliva	16:30 – 18:30	EIA	44.26 pg/ml	NA	NA
Gordon et al. (2010a)	plasma	16:00 – 20:00	EIA	NA	306.01 pg/mL	NA
Gordon et al. (2010b)	plasma	16:00 – 20:00	EIA	NA	401.98 pg/mL	NA
Gordon et al. (2010c)	plasma	16:00 – 20:00	EIA	NA	354.00 pg/mL	NA
Gordon et al. (2017)	plasma	16:00 – 20:00	EIA	NA	NA	NA
Gray et al. (2007)	urine	08.00 - 17.30	EIA	NA	NA	2.00 pg/mg (ratio to creatinine)
Mascaro et al. (2014)	plasma	7:30 - 15:25	RIA	NA	8.78 pg/mL	NA
Miura et al. (2015)	urine	11:00 -14:00	RIA	NA	NA	114.60 IU/mL (ratio to creatinine)
Naber et al. (2010)	NA	NA	NA	NA	NA	NA
Naber et al. (2013)	NA	NA	NA	NA	NA	NA
Vittner et al. (2018)	saliva	13:00 - 15:00	EIA	142.99 pg/mL	NA	NA
Vittner et al. (2019)	saliva	13:00 - 15:00	EIA	142.99 pg/mL	NA	NA
Weisman et al. (2012)	saliva	13.00 - 17.00	EIA	23.20 pg/mL	NA	NA
Weisman et al. (2013)	NA	NA	NA	NA	NA	NA
Weisman et al. (2014)	saliva	13.00 - 17.00	EIA	23.20 pg/mL	NA	NA

Weisman et al. (2016)	saliva	13.00 - 17.00	EIA	23.20 pg/mL	NA	NA

Note. NA, not applicable; EIA, Enzyme Immunoassay; RIA, Radioimmunoassay.



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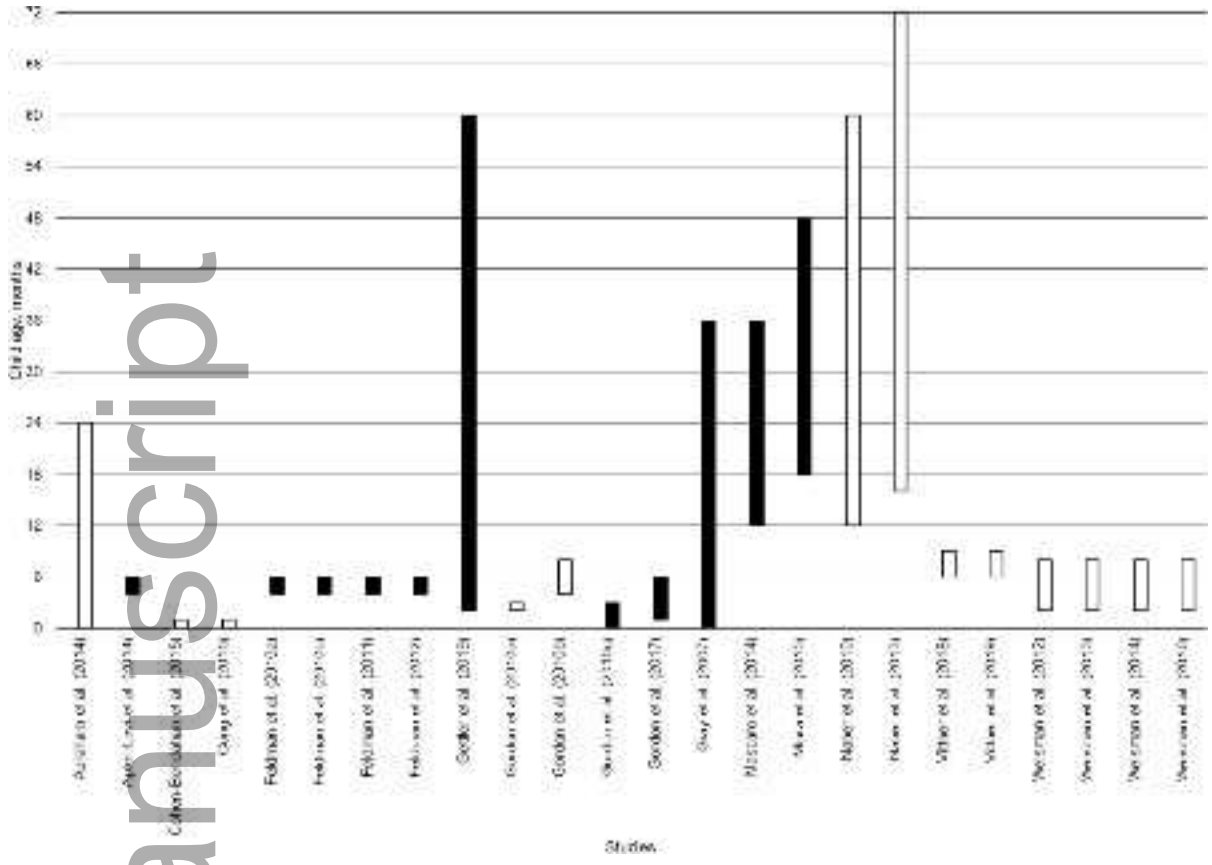

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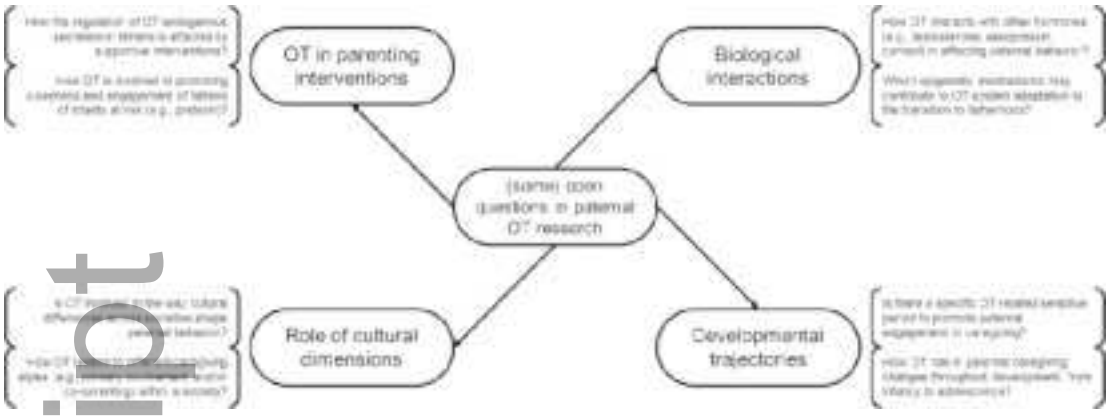

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