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Review

Developmental programming of oxytocin through variation in early-life stress: Four meta-analyses and a theoretical reinterpretation

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ABSTRACT

Despite evidence supporting a role for oxytocin (OT) in regulating social behavior, surprisingly little is known about how this neuropeptide is calibrated during development. We systematically reviewed empirical studies in humans ($k = 86$ publications reporting on 66 independent samples; $N = 7319$) that examined associations between early-life stress and three OT system components: endogenous OT, methylation of the OT receptor gene (*OXTRm*), and biological and behavioral responses to intranasally administered OT. In a series of meta-analyses, we found some evidence that people who grew up under more adverse conditions tend to have lower endogenous OT (children: $r = .12$; adults: $r = .09$), that early adversity is associated with higher levels of *OXTRm* ($r = .02$), and that adults who report lower levels of childhood adversity tend to show more positive responses to intranasally administered OT ($r = .12$). These results were found in typical populations, and were in most cases absent in clinical samples. We discuss these findings in terms of both the prevailing medical model (focusing on the harmful effects of early-life stress) and the adaptive calibration model (focusing on developmental adaptation of biobehavioral systems to early conditions) and suggest that an adaptation-based approach could meaningfully advance research and intervention on the sequelae of early adversity.

Knowledge of the oxytocin-arginine vasopressin (OT-AVP) neurosecretory system has become increasingly relevant to psychology, psychiatry and neurobiology. Decades of research, beginning with the study of socially monogamous rodents, has delineated the role of these neuropeptides in linking social behavior to physiology across the lifespan (Carter et al., 2020). Research on the OT-AVP system has more recently expanded into the human clinical domain, focusing on the role of OT in an array of both typical behaviors and clinical conditions (Hurlemann & Grinevich, 2018; Sharma, Gonda, Dome, & Tarazi, 2020; Torres, Martins, Santos, Prata, & Veríssimo, 2018), especially in relation to social bonding and affiliation (Feldman & Bakermans-Kranenburg, 2017; Feldman, Monakhov, Pratt, & Ebstein, 2016). A large body of animal research, and an emerging human literature, has examined the role of the OT-AVP system in the expression of a wide range of social traits and behaviors in both males and females, including parental care (Carter, 2017; Feldman, 2017; Feldman et al., 2016; Feldman & Bakermans-Kranenburg, 2017), mating behavior (Borrow & Cameron, 2012; Carter & Perkeybile, 2018), social cognition (e.g. Baribeau & Anagnostou, 2015; Grinevich & Stoop, 2018; Lopatina, Komleva, Gorina, Higashida, & Salmina, 2018), and conspecific aggression (Bosch, 2013; Terranova, Ferris, & Albers, 2017). Despite research supporting a possible role for the OT-AVP neurosecretory system in regulating social behavior, surprisingly little is understood about how the system is calibrated during development. This has limited our understanding of

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the role of the OT-AVP system in mediating the effects of different early environmental conditions on a range of phenotypic outcomes.

In this paper, we systematically review human research on developmental programming of the OT-AVP neurosecretory system. We also consider the hypothesis that variation in the OT-AVP system functions to regulate development of life history-related traits and behaviors in relation to familial and ecological conditions encountered over ontogeny. We first provide background on the OT-AVP system, emphasizing its plasticity and role in regulating adaptive changes in biobehavioral systems. Then we discuss measurement of childhood adversity and the three OT system components addressed in this review: endogenous OT, methylation of the OT receptor gene (*OXTRm*), and biological and behavioral responses to exogenously administered OT. Finally, we review empirical studies in humans that examine associations between childhood adversity and these three OT system components, based on 86 empirical publications that met eligibility criteria. This includes both a meta-analytic review of the literature on these associations ($k = 66$ independent samples), and a related narrative review, which discusses the meta-analytic findings and highlights some additional research findings that were not part of the meta-analysis.

Most research on the effects of childhood adversity on the OT-AVP system has been informed by the widely accepted medical model, which focuses on the harmful effects of early life stress. As background for the current review, we present the medical model, but argue that it has limited empirical progress by constraining researchers to address certain questions, but not others, regarding development of the OT-AVP system. Most critically, the medical model does not advance a framework for understanding *developmental adaptation to stress*. To fill in this gap, we also present life history theory, an evolutionary-developmental framework that has been used to explain adaptive responses to early adversity. In the Discussion, we summarize our findings and discuss them in terms of the medical model, on the one hand, and from the perspective of life history theory, on the other, focusing in particular on the adaptive calibration model (ACM; Del Giudice, Ellis, & Shirtcliff, 2011; Ellis & Del Giudice, 2014, 2019). The use of a life history framework, and the ACM more specifically, suggests alternative ways of interpreting some of the data (calling into question some conclusions of the medical model), affords broader integration of knowledge, suggests new hypotheses and lines of research to follow, and may lead to less stigmatizing ways of approaching interventions to address the sequelae of early adversity.

1. The medical model of stress and development

A large literature has previously implicated OT-AVP system parameters in the expression of many social traits and behaviors (e.g., Bakermans-Kranenburg & Van IJzendoorn, 2008; Bakermans-Kranenburg & van IJzendoorn, 2013; Feldman et al., 2016; Jurek & Neumann, 2018; Kraaijenvanger et al., 2019; Kumsta & Heinrichs, 2013; Maud, Ryan, McIntosh, & Olsson, 2018); however, these past reviews have often viewed these traits and behaviors through a medical lens, focusing especially on the role of low endogenous OT or elevated *OXTRm* in behavior problems and psychological disorders (e.g., internalizing problems, callous-unemotional traits, affect regulation problems). Indeed, peripheral levels of OT and AVP or variations in their receptors have been associated with functioning in variety of psychological disorders, including Williams Syndrome (Dai et al., 2012), autism spectrum disorders (Oztan et al., 2018), schizophrenia (Rubin et al., 2014, 2018), anxiety disorders (Naja & Aoun, 2017; Gottschalk & Domschke, 2018), depression (Cyranowski et al., 2008; Goekoop, de Winter, Wolterbeek, van Kempen, & Wiegant, 2011), postpartum depression (Bell et al., 2015; Zelkowitz et al., 2014), post-traumatic stress disorder (Sharma et al., 2020), borderline personality disorder (Brüne, 2016), eating disorders (Aulinas et al., 2019), and substance abuse (Buisman-Pijlman et al., 2014). Accordingly, the use of exogenous OT has been explored as a treatment for a number of these conditions (Bernaerts, Boets, Bosmans, Steyaert, & Alaerts, 2020; Bowen & Neumann, 2018; Carter et al., 2020; Sharma et al., 2020). In a meta-analysis of this literature (Bakermans-Kranenburg & van IJzendoorn, 2013), only administration of exogenous OT to treat autism spectrum disorders, but not other disorders, showed a significant combined effect size.

The large scientific literature examining OT in both health and illness, including research on the capacity of OT to act as a "natural medicine" in the face of adversity or trauma (Carter et al., 2020), converges with the medical model. That model conceptualizes different patterns of physiology and behavior as "adaptive versus maladaptive" depending on the extent to which they promote versus threaten people's health, safety, and psychological well-being. From this perspective, there are optimal levels of basal OT and OT responsivity to context for promoting health and well-being; deviations from these optima (including recurring over or under activity of the OT-AVP system) are conceptualized as dysfunctional deviations from the norm, usually arising from a combination of excessive stress exposure and genetic or epigenetic vulnerability. Here are two illustrative statements from recent literature reviews that capture the medical model of stress and development in relation to OT:

> Studies have shown that traumatic experiences may affect hormonal systems mediated by the hypothalamic-pituitary-adrenal (HPA) axis and the oxytocinergic system. This effect is the result of long-term impairments in hypothalamic structures and negative feedback mechanisms within the HPA axis, structures that mediate the response to stress. This deregulation reduces the production and release of cortisol and oxytocin (OXT), which may alter stress responses and lead to increased vulnerability to impairments from stressful experiences (Donadon, Martin-Santos, & Osório, F. de L., 2018, p. 1).

> In this review, we examined the literature linking early life adversity to oxytocinergic dysregulation as a mechanism involved in the susceptibility to later psychopathology. ... Overall, the data indicates that early adversity produces persistent effects on oxytocinergic pathways. Specifically, studies of early life adversity demonstrate 1) differences in peripheral and central oxytocin levels, 2) altered responses to exogenous oxytocin administration, and 3) moderating influence of oxytocin receptor polymorphisms and epigenetic changes on vulnerability to psychopathology (Tobon, Newport, & Nemeroff, 2018, p. 9).

2. Limitations of the medical model from an evolutionary-developmental perspective

Although the medical model has inspired a substantial body of research on the relations between early life stress and functioning of the OT system, as reviewed herein, this approach has also constrained empirical progress. The medical model does not address how natural selection organized developmental systems to respond to context, and thus also to adversity. This omission has resulted in a functionally agnostic approach that misses stress-mediated developmental adaptations. Specifically, the medical model has a limited conceptualization of adaptation. Evolutionary models conceptualize different developmental trajectories as "adaptive versus maladaptive" depending on the extent to which they promote versus undermine survival and reproductive success in different ecological contexts (e.g., Hinde, 1991). 'Adaptive' in this sense is not meant to carry any normative weight; rather, it is a descriptive label for developmental processes that function (or at least once did) to increase the match between an individual and their environment. Although adaptive in an evolutionary sense does not imply mental health or disorder in a clinical sense, adaptations that increase survival/reproductive success may induce tradeoffs with costs to physical or mental health over time (as discussed below).

Consideration of evolutionarily adaptive processes leads one to ask

functional questions about variation in systems and behavior (Tinbergen, 1963). Asking such questions about the role of the OT-AVP system in regulating behavior leads to conceptualizing the data in ways that differ from conceptualizations of the medical model. From an evolutionary-developmental perspective, stressful developmental experiences and environmental exposures should not so much impair neurobiological systems as direct or regulate them toward patterns of functioning that are adaptive under stressful conditions (Belsky, Steinberg, & Draper, 1991; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011; Ellis & Del Giudice, 2019; Hinde, 1991). Central to this evolutionary-developmental perspective is the assumption that our neurohormonal systems evolved to respond adaptively—by calibrating both recurring set points and responsivity patterns—to the range of species-typical environmental conditions encountered by children, from safe and supportive to dangerous and unpredictable (Boyce & Ellis, 2005; Del Giudice et al., 2011).

This perspective moves us beyond the central focus of the medical model on the disruptive effects of trauma toward a broader focus on how developmental experiences and environmental exposures, as recurrently experienced over our evolutionary history, adaptively calibrate biobehavioral processes, including the OT-AVP system. Studies included in the current review that tested for the mediating effects of OT on relations between childhood adversity and later development often focused on dysfunctional, dysregulated, or maladaptive developmental outcomes, rather than on adaptive variation in stress-sensitive behavioral domains, such as defensive behaviors, competitive risk-taking, learning, attachment, affiliation, and reproductive functioning.

3. Developmental programming of the OT-AVP system

Life history theory is a major framework in evolutionary biology and psychology for explaining patterns of developmental programming (e.g., Belsky et al., 1991; Chisholm, 1999; Ellis, Figueredo, Brumbach, & Schlomer, 2009; Hill & Kaplan, 1999; Stearns, 1992). Life history theory addresses how organisms allocate their limited time and energy to the various activities that comprise the life cycle, namely, physical and cognitive growth, maintenance of bodily tissues, mating and parenting. Since all of these activities contribute to fitness, devoting time and energy to one will typically involve benefits as well as costs, engendering trade-offs between different fitness components. Such tradeoffs are central to developmental adaptations to stress—one system is diminished so that another can be enhanced or preserved— such as when an increased inflammatory host response to fight infection trades off against lower ovarian function in women or reduced musculoskeletal function in men. Tradeoffs are evidenced by the costs to mental and physical health incurred by children growing up in harsh environments (e.g., McCrory, De Brito, & Viding, 2010; Shonkoff et al., 2012). Over development, tradeoffs coordinate morphology, physiology, and behavior in ways that promote reproductive fitness (or once did) under different environmental conditions recurrently experienced over evolutionary history (Belsky et al., 1991; Del Giudice, 2020; Ellis et al., 2009). These coordinated patterns (instantiated in such characteristics as timing of reproduction, levels of risky and aggressive behaviors, and parenting quality) are referred to as *life history strategies*. Developmental life history models have proposed that early exposures to harsh, unpredictable environments induce tradeoffs that regulate development toward "faster" life history strategies (e.g., earlier age at reproduction, more risky and aggressive behavior, lower parental investment), whereas growing up in more safe, stable environments regulates development toward "slower" life history strategies (e.g., later age at reproduction, more stable pairbonds, higher investment in parenting) (Belsky et al., 1991; Chisholm, 1999; Ellis et al., 2009).

Rodent research dating back to the early 1990s suggests that OT-AVP neural pathways are sensitive to early life stress (reviewed in Kompier, Keysers, Lucassen, Gazzola, & Krugers, 2019). This research has used a variety of species and a diversity of experimental paradigms, resulting in complex outcomes. Although rodent studies often lack sufficient statistical power (Bonapersona et al., 2019; Button et al., 2013), variation apparently exists within and between species regarding the effects of early rearing conditions on development of the OT-AVP system and life history-related traits and behaviors. Broadly speaking, the rodent literature presents some evidence for regulation of three OT-AVP pathways by early life stress: (a) persistent upregulation of AVP gene expression and alterations in anxiety and aggression in non-monogamous male rodents (Kompier et al., 2019; Veenema, Blume, Niederle, Buwalda, & Neumann, 2006; Veenema & Neumann, 2009; Zhang et al., 2012); (b) alterations in both OT and AVP system parameters and related changes in parental caregiving in non-monogamous female rodents (Champagne & Meaney, 2006, 2007; Murgatroyd et al., 2015; Murgatroyd & Nephew, 2013; Murgatroyd, Peña, Podda, Nestler, & Nephew, 2015); and (c) changes to OT and AVP pathways, and subsequently altered parental and alloparental behaviors, in both sexes in socially monogamous rodents (Carter and Perkeybile, 2018; Bales & Carter, 2003; Bales et al., 2007, Bales, Boone, Epperson, Hoffman, & Carter, 2011; Perkeybile et al., 2019). These patterns in nonhuman mammals provide some support for the hypothesis that changes in OT-AVP pathways function as mediating mechanisms through which variations in early-life stress affect a range of individual differences in traits and behaviors that may be related to life history strategies.

In the current paper, we attempt to systematically examine one part of this model in humans: the path from early life adversity to OT system parameters. The dominance of the medical model has constrained human research on the effects of early adversity on the functioning of the OT-AVP system, limiting our understanding of the role of this system in regulating functional outcomes in the context of adversity. This limitation, together with various methodological challenges discussed below, has resulted in a somewhat disjointed literature that reads like a heterogeneous array of more or less replicable findings rather than an integrated body of knowledge. Here we attempt to bring some order to this literature through four meta-analyses and narrative review of research findings. In the Discussion, we suggest that greater insight, integration of knowledge, and empirical achievement could be realized by employing an evolutionary-developmental perspective (particularly life history theory, and the ACM).

4. Background

The OT-AVP neurosecretory system is a network of ancient neurons, peptides, and receptors that have been involved in regulating organismic physiology and behavior for over 500 million years (Beets, Temmerman, Janssen, & Schoofs, 2013; Feldman et al., 2016; Grinevich, Knobloch-Bollmann, Eliava, Busnelli, & Chini, 2016; Yamashita & Kitano, 2013). Like all hormonal systems, the OT-AVP system has two distinct components: the *signal component* (including the OT-AVP molecules and the neurons that release them into peripheral and central neural circulation) and the *receptor component* (including 3 AVP receptors and 1 OT receptor distributed throughout the brain and body).

Systems involved in the process of developmental programming are characterized by a high degree of plasticity and sensitivity to environmental cues. The OT-AVP system meets these criteria. The activity of OT or AVP synthesizing neurons in various brain regions are remarkably variable throughout development and highly responsive to stress (Di & Tasker, 2004; Theodosis, 2002). OT and AVP are detected very early in development (as early as 11 weeks of gestation in humans and 14 days of gestation in rodents; reviewed in Kompier et al., 2019). During the gestational, neonatal, and juvenile periods, OT and AVP synthesizing cells undergo changes in ratio (Hammock, 2015), and OT-AVP receptor distributions/expressions ebb and flow throughout these developmental periods. The apparent plasticity of this system throughout development potentially enables high sensitivity to developmental experiences and environmental exposures.

In mammals, OT and AVP serve as a dynamic and integrated system,

permitting adaptive changes in social behavior, stress responsivity, and immune reactivity (Carter et al., 2020; Caldwell, 2017; Winter & Jurek, 2019; Volpi et al., 2004; Li, Wang, Wang, & Wang, 2017). AVP has the capacity to influence the OT receptor, contributing to the capacity of both molecules to respond to diverse social and environmental demands. Before the recent proliferation in research on OT as a "social bonding hormone," the peptide was well known as a signal molecule mainly associated with female reproductive and maternal traits and behaviors, including childbirth and lactation (Higuchi, Honda, Fukuoka, Negoro, & Wakabayashi, 1985; Soloff, Alexandrova, & Fernstrom, 1979), from which the name 'oxytocin' (Greek for speedy delivery) is etymologically derived. AVP, an evolutionary paralogue of OT, has traditionally been recognized for its links to osmotic balance (Robertson, 1974), vasoconstriction (Cowley Jr, Quillen Jr, & Skelton, 1983), and the hypothalamic-pituitary-adrenal (HPA) stress response (Scott & Dinan, 1998).

Table 1
Effects of early adversity on endogenous OT (basal OT and OT responsivity to context) in children.

Study	Sample	Developmental stress exposure (DSE)	OT measure	Associations between DSE and OT measure[a]	Behavioral outcome
BASAL OT					
Apter-Levy et al. (2013); Priel et al. (2019). Same sample	Families: mother, father, and child (ages 6–10 years). Clinical sample: maternal MDD (*N*=46). Community-based control sample (*N*=103).	Prospective. Exposure to chronic maternal depression at 9 months of age and 6 years of age. Maternal sensitivity at age 6.	Basal salivary OT in all family members (child: ages 6 and 10).	Maternal MDD = ↓OT in mothers, fathers, and children (age 6); ↓child salivary OT at age 10. ↓Maternal sensitivity = ↓child OT at age 6.	Maternal MDD = ↓maternal sensitivity and child OT = ↓ child engagement and synchrony = ↑child externalizing and internalizing problems.
Feldman et al. (2013).	Mothers, fathers, and children (birth to age 3). Community sample (*N* = 50 families at child age 3).	Prospective. Observed reductions in parental caregiving during infant-parent play (1 and 6 mo. postpartum).	Basal salivary OT (age 3).	↓OT in children, but only if mothers are homozygous for CD38 rs3796863 C allele.	At age 3, ↓OT = ↓social reciprocity with a friend
Mizushima et al. (2015).	Children (mean age: 12–13 yrs). Court-referred sample (child abuse/neglect; *n* = 38); community-based comparison group (*n* = 26).	Records based. "Settled group": living in residential care facility for ≥ 1 yr. "Unsettled group": living with parents or in care facility for < 1 yr.	Basal salivary OT (awakening and bedtime). Change in OT from awakening to bedtime.	Settled group: ↑basal salivary OT at bedtime (compared to unsettled group), with settled group showing marked rise in OT from awakening to bedtime. Other OT variables: non-significant group differences.	Salivary OT unrelated to current depressive symptoms.
Ulmer-Yaniv et al. (2018); Yirmiya, Motsan, Zagoory-Sharon, and Feldman (2020). Same sample.	Mothers and children (ages 2–12). Community sample exposed to continuous wartime trauma (*n* = 101); non-exposed comparison group (*n* = 76).	Prospective. Behavioral observations of sensitive parenting (child mean ages: 3, 9, and 12 years).	Basal salivary OT (child ages 9 and 12). Salivary OT responsivity to an attachment induction paradigm (child age 12).	Wartime exposure: ↓maternal basal OT (child age 9); no relation with child basal OT at age 9, but ↓basal child OT at age 12, which increased in response to attachment induction when mother displays high sensitive parenting.	Maternal wartime exposure = ↓maternal OT = ↓child OT = ↑child anxiety symptoms.
Abraham et al. (2019)	Primary caregivers (first-time mothers or fathers) and children (infancy to age 6; *N* = 45 families). Community sample.	Concurrent. Parental brain responses to infant stimuli. Observed parental sensitivity (child age 3).	Basal salivary OT in infancy and at age 3.	↓Parental bilateral amygdala activity = ↓parental sensitivity = ↓child OT at 3 years.	↓child OT = ↑ child somatic symptoms (e.g., headaches, pain, fatigue) at 6 years (non-significant trend; r = -.21)
Fujiwara et al. (2019)	Mothers and infants. Community sample (*N* = 115 family lines).	Concurrent. Parental rejection of infant by mother.	Basal salivary OT (infant mean age: 5.46 months).	No main effects of parenting on OT. For infants carrying the A allele of OXTRrs2254298, ↑maternal rejection = ↑OT.	NA
Suzuki et al. (2020)	Children (ages 2–9 years). Court-referred sample (*n* = 21); community-based comparison group (*n* = 29).	Records based. Residence in childcare facility, with prior history of physical, sexual, or emotional abuse or neglect.	Basal salivary OT	↓salivary OT	Among children with abuse/neglect history: ↓OT = ↓visual attention to eyes as a social cue = ↑social-emotional difficulties.
OT RESPONSIVITY TO CONTEXT					
Seltzer et al. (2014).	Children (ages 8–11). Court or CPS-referred sample (*n* = 37); community-based comparison group (*n* = 36).	Records based. Court or CPS-identified history of physical abuse in childhood.	Urinary OT at baseline and in response to TSST-C	Abused girls: ↑urinary OT, at baseline and in response to the Trier, relative to controls. Abused boys: No differences from controls.	NA
Pratt et al. (2015). Same sample as: Apter-Levy et al. (2013); Priel et al. (2019)	Mothers and children (birth to age 6). Clinical sample: Maternal diagnosis for MDD (*n* = 41). Controls: no MDD (*n* = 56).	Prospective. Chronic maternal depression from birth to age 6.	Urinary OT at baseline and in response to family social contact.	↓Child baseline OT and ↓child OT responsivity (age 6).	↓ Child OT responsivity = ↑child social withdrawal, ↑Axis-I psychopathology
Nawa, Nakamura, and Fujiwara (2020)	Mothers and children (*n* = 34 dyads). Community sample exposed to Great East Japan Earthquake; no control group.	Prospective. Family exposure to earthquake (e.g., house damaged) and related maternal distress (child ages 3–5 years).	Salivary OT in response to playful mother-child interaction (child mean age: 8.8 years).	Small negative changes (non-significant) in child OT following playful interaction. Child OT responsivity was not predicted by degree of earthquake trauma or maternal distress.	NA

Note. CPS, child protective services. DSE, developmental stress exposure. MDD, major depressive disorder. OT, oxytocin. TSST-C, Trier Social Stress Test for children.
[a] Outcome of developmental stress exposure (higher early-life stress).

5. The "Signal" component: synthesis and release of OT and AVP into central and peripheral circulation

OT and AVP act both as signal molecules in the periphery (hormones) and in the brain, often referred to as neuropeptides or neuromodulators (Kupfermann, 1979; Stoop, 2012). Although OT and AVP are mainly synthesized in the hypothalamus of the mammalian brain, OT and AVP genes (*OXT* and *AVP)* are expressed in many other brain regions (Grinevich & Stoop, 2018; Knobloch & Grinevich, 2014) as well as in the immune system (Li et al., 2017), the heart and vasculature (Jankowski et al., 1998), enteric neurons in the lining of the GI tract (Welch, Margolis, Li, & Gershon, 2014), the ovaries and testis, adrenal medulla and more (reviewed in Gimpl & Fahrenholz, 2001). From these various sites of synthesis, OT and AVP act on a global distribution of receptors throughout various neurological and physiological substrates (Jurek & Neumann, 2018).

5.1. Measurement of signal molecules in the periphery (endogenous OT)

In the current review, all studies of endogenous OT (as presented in Tables 1-2) assessed the peptide in an unstimulated state (basal OT), while some also assessed changes in OT in response to external stimuli such as the Trier Social Stress Test, mechanically-delivered massage, or playful mother-child interactions (OT responsivity). There is much debate in the field regarding the most reliable and valid methods of collecting peripheral OT in bodily fluids (e.g., use of blood, saliva, or urine) and for measuring OT analytes once samples have been collected (e.g., immunoassay versus mass spectrometry), with or without prior sample extraction (which can remove up to 99% of the OT; MacLean et al., 2019). The studies included in the current review collectively employed all of these methods of sample collection, preparation, and measurement, which together with differences in time of day when samples are collected and fasting versus post-prandial sampling contribute to the wide variation in OT concentrations found across studies (reviewed in MacLean et al., 2019). In the studies included in the current review, OT means and standard deviations (pg/ml) ranged from low ($M = 0.79$, $SD = 0.39$; Boeck, Gumpp, et al., 2018, in extracted blood samples collected in the afternoon using radioimmunoassay in a traumatized Caucasian sample of new mothers) to high ($M = 823.9$, $SD = 531.6$; Olff et al., 2013, in whole blood samples collected in the morning under fasting conditions using enzyme immunoassay in a traumatized African American adult sample).

The predictive and convergent validity of plasma, salivary, and urinary OT in mothers and fathers was assessed by Feldman, Gordon, and Zagoory-Sharon (2011); plasma and salivary OT correlated $r = .41$ (see also Grewen, Davenport, & Light, 2010). In this study, plasma and salivary OT each significantly predicted a range of theoretically relevant outcomes: parent and child social engagement, positive communication sequences between parent and child, parental attachment relationships with own parents, partner, and infant. These data are suggestive of the validity of salivary and plasma OT measures, although the findings still need to be independently replicated. Urinary OT, by contrast, did not correlate with either plasma or salivary OT and did not predict any of these outcomes. Thus, the small number of studies in the current review that employed urinary measures may warrant cautious interpretation.

6. The receptor component: binding sites for OT and AVP

In both the periphery and the central nervous system, OT and AVP can act on four identified receptors: the oxytocin receptor (OTR), and the vasopressin 1a (V1aR), vasopressin 1b (V1bR), and vasopressin 2 (V2) receptors. These receptors all belong to the G protein-coupled receptor (GPCR) superfamily which, like the nonapeptides, appear to have arisen quite early in the evolution of animals (Grinevich et al., 2016; Yamashita & Kitano, 2013). Due to their evolutionary homology, there is a high degree of cross-reactivity among these four receptors and both OT and AVP. For example, although OT binds with much more specificity to OTR, AVP has been shown to bind with similar affinity to OTR as it does with all three AVP receptors (Carter, 2017; Song & Albers, 2018; Stoop, 2012). Furthermore, OT has been shown to bind to V1b receptors in the stress axis to release adrenocorticotropin hormone (ACTH) from the pituitary, thus stimulating an HPA response (Nakamura et al., 2008). The OTR has been identified in a broad spectrum of peripheral organs and tissues including myoepithelium of the mammary gland, myometrium of the uterus, endometrium decidua, ovary, testis, epididymis, vas deferens, kidney, heart, thymus, pancreas, and adipocytes (reviewed in Gimpl & Fahrenholz, 2001; Kimura et al., 2003; Yang, Wang, Han, & Wang, 2013). The OTR is also expressed throughout the mammalian brain and spinal cord (Grinevich & Stoop, 2018).

6.1. Measurement of OT receptor methylation (OXTRm)

The current review included a set of studies (presented in Table 3) that assessed methylation of the OT receptor gene (*OXTRm*). Differential methylation of *OXTR* is associated with different levels of OT receptor expression across a range of brain regions and peripheral tissues (Beery, McEwen, MacIsaac, Francis, & Kobor, 2016). This variation is important because OT primarily exerts it effects through binding to OT receptors, which are encoded by *OXTR*. Although a variety of epigenetic modifications have been discovered and quantified, with the capacity to suppress or in some cases enhance gene expression, modifications involving DNA methylation are commonly examined in OT research. *OXTRm,* which generally suppresses *OXTR* transcription, apparently correlates with a variety of social traits and behaviors (Beery et al., 2016; Kraaijenvanger et al., 2019; Kumsta & Heinrichs, 2013; Maud et al., 2018). In addition to genetic influences (Min et al., 2021), methylation is potentially influenced by developmental experiences and environmental exposures (e.g., Meaney, 2010).

The most commonly used techniques to assess methylation are epigenome wide analyses and candidate gene approaches. In human research, the epigenome wide approach is increasingly used (e.g., Rijlaarsdam et al., 2016) but still rarely represented in studies on the oxytocinergic system (but see Dall' Aglio et al., 2020, for an exception). All studies included in the current review used the candidate (epi-)gene approach. Methylation levels were quantified in various sites in the CpG island of the *OXTR* in DNA extracted from white blood cells, buccal epithelial cells, or saliva. As the *OXTR* CpG island is large, constituting approximately 2.5 kilobases, methylation patterns can vary across different sites, and there is a lack of clarity regarding the best sites to target for analysis. Whereas some studies included in the current review assessed average methylation across multiple CpG sites (i.e., methylation blocks; e.g., Smearman et al., 2016; Unternaehrer et al., 2015), or even assessed mean methylation across the OT receptor gene sequence (Robakis et al., 2020), other studies targeted individual CpG sites within the island (e.g., Fujisawa et al., 2019; Gonzalez, Wroblewski, Allen, Coan, & Connelly, 2020). As discussed below, this variation presents challenges when comparing results across studies. Although measures of DNA methylation in peripheral tissues (e.g. blood, buccal cells, or saliva) do not serve as direct indicators of DNA methylation in central neural tissues, methylation in peripheral tissues does not need to correspond directly to methylation in central neural tissues to be of importance to developmental research (see extended discussion in Aberg et al., 2013; Lancaster, Morris, & Connelly, 2018).

7. Exogenous OT treatment

The current review includes a set of studies that assessed biological or behavioral responses to exogenous OT, administered via intranasal spray (see Table 4). An early meta-analysis of 23 studies (Van IJzendoorn & Bakermans-Kranenburg, 2012) showed that intranasal OT administration (vs. placebo) improved recognition of facial expressions of emotions ($d = 0.21$), enhanced levels of in-group trust ($d = 0.43$) and

Table 2
Effects of childhood adversity on endogenous OT (basal OT and OT responsivity to context) in adult community and clinical samples.

Study	Sample	Developmental stress exposure	OT Measure	Associations between DSE and OT measure[a]	Behavioral outcome
BASAL OT IN COMMUNITY SAMPLES					
Gordon et al. (2008); Feldman et al. (2012). Separate samples.	Adults. Community samples. Gordon et al.: *N*=45; 24 F. Feldman et al.: *N*=352; 191 F.	Retrospective. Low maternal/paternal care in childhood.	Basal plasma OT	↓plasma OT	↓OT = ↑psychological distress, ↑depression, ↓frequency of parental touch and gaze synchrony with infants
Heim et al. (2009).	Adults, female. Community sample (*N*=22).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Basal central OT levels in cerebrospinal fluid.	↓OT. OT concentrations decreased in relation to the number of different forms of maltreatment.	↓OT = ↑anxiety symptoms
Opacka-Juffry and Mohiyeddini (2012). Mohiyeddini, Opacka-Juffry, and Gross (2014). Same sample.	Adults, male. Community sample (*N*=90).	Retrospective. Cumulative exposure to stressful experiences and events (up to 12 years; 13–18 years)	Basal plasma OT	Early cumulative stress (0–12 years old) = ↓OT	↓OT = ↑depressive symptoms, ↑trait anxiety, ↑emotional suppression. Mothers with ↑early cumulative stress + ↑emotional suppression = lowest OT levels.
Bhandari, Bakermans-Kranenburg et al. (2014)	Adults, female. College students (*N*=102).	Retrospective. History of childhood emotional maltreatment	Basal Salivary OT	↑OT	↑emotional maltreatment = ↑OT = ↑positive evaluation of happy infant expressions (but unrelated to evaluation of sad infant expressions).
Eapen et al. (2014)	Adults, community sample. New mothers (*N*=57).	Retrospective. Recalled maternal and paternal indifferences, abuse, and over-control	Basal plasma OT during pregnancy and 3 months postpartum.	↑Paternal indifference, abuse, and over-control = ↓OT postpartum. Null relations with pregnancy OT, and null effects of maternal parenting behaviors on OT.	↓Postpartum OT = ↑postpartum depression symptoms, adult separation anxiety, and attachment avoidance/anxiety.
Mizuki and Fujiwara (2015)	Adults, community sample (*N*=81; 49 F). Parents of young children.	Retrospective. Non-severe childhood abuse/neglect (physical, sexual, and/or emotional)	Basal urinary OT	Non-severe physical abuse = ↑urinary OT.	NA
Scott (2017).	Young adults. Probationers/parolees (*n* = 54; 11 F); college students with early adversity (*n* = 47; 28 F)	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Salivary OT	↑emotional abuse, ↑sexual abuse = ↓OT. Null relations with other abuse/neglect measures.	↓OT = ↑callous-unemotional traits, ↑proactive aggression.
Boeck, Gumpp, et al. (2018); Krause et al. (2018). Same sample. Boeck, Krause et al. (2018). Partial sample overlap.	Adults, female, community sample. Postpartum mothers, over-sampled for child maltreatment (Ns = 49 and 67).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Plasma OT. Routine cellular respiration and ATP-turnover-related respiration. Telomere length in selected immune cell subsets	No association between abuse/neglect and OT. ↑OT = ↑telomere length in memory cytotoxic T cells. In mothers with abuse/neglect history: ↑OT = ↓immunocellular oxygen consumption related to basal mitochondrial respiration and ATP turnover.	NA
Mielke et al. (2018).	Adults, female, community sample (*N*=66). Over-sampled for physical or sexual abuse.	Retrospective. History of childhood maltreatment.	Basal Plasma OT	No main effect on OT. In women with maltreatment history: ↑OT = ↓ gray matter volume (GMV) in amygdala and hypothalamus. In women without maltreatment history: ↑OT = ↑GMV in nucleus accumbens and hypothalamus.	NA
Perry-Paldi et al. (2019)	Adults. Undergraduate students. (*N*=40; 16 F).	Retrospective. Early life stress (ELS): Composite of abuse, neglect, and other negative life events	Basal plasma OT and AVP	No main effects of ELS on plasma OT or AVP.	In students with high ELS: ↑OT = ↓accuracy in detecting infidelity; ↑AVP = ↑accuracy in detecting infidelity and threats. In students with low ELS: ↑OT= ↑accuracy in detecting infidelity.
Müller et al. (2019)	Adults, community sample (*N*=121; 61 F).	Retrospective. History of childhood emotional neglect.	Basal plasma OT	↓OT	↓OT = insecure attachment representations. ↓OT mediated the effect of emotional neglect on attachment insecurity.
Fujiwara et al. (2019)	Grandmothers, mothers. Community sample (*N* = 115 family lines).	Retrospective. Mother's and grand-mother's experiences of low maternal care and high maternal overprotection in childhood. Low maternal	Basal salivary OT	No main effects of parenting on OT. For mothers carrying the AA allele of *OXTR*rs53576, ↑maternal overprotection = ↓OT.	NA

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Table 2 (*continued*)

Study	Sample	Developmental stress exposure	OT Measure	Associations between DSE and OT measure[a]	Behavioral outcome
		involvement by grandmother.			
OT RESPONSIVITY TO CONTEXT IN COMMUNITY SAMPLES					
Munro et al. (2013)	Adults, female. College students (*N* =15).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Plasma OT at baseline and in response to emotional film clip	No relation with baseline OT. Trend toward lower OT response to abandonment scene.	NA
Riem et al. (2017)	Adult men. College students (*N* = 51).	Retrospective. Emotional abuse/neglect	Salivary OT at baseline and in response to mechanically-delivered massage (vs. control condition)	↓Baseline OT. In men with high (but not low) reported abuse/neglect: massage led to a larger drop in OT levels over time.	↓OT after massage = increased handgrip force during exposure to infant crying and laughter (less sensitive response to infant cues).
Julian et al. (2018).	Adults, community sample. Low-income mothers of young children (*N*=33 mother-child dyads).	Retrospective. Adverse Childhood Experiences (ACEs), a measure of cumulative stress.	Salivary OT at baseline and in response to mother-child play (storybook reading and games)	No significant correlations with OT.	In mothers with low ACES: ↑ baseline OT and ↑OT responsivity = ↑observed positive parenting. The opposite was true for mothers with high ACES.
Boccia, Cook, Marson, & Pedersen, 2021	Adults, community sample (*N*=128; 91 F).	Retrospective. Parental history of divorce. Maternal/paternal care, indifference, abuse, and over-control/protective in childhood.	Urinary OT following questions about family and personal relationships.	Parental divorce, ↑maternal over-control/protective, ↑maternal abuse, ↑paternal indifference = ↓OT. Null relations with other parenting measures.	↑OT = ↑attachment anxiety, ↑discomfort with closeness, and ↓need for approval; ↓compulsive caregiving.
BASAL OT AND OT RESPONSIVITY IN BPD PATIENTS					
Bertsch, Schmidinger, Neumann, and Herpertz (2013).	Adults, female. Clinical sample (BPD; *n*=34); community-based control group (*n*=40).	Retrospective. Childhood history of emotional neglect/abuse	Basal plasma OT	↓OT.	↓OT = ↑BPD symptoms severity and aggressiveness.
Bomann et al. (2017)	Adults, female. Clinical sample (BPD, *n=18*); community-based control group (*n*=20).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Basal plasma OT	No significant relations with OT.	In the BPD group, ↑OT = ↑probability of being in a current romantic relationship.
Ebert, Edel, Gilbert, and Brüne (2018)	Adults, female. Clinical sample (BPD, *n=57*); community-based control group (*n*=43).	Retrospective. Recalled maternal and paternal emotional warmth, rejection/punishment, and control/over-protection	Basal plasma OT	In BPD patients, ↑maternal and paternal emotional warmth = ↑OT. Null relations with rejection/punishment and control/over-protection, and null effects in control group.	NA
Jobst et al. (2014)	Adults, female. Clinical sample (BPD, *n=22*); community-based control group (*n*=21).	Retrospective. History of childhood emotional/ physical abuse	Plasma OT at baseline and in response to a social exclusion manipulation	No significant relations with baseline OT. In the BPD group: ↑emotional/physical abuse = slower return of OT to baseline following social exclusion	NA
BASAL OT IN PATIENTS WITH MOOD DISORDERS					
Crowley, Pedersen, Leserman, and Girdler (2015)	Adults, female. Clinical sample (menstrually-related mood disorders, *n*=20). Healthy community-based control group (*n*=40)	Retrospective. Early sexual abuse.	Basal plasma OT	↑OT	Among women who experienced sexual abuse: ↑OT = ↓premenstrual somatic and psychological symptoms
Jobst et al. (2015)	Adults. Clinical sample (chronic depression, *n* = 21; 6 F). Healthy controls (*n* = 21; 6 F).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Basal plasma OT	No significant relations with basal OT.	
Kluczniok et al. (2019).	Adults, mothers. Clinical sample: depression history (*n* = 23) or BPD (*n* = 7); community-based control group (*n=22*).	Retrospective. History of childhood maltreatment (e.g., parental antipathy)	Basal Plasma OT	↑Parental antipathy = ↓ OT	OT unrelated to either BPD or depression.
Galbally et al. (2020)	Adults, mothers. Clinical sample: Depressed *n* = 41). Controls: Not-depressed (*n* = 162).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Basal plasma OT in early pregnancy, 3rd trimester, 6 mo. and 12 mo. postpartum	No significant relation with basal OT.	OT was unrelated to maternal depression.
BASAL OT AND OT RESPONSIVITY IN PATIENTS WITH TRAUMATIC STRESS-RELATED DISORDERS					
Olff et al. (2013)	Adults, African American, low-SES, high trauma exposure; 32% meet criteria for PTSD. *N*=88; 65 F.	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Basal plasma OT	↑OT	NA
Frijland et al. (2015)	Adults, male police officers. Clinical sample:	Retrospective. Childhood emotional abuse.	Basal salivary OT and AVP.	No significant relations with OT or AVP.	

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Table 2 (*continued*)

Study	Sample	Developmental stress exposure	OT Measure	Associations between DSE and OT measure[a]	Behavioral outcome
	PTSD patients (n = 21). Controls: healthy trauma-exposed police officers without PTSD (n = 20).				Controlling for emotional abuse, PTSD patients had lower OT levels than controls.
Pierrehumbert et al. (2010)	Adults. Clinic-based sample (sexual abuse, n=26, women only); hospital-referred sample (cancer, n=25; 13 F); community-based control group (n=29; 16F).	Retrospective. History of childhood sexual abuse (females only); history of childhood cancer (both sexes)	Plasma OT before, immediately after, and 20 min after TSST	History of sexual abuse: ↑plasma OT immediately before and after TSST; ↓Plasma OT 20 min after TSST. History of cancer: ↑plasma OT (all time points)	NA
BASAL OT IN PATIENTS WITH OTHER PSYCHOLOGICAL DISORDERS					
Chatzittofis et al. (2014)	Adults, clinical sample (suicide attempts; N=28).	Retrospective. Exposure to violence (childhood and adulthood).	Basal cerebrospinal fluid (CSF) and plasma OT	Neither child nor adult violence exposures related to OT. Revictimization (child + adult exposure) = ↓plasma OT but not ↓CSF OT.	NA
Fragkaki, Verhagen, van Herwaarden, and Cima (2019), Fragkaki, Glennon, & Cima, 2020). Separate samples.	Youth (ages 13–23), male (Ns=57 and 91). Living in residential care facility (referred for severe behavioral problems).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Basal Salivary OT	No main effects of abuse/neglect. Interaction effect only. Among youth with high callous-unemotional traits: ↑emotional neglect = ↑OT.	NA

Note. ATP, adenosine triphosphate. AVP, arginine vasopressin. BPD, borderline personality disorder. F, Female. GMV, gray matter volume. MDD, major depressive disorder. OT, oxytocin. PTSD, Post-traumatic stress disorder. SES, socioeconomic status. TSST, Trier Social Stress Test.

[a] Outcome of developmental stress exposure (higher early-life stress).

increased outgroup distrust (d = 0.21). A later meta-analysis of 66 fMRI studies (Wang, Yan, Li, & Ma, 2017) found that intranasal OT increased neural activity in social and emotional brain networks. Such effects could occur through two pathways: (1) Intranasal OT could enter the brain and mimic neurohormonal OT release, and/or (2) intranasal OT that does not enter the brain could act on OT and AVP receptors in the periphery (Leng & Ludwig, 2016).

A criticism of intranasal OT administration is that it exceeds endogenous levels (thus potentially altering or interfering with the evolved functions of the peptide). Researchers generally administer large doses of OT intranasally (ranging from 15 IU to more than 7000 IU in clinical studies; Bakermans-Kranenburg & van IJzendoorn, 2013), with only a tiny fraction of that reaching cerebrospinal fluid within 1 h (Leng & Ludwig, 2016). In the studies included in the current review, the range of variation was relatively limited, with dosages of exogenously administered OT ranging from 16 to 40 IU. Different dosages of intranasal OT have different effects on brain and behavior, but our understanding of such dose-response curves is currently limited (Quintana et al., 2021). Further, intranasal OT may not replicate the effects of endogenous OT, which are likely to vary according to emotional context, the specific brain regions affected, and potential individual differences in receptor availability or sensitivity. Finally, factors such as the metabolism of OT or the receptors that are stimulated by the peptide, especially in its exogenous form, are only now becoming apparent (Carter et al., 2020). At the same time, intranasal OT has notable advantages: it is easy to administer, has known effects on brain and behavior, its negative side-effects seem limited (MacDonald et al., 2011; Verhees et al., 2018), and the administered peptide stays in the system. Indeed, the physiological effects of intranasal OT can be clearly detected in salivary OT several hours after administration (Van IJzendoorn, Bhandari, van der Veen, Grewen, & Bakermans-Kranenburg, 2012). In addition, a meta-analysis revealed that participants were not able to guess whether they had received OT or a placebo (Van IJzendoorn & Bakermans-Kranenburg, 2012), thus providing the basis for genuine double-blind, placebo-controlled experiments. In total, intranasal OT has both limitations and strengths, which should be taken into account when considering its interactions with early life stress.

8. Assessment of childhood experience and exposures

As shown Tables 1-4, the studies included in the current review assessed childhood experiences and exposures in a variety of ways. The majority of the studies employed adult retrospective measures of the individual's early environment. Other studies prospectively or concurrently assessed developmental experiences and environmental exposures during childhood. Finally, other studies utilized case records (e.g. referrals to Child Protective Services [CPS], hospital records, institutional rearing). Comparison of results based on prospective versus retrospective reports of early life adversity is challenging, as it is now well-documented that these two sources of information are only weakly to moderately correlated (Baldwin, Reuben, Newbury, & Danese, 2019; Newbury et al., 2018; Reuben et al., 2016). Both prospective and adult retrospective accounts of adverse childhood experiences have been found to predict mental and physical health outcomes (Newbury et al., 2018; Reuben et al., 2016), though often in distinctive ways.

In the current review, adult retrospective studies employed tools such as the Childhood Trauma Questionnaire (CTQ) or Adverse Childhood Experiences scale (ACEs) to assess experiences of trauma, neglect, and abuse in childhood. Other studies used a variety of retrospective measures to assess more typical variation in potentially stressful parent-child processes, such as the Parental Bonding Inventory (which measures perceived maternal or paternal care) or measures of maternal love-withdrawal. The prospective studies also employed various measures of typical childhood experiences and exposures (e.g., maternal depression, insensitive parenting). Taken together, a strength of the set of publications included in the current review was the use of multiple methods to assess a variety of stressful early experiences and environmental exposures, ranging from typical to traumatic. That strength is also a limitation, however, because the variation in timing and type of childhood adversities means that the different studies are not directly comparable. This "apples and oranges" problem calls for additional caution when interpreting the results, albeit apples and oranges both belong to the class of fruit.

Table 3
Effects of early life stress on OXTR gene methylation in humans.

Study	Sample	Developmental stress exposure (DSE)	*OXTR*m measure	Associations between DSE and *OXTR*m measure[a]	Behavioral outcome
EFFECT OF EARLY LIFE STRESS ON *OXTRm* IN ADULTS					
Unternaehrer et al. (2015).	Adults. College students (*N*=85, 67 F).	Retrospective. Extreme groups design comparing low vs. high maternal care in childhood.	*OXTR*m in blood DNA in adulthood	↑*OXTR*m in one of two *OXTR* target sequences studied.	NA
Needham et al. (2015)	Adults. Middle-to-old age. Community sample (*N*=1231; 628 F).	Retrospective. Low socioeconomic status (maternal education).	*OXTR*m in purified monocytes	↑*OXTR*m in non-shore/shelf, non-promoter sites, but not in shore/shelf, promoter sites. ↑*AVP*m in non-promoter and shore/shelf sites. ↓*AVPm* in non-shore/shelf sites.	NA
Kimmel et al. (2016)	Adults, New mothers. Clinical sample: History of MDD or bipolar disorder (*N*=51; 43% developed PPD)	Retrospective. Childhood sexual abuse.	*OXTR*m in blood DNA (during pregnancy) in a region proximal to an estrogen receptor binding region	↑*OXTR*m, but only in women who did not develop PPD symptoms.	NA
Smearman et al. (2016).	African American adults, low SES, clinical sample. Recruited at clinics treating post-traumatic stress disorder (*N=393*; 279 F).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	*OXTR*m in blood DNA in adulthood	↑*OXTR*m in 2/18 CpG sites (not statistically significant after correction for multiple testing).	For CpG sites within exon 1 of *OXTR* promoter region: ↓methylation = ↑depression and anxiety in participants reporting abuse. For sites located in intron 3: ↑methylation = ↑depression and anxiety in participants reporting abuse.
Gouin et al. (2017).	Community sample, young adults. Longitudinal study (age 6–27; *N*=46; 23 F).	Prospective. Extreme groups methodology: Low SES (age 6–12, prospective) and high physical/sexual abuse in childhood (retrospective). Comparison group: high SES and low abuse.	*OXTR*m in blood DNA in adulthood (mean age 27)	No significant overall effect on *OXTRm.* In females (but not males): ↑early adversity = ↑*OXTRm* in one CpG site within the first intron.	In females (but not males): ↑*OXTR*m in one CpG site within the promoter = ↑childhood trajectories of anxiousness
Krause et al. (2018)	Adults, new mothers (3 months post-partum). Community sample (*N*=49).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	*OXTR* protein expression in peripheral blood mononuclear cells.	↓OXTR protein expression (consistent with ↑*OXTR*m)	Attachment insecurity in mothers = ↓OXTR protein expression
Womersley et al. (2019)	Adults. *N* = 63; 35 F). Clinical sample: Social anxiety disorder (70%). Control sample: No social anxiety disorder (30%).	Retrospective. History of emotional neglect.	*OXTR*m in whole blood DNA	No significant relation with *OXTR*m or amygdalar or hippocampal volumes.	N/A
Kogan, Bae, Cho, Smith, and Nishitani (2019, 2020); Brown, Kogan, and Cho (2020). Same sample.	African American men in rural South. Community sample. Longitudinal. (*N*=505; subsample of 192 fathers)	Prospective design. Retrospective history of childhood abuse/neglect (physical, sexual, and/or emotional). Current socioeconomic instability and contextual stress (ages 19–22). Father involvement (ages 22–25).	*OXTR*m in salivary DNA in adulthood (*M* = age 22; *N* = 358; *n* = 151 fathers).	Childhood abuse/neglect: no direct effect on *OXTR*m. Indirect effect: ↑Childhood abuse/neglect = ↑current socioeconomic instability = ↑*OXTR*m	↑*OXTR*m = ↓supportive romantic relationships, ↓father involvement. ↑Current contextual stress X ↑*OXTR*m = ↑defensive/ hostile relational schemas.
Gonzalez et al. (2020)	Adolescence (age 13) to adulthood (age 33). Community sample. Longitudinal (*N* = 184; 98 F).	Prospective. Neighborhood harshness, family harshness, parental abusiveness/ disorder (age 13).	*OXTR*m in blood DNA (ages 29–32; *n* = 112); reward anticipation fMRI paradigm (ages 23–27; *n* = 82)	No significant relations with *OXTR*m	Moderator effect: ↑*OXTR*m blunted association between ↑neighborhood harshness and ↑neural activation in anticipation of rewards.
Lesemann et al. (2020)	Young adult women. Community sample (*N* = *81*).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	OT gene methylation (*OXT*m) and *OXTR*m in salivary DNA. EEG responses to faces	Null relations with *OXT*m and *OXTR*m.	Abuse/neglect history interacted with *OXT*m and *OXTR*m to predict EEG responses to faces.
Robakis et al. (2020)	Pregnant women oversampled for history of depression (36%). Community sample (*N* = 54).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Buccal cell DNA. Large-scale analysis of methylation patterns across epigenetically active areas of genome, including *OXTR*.	Null relations with *OXTR*m.	NA
EFFECT OF EARLY LIFE STRESS ON *OXTRm* in CHILDREN					
Cecil et al. (2014).	Children (birth to age 13) with early-onset and persistent conduct problems. Community sample (*N*=339, 50% female).	Prospective (prenatal, birth to age 7, age 8–9). Five domains: stressful life events, contextual risks, parental risks, interpersonal risks, and direct victimization.	Cord blood *OXTR*m in newborns and blood *OXTR*m at age 7 and 9.	Multiple null effects across "risk" categories. For children high in internalizing problems: ↑parental risks (e.g., parental psychopathology, substance use) across developmental	For youth with low internalizing problems: ↑*OXTR*m at birth = ↓experience of victimization (birth to age 7) and ↑callous-unemotional traits (age 13).

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Table 3 (*continued*)

Study	Sample	Developmental stress exposure (DSE)	*OXTR*m measure	Associations between DSE and *OXTR*m measure[a]	Behavioral outcome
				periods = ↑*OXTR*m at ages 7 and 9.	
Moore et al. (2017).	Mother-infant dyads, community sample. Followed to age 4–5 (*N*=94, 39 girls).	Prospective. Extreme groups methodology: high vs. low physical contact with infant (based on maternal daily diary).	*OXTR*m in Buccal Epithelial Cell DNA (mean age 4.5)	No significant findings.	Low contact from caregiver: ↑infant distress.
King et al. (2017); Lecompte et al., 2021. MacKinnon et al. (2020). Same sample	Mother-child dyads. Community and clinical sample. Mothers over-sampled for depressive symptomology (*N*=218; 110 F children)	Prospective. Exposure to maternal depression (prenatal and postnatal). Maternal interactive behaviors with child (*M* age: 2.9 yr.; *N* = 161): sensitivity/responsiveness and positive structuring.	Child *OXTRm* in salivary DNA at 2.9 years of age.	No significant effects of maternal depression. ↑Maternal structuring behaviors = ↓*OXTR*m in child. No relation with maternal sensitivity.	↑*OXTR*m and ↓*AVP* intergene methylation in mothers = ↑perinatal depression symptoms in mothers. ↓*OXTR*m in child = ↑positive, cheerful behavior toward mother and ↑theory of mind among children whose mothers displayed ↑maternal structuring.
Krol, Moulder, Lillard, Grossmann, and Connelly (2019).	Mothers and infants (followed from 5 to 18 months of age). Community sample (*N*=101 dyads; 50 F infants).	Prospective. Low maternal engagement (behavioral observation of talkativeness, proximity, and attention) at 5 months of age.	*OXTR*m in salivary DNA in children at 5 and 18 months of age	↓Maternal engagement = ↑ change in *OXTR*m from 5 to 18 months. *OXTRm* was dynamic in infancy but relatively stable in motherhood.	↑*OXTR*m = ↑negative affectivity (e.g., discomfort, fear, sadness) at age 18 months.
Fujisawa et al. (2019).	Children and youth (aged 6–20 years). Clinical sample: recruited from hospitals and welfare facilities (*n* = 44; 17 F). Community-based comparison (*n*=41; 13 F).	Records-based. Child maltreatment (physical, emotional, sexual abuse, and/or neglect early in life); verified with hospital or welfare facility records.	*OXTR*m in blood DNA. Gray matter volume (GMV) in left orbitofrontal cortex (mean ages 11.4 and 14.5 yrs. for mal-treatment and control groups, respectively)	↑*OXTR*m at CpG 5,6 (with correction for multiple testing). ↓ GMV in orbitofrontal cortex.	↑*OXTR*m at CpG 5,6 = ↓ GMV in orbitofrontal cortex. ↓GMV mediated the relation between ↑*OXTR*m and insecure attachment style.

Note. *AVPm*, arginine vasopressin gene methylation. CpG sites, nucleotide sites where gene methylation commonly occurs. DSE, developmental stress exposure. F, female. EEG, electroencephalographic. GMV, gray matter volume. MDD, major depressive disorder. *OXTRm*, oxytocin receptor gene methylation. PPD, post-partum depression. PTSD, posttraumatic stress disorder

[a] Outcome of developmental stress exposure (higher early-life stress).

9. Overview

We conducted a systematic review of the empirical literature on the relations between childhood experiences and variation in the development/expression of OT system parameters in humans. Our goal was to quantitatively and qualitatively synthesize this body of research, extracting major themes relevant to understanding calibration of the OT-AVP system. The quantitative portion of our review involved a series of meta-analyses that tested three hypotheses regarding the effects of early adversity on OT system parameters: (1) higher levels of early adversity are associated with lower levels of endogenous basal OT (e.g., Donadon et al., 2018); (2) higher levels of early adversity are associated with higher levels of *OXTRm* (e.g., Kraaijenvanger et al., 2019); and (3) the positive effects of exogenously administered OT on biological and behavioral outcomes are reduced or absent in individuals with adverse childhood/caregiving experiences (Bakermans-Kranenburg & van IJzendoorn, 2013). The qualitative part of our review is based on the same research literature as the meta-analysis (though it includes a broader set of variables within that literature). Whereas the quantitative review focused on endogenous OT and *OXTRm* as outcomes of early adversity, and on early adversity as a moderator of exogenous OT, the qualitative review explores endogenous OT and *OXTRm* as mediators of early adversity, considering their role in regulating biological and behavioral outcomes.

The presentation of the Results is divided into 4 sections. The first two sections focus on endogenous OT. Given the important distinction between prospective and retrospective reporting of early adversity (discussed above), we divided the endogenous OT research literature into two categories: concurrent or prospective childhood studies (Table 1) and retrospective adult studies (Table 2). Within the studies on adults, two types of studies can be distinguished: (a) community-based studies, which generally excluded participants with diagnoses for psychological disorders, and (b) clinical samples, mostly case-controls studies, including patients with diagnoses for borderline personality disorder, major depressive disorder, or traumatic stress-related disorders. Community-based studies can be found in the upper part of Table 2, and studies on clinical samples are presented in the lower part of the table. The literature on childhood trauma and endogenous OT (in both children and adults) was recently meta-analyzed by Engel et al. (2019). That meta-analysis included $k = 16$ independent samples comparing endogenous OT in individuals with varying childhood trauma exposures. The current meta-analysis on the topic included $k = 40$ independent samples (Tables 1-2; $k = 9$ child samples, and $k = 31$ adult samples), encompassing stressful childhood experiences that ranged from typical to traumatic. The large number of studies in the current review allowed us to conduct moderator analyses to distinguish between the effects of early life stress in typical versus clinical populations, and to distinguish between the effects of typical versus more severe adverse childhood experiences. The third and fourth sections of the Results focus on relations between childhood adversity exposures and *OXTRm* (Table 3; $k = 15$ independent samples) and biological or behavioral responses to exogenously administered intranasal OT (Table 4; $k = 11$ independent samples). Neither of these literatures have been previously meta-analyzed.

10. Method

To be included in this systematic review, publications had to (a) report on stressful childhood experiences/exposures (birth to age 18; either prospectively or retrospectively), (b) include a measure of either endogenous OT, a biological or behavioral response to exogenously administered OT, or methylation/expression of the OT receptor, and (c)

Table 4
Effects of early life stress on biobehavioral responses to intranasal OT administration in humans.

Study	Sample	Developmental stress exposure (DSE)	Intranasal OT measurement context	Associations between DSE and effect of intranasal OT on biological outcomes	Associations between DSE and effect of intranasal OT on behavioral outcomes
RESPONSE TO INTRANASAL OT UNDER NEUTRAL CONDITIONS					
Meinlschmidt and Heim (2007).	Adult men. College students. Early parental separation (n = 9); control group: no parental separation (n = 10).	Retrospective. Parental relationship dissolution before age 13, resulting in prolonged separation from one parent.	Salivary cortisol response to intranasal OT (vs. placebo) administered at rest.	OT resulted in attenuated cortisol decreases in men who experienced early parental separation (relative to controls).	NA
Van IJzendoorn et al. (2011); Huffmeijer et al. (2012, 2013). Same sample	Adult women. College students (N = 57).	Retrospective. Extreme groups design. High vs. low reported history of maternal love withdrawal (withholding love/ affection following failure or misbehavior).	Effect of intranasal OT (vs. placebo) on (a) charitable donations and (b) neural processing of facial stimuli using event-related potentials (ERPs).	ERPs: OT increased attention to feedback stimuli (late positive potential) and enhanced the processing of emotional faces (vertex positive potential). OT enhanced processing of happy and disgusted faces primarily in women reporting lower love withdrawal.	Among women reporting high love withdrawal: OT did not affect charitable donations, while OT + greater relative right frontal brain activity reduced donations. Among women reporting low love-withdrawal: OT increased charitable contributions.
Ebert et al. (2013)	Adults. Clinical sample: BPD patients (n = 13, 8 F); healthy control group (n =13, 10 F).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Effect of intranasal OT (vs. placebo) on willingness to transfer money to others.	NA	In BPD patients (but not controls): ↑emotional neglect = ↓willingness to transfer money in response to OT.
Riem, van IJzendoorn, et al. (2013). Same sample as Bakermans-Kranenburg et al. (2012).	Adult women. Community sample (N = 44).	Retrospective. Maternal love withdrawal (withholding love/ affection following failure or misbehavior).	Effect of intranasal OT (vs. placebo) on resting state functional connectivity between various brain regions.	↓Functional connectivity between brain stem and posterior cingulate cortex (PCC). For women low in maternal love-withdrawal: OT = ↑functional connectivity between PCC, cerebellum, and postcentral gyrus.	NA
Riem, Bakermans-Kranenburg, et al. (2013), Riem, Bakermans-Kranenburg, Voorthuis, & van IJzendoorn, M. H., 2014). Bhandari, van der Veen, et al. (2014). Same sample.	Adult women. College students. *Ns*=54 and 102.	Retrospective. Maternal love withdrawal (withholding love/ affection following failure or misbehavior). Emotional abuse/neglect	Effect of intranasal OT (vs. placebo) on (a) desire to help an ostracized player in a social exclusion game, (b) neural activity during a theory of mind task (inferring mental states from the eyes), and (c) memory for infant cues (happy vs. sad facial expressions and vocalizations).	OT = ↑activation in the insula. OT = ↑activation in the superior temporal gyrus only in women who reported high maternal love withdrawal.	Only for women reporting low love-withdrawal: OT = ↑ball-throws to ostracized player. OT = ↑mind-reading abilities in the high love-withdrawal group, but ↓mind-reading performance in low love withdrawal group. Only for women reporting high abuse/ neglect: OT = ↓accuracy in remembering infant cues.
Feeser et al. (2014)	Adult men. Community sample (N = 82).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Effect of intranasal OT (vs. placebo) on emotional face recognition task.	NA	For men low in abuse/ neglect: OT = ↑recognition of avoidance-related emotions. No effects of OT on emotion recognition in men high on abuse/neglect.
Walsh et al. (2018).	Adult women. Clinical sample: premenstrual dysphoric disorder (N = 10); no control group.	Retrospective. History of childhood abuse (physical or sexual abuse prior to the age of 13)	Treatment response by women to repeated intranasal OT (vs. placebo) prior to menstrual onset.	NA	Following OT administration: ↑premenstrual emotional symptoms in women with abuse history; ↓premenstrual emotional symptoms in women without abuse history.
Riem et al. (2019); Schoormans, Kop, Kunst, and Riem (2020). Same sample	Adult women. College students (N = 180).	Retrospective. Maternal love withdrawal (withholding love/ affection following failure or misbehavior); history of childhood abuse/neglect	Effect of intranasal OT (vs. placebo) on (a) basal heart rate variability and (b) interpersonal distance (approaching a virtual person or stopping an approaching virtual person at a preferred distance). Virtual person displayed range of emotions (e.g., fear, disgust).	Following OT administration: reduced parasympathetic and sympathetic activity only in women with positive childhood rearing experiences; no effect in women with negative childhood experiences (love withdrawal/abuse-neglect).	Women with low maternal love withdrawal: OT = ↓interpersonal distance during active and passive approach; OT = ↓ anxiety, particularly when approached by person displaying disgust. No effects of OT in women with high maternal love withdrawal.
Schwaiger, Heinrichs, & Kumsta, 2019.	Adults, Community sample (N = 80, 54 F)	Retrospective. Extreme groups design. High vs. low reported history of childhood abuse/neglect	Effect of intranasal OT (vs. placebo) on theory of mind (inferring mental states	NA	Following OT administration: ↑emotion recognition (specifically of fearful/angry faces) in high

(*continued on next page*)

Table 4 (*continued*)

Study	Sample	Developmental stress exposure (DSE)	Intranasal OT measurement context	Associations between DSE and effect of intranasal OT on biological outcomes	Associations between DSE and effect of intranasal OT on behavioral outcomes
		(physical, sexual, and/or emotional)	from the eyes) and emotion recognition task.		abuse/neglect group; ↑mind-reading in all participants (first experiment only).
Perry-Paldi et al. (2019)	Adults. College students ($N = 84$, 42 female).	Retrospective. Number of negative events experienced during childhood. History of childhood maltreatment.	Effects of intranasal OT (vs. placebo) on detection of a picture of an act of infidelity or of a threat to personal safety (out of a matrix of pictures).	NA	Following OT administration: ↑accuracy in detecting acts of infidelity only in participants with low levels of early life stress. No change in accuracy in detecting safety threats.
Fragkaki and Cima (2019)	Male youth ($N = 100$; *M*age = 16.50 yrs). Living in residential care facility (referred for severe behavioral problems).	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Effects of intranasal OT (vs. placebo) on empathy and emotion recognition.		Abuse/neglect did not moderate the effect of OT administration on empathy or emotion recognition
RESPONSE TO INTRANASAL OT UNDER MANIPULATED EXPERIMENTAL CONDITIONS					
Bakermans-Kranenburg et al. (2012). Same sample as Riem, van IJzendoorn, et al. (2013).	Adult women, nulliparous. Community sample ($N = 42$).	Retrospective. Harsh discipline (parent-to-child physical and verbal aggression) during childhood.	Effect of intranasal OT (vs. placebo) on handgrip force in response to infant crying and infant laughter.	NA	In women not reporting harsh discipline: OT = reduced handgrip force in response to infant crying. No change in handgrip force (OT vs. placebo) in women not reporting harsh discipline.
Grimm et al. (2014); Fan et al. (2015)	Adult men. Community sample ($N = 32$)	Retrospective. Extreme groups design. High vs. low reported history of childhood abuse/neglect (physical, sexual, and/or emotional)	Effect of intranasal OT (vs. placebo) on salivary cortisol reactivity, amygdala-hippocampal connectivity, and deactivation of limbic regions involved in stress responsivity (e.g., hippocampus) during an arithmetic-based stress test.	Following OT administration: ↑Limbic deactivation, ↓amygdala-hippocampal connectivity, and ↑cortisol reactivity in men with ↑child abuse/neglect history, but the opposite in men with ↓abuse/neglect history	NA
Maier et al. (2020)	Adults, Community sample ($N = 58$, 30 F)	Retrospective. History of childhood abuse/neglect (physical, sexual, and/or emotional).	Effect of intranasal OT (vs. placebo) on changes in neural reactivity and connectivity during exposure to stress-related vs. sport-related odors in sweat.	Stress-related odor (vs. sport odor) increased amygdala activation in placebo but not OT condition; this stress-specific attenuating effect of OT was stronger in participants reporting higher abuse/neglect.	
Riem, Kunst, Bekker, Fallon, & Kupper, 2020. Same sample as: Riem et al. (2019); Schoormans et al. (2020).	Adult women. College students ($N = 180$).	Retrospective. History of childhood abuse/neglect; insensitive disciplinary parenting (love-withdrawal).	Heart rate variability, salivary cortisol, and state anxiety in response to intranasal OT (vs. placebo) and social support (vs. non-support) from friend during virtual TSST	In all participants: OT administration + social support = ↓heart rate variability during TSST, ↓anxiety and ↓cortisol before and after TSST.	Following OT administration: reduced anxiety and cortisol levels during TSST recovery, but only in women with higher reported childhood adversity who received support from a friend.

Note. BPD, borderline personality disorder. DSE, developmental stress exposure. ELA, early life adversity. F, Female. OT, oxytocin. PCC, posterior cingulate cortex. TSST, Trier social stress test.

evaluate the association between a and b. Although AVP is hypothesized to also be integrally involved in developmental programming, there was not adequate human research to include AVP in this review. Given our interest in adaptive calibration, we included challenging childhood experiences and exposures that ranged from typical (e.g., insensitive parenting) to extreme (e.g., child maltreatment). We excluded studies that employed adult attachment style (e.g., insecure attachment) as the indicator of early life stress, that focused exclusively on prenatal stress, or that focused on *OXT* or *OXTR* gene polymorphisms as the indicator of OT system functioning. We also excluded non-human animal studies. We reviewed only quantitative research studies published in journals and dissertations. Qualitative studies, case studies, book chapters, conference abstracts, and unpublished works were excluded.

Two researchers (AH and BE) searched the electronic databases Google Scholar and PubMed for key terms (i.e., adverse childhood experiences, child maltreatment, childhood trauma, neglect, abuse, or early life stress with oxytocin or oxytocin receptor methylation). Any divergences that occurred regarding publications meeting inclusion criteria were discussed until consensus was reached. Our last search was completed on 11/14/2020. To determine article eligibility, we first screened article titles, then if warranted read article abstracts, then if warranted read full texts. For articles that met inclusion criteria, we conducted forward citation searches (by screening papers that cited the identified articles) and backward citation searches (by screening the reference lists of the identified articles). We also conducted backward citation searches on published reviews. The search strategy was somewhat atypical insofar as its goal was to comprehensively locate eligible publications through citation searches (i.e., we identified all eligible publications that either cited or were cited by other eligible publications); as such, we do not have a flow chart with specific numbers of publications screened and eliminated in various steps. This process resulted in a total of 89 publications that met inclusion criteria (88

journal articles plus 1 dissertation). Two publications were subsequently eliminated because they employed samples of cocaine or heroin addicts (Flanagan, Baker, McRae-Clark, Brady, & Moran-Santa Maria, 2015; Gerra et al., 2017); OT is known to play a role in susceptibility to addiction (Bowen & Neumann, 2018; Buisman-Pijlman et al., 2014), and opioids have been found to interfere with OT function (Daigle et al., 2020). A third publication (Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005) was eliminated due to apparent errors in the urinary OT analyses (Anderson, 2006). Thus, the final sample included 86 publications (as presented in Tables 1–4) that were included in the qualitative analysis. Those publications reported on 66 unique samples with pertinent variables to be included in the meta-analyses.

Moderator extraction was performed by all co-authors. The following details regarding methodology and results were extracted from each article: sample size; sample attrition; sample characteristics (participant age, % female, country, ethnicity, socioeconomic status, adult vs. child participants, community vs. clinical sample); whether the sample encompassed a high degree of childhood adversity exposure; study design (prospective, concurrent, or retrospective); type of developmental stress exposure (e.g., parental psychopathology, insensitive parenting, physical maltreatment, emotional neglect, sexual abuse, institutional rearing, wartime exposure); measurement reliability of the developmental stress exposure measure; the measured OT system component (endogenous OT, *OXTRm*, or a biological/behavioral response to exogenous OT); endogenous OT specimen (saliva, plasma, urine, or cerebrospinal fluid); measurement of OT analytes (immunoassay vs. mass spectrometry, with or without prior sample extraction); whether endogenous OT was assessed at a resting state (unstimulated) or in response to environmental stimulation; mean endogenous OT levels (pg/ml) and standard deviations; *OXTRm* specimen (blood DNA vs. salivary or buccal cell DNA); exogenous OT dosage (IU); and any reported behavioral correlates of variation in the measured OT parameter. Effect size extraction (association between developmental stress exposure and the measured OT system component) and whether the effect size was computed or had to be estimated (e.g., only reported as non-significant) was based on consensus between two authors (MJB-K and MHvIJ). Intercoder reliabilities for effect size, sample size and moderator coding were adequate, with a mean of .89 ($k = 15$, kappa and ICC, single measurement, exact agreement).

11. Results

11.1. Effects of childhood adversity on endogenous OT in children (Table 1)

The first meta-analysis aimed to evaluate the hypothesis that higher levels of early adversity are associated with lower levels of endogenous basal OT in children. The meta-analysis was based on 11 eligible publications (Table 1) reporting on $k = 9$ independent samples (see Figure 1 for a forest plot) with 17 effect sizes.[1] The 9 samples included $N = 623$ participants (with *N*s ranging from 35 to 149). Because effect sizes were nested within studies, a multilevel random effects model was tested using the metafor and dmetar packages in R (Assink & Wibbelink, 2016; Harrer et al., 2019) to determine whether the levels for both within and between study variations were required for the computation of the combined effect size and for moderator analyses. The Hartung-Knapp adjustment of confidence intervals for random effects models was applied, and the method to estimate tau-square was the restricted maximum likelihood (REML) approach (see Assink & Wibbelink, 2016).

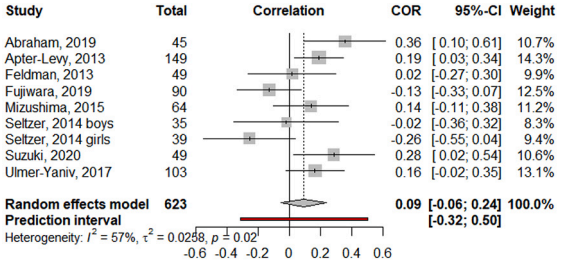

Fig. 1. Effect sizes for the association between adverse childhood experiences and basal OT levels in children.
Note: In case of overlapping samples, one publication is referred in the figure but data from the various publications were included (i.e., the effect size in the figure for Apter-Levy et al., 2013 is also based on Priel et al., 2019 and Pratt et al., 2015; and the effect size for Ulmer-Yaniv et al. (2018) is also based on Yirmiya et al., 2020).

The model without the within-study level showed an equivalent fit compared to the full model (full model: df = 3, AICc = −6.688, loglik = 7.344; reduced model: df = 2, AICc = −9.765, loglik = 7.344; LRT = 0.00, $p = .99$), thus analyses were conducted with the model only including the between-study level. Results within studies were combined using a random effects model. The combined effect size of the 9 studies was $r = .091$ (95% CI -.057, .239; $t = 1.42$, $p = .193$), with a 95% prediction interval (PI) of -.318, .500. Across the full set of studies, the hypothesis that higher levels of early adversity would be associated with lower levels of endogenous basal OT was not supported. The set of studies was heterogeneous, $Q(8) = 18.76$, $p = .016$. Only one effect size had to be estimated, thus the moderating effect of estimation of effect size could not be tested. Because the combined effect size was non-significant, a test for publication bias was not conducted.

Two studies used urine samples for OT assessment. The set of seven studies without these controversial urine samples showed a combined effect size of $r = .142$ (95% CI -.0036, .290; 95% PI: -.221, .504), $t = 2.34$, $p = .058$. The only study using blood had an effect size of $r = .137$ (95% CI -.105, .379), very similar to the combined effect size of the six studies using saliva ($r = .143$, 95% CI -.041, .326). Extraction was only done in the urine studies, and thus did not affect effect sizes in studies using blood or saliva. All studies used immunoassay to measure OT. Overall, we did not find clear evidence for our hypothesis that more early adversities predict lower levels of basal OT in children. However, in the sub-set of studies excluding the urine samples, there was a combined effect size in the expected direction ($r = .142$); greater early adversity exposure was (non-significantly) associated with lower OT.

The moderation test for clinical groups (including participants in residential care or with documented child maltreatment) versus nonclinical groups (participants living with their families in community settings who did not have documented maltreatment histories) showed a non-significant contrast, $Q(1) = 0.26$, $p = .61$. The set of five non-clinical samples showed a combined effect size of $r = .119$, (95% CI −0.105, 0.342), and in the set of four clinical samples the combined effect size was $r = 0.046$ (95% CI −0.323, 0.417). Because all clinical samples had also experienced more severe childhood adversity, a separate moderator test for type of adversity was impossible. The continuous moderators child age at OT assessment ($p = .960$) and gender distribution of the sample ($p = .910$) were not significant.

If the largest study with the most precise effect estimate (in terms of the confidence and prediction intervals, although not necessarily in terms of quality and validity) is taken as a criterion, the study of Apter-Levy et al. (2013; $N = 149$; $r = .19$) might serve as a plausibility check for the meta-analytic result (inspired by Slavin, 1995). The 95% CI (−0.105, 0.342) of the meta-analytic combined effect size for non-clinical groups ($r = .119$) encompasses this effect size, showing convergence between the two estimates. Thus, there is some basis for the suggestion that more adversity predicts lower OT levels, specifically in nonclinical child studies.

[1] Note that Table 1 shows 12 publications. One study (Nawa et al., 2020) met eligibility criteria but was not included in the meta-analysis because it exclusively assessed relations between early life stress and OT responsivity in children.

Most studies shown in Table 1 prospectively assessed early life adversity in children. These studies are important for consideration of OT within a developmental programming framework. Prospective studies that begin in childhood enable longitudinal testing of OT as mediating mechanism in the relations between developmental stress exposures and later behavioral outcomes. Although the data did not allow for a meta-analytic combination of the studies, we provide a narrative summary here.

Across the non-clinical studies, there appeared to be some evidence that lower levels of OT may partially mediate the effects of stressful family and ecological conditions on the development of more anxious and less prosocial phenotypes. Ulmer-Yaniv et al. (2018; see also Yirmiya et al., 2020) found that lower maternal sensitivity predicted lower child OT, which in turn predicted more child anxiety symptoms. Priel, Djalovski, Zagoory-Sharon, and Feldman (2019); see also Apter-Levy et al., 2013) also found that lower maternal sensitivity predicted lower child OT, which in turn predicted lower child engagement, which in turn was associated with more internalizing (and externalizing) behaviors. In the same sample, chronic maternal depression predicted lower child OT responsivity, which in turn predicted greater child social withdrawal (Pratt et al., 2015). Abraham, Hendler, Zagoory-Sharon, and Feldman (2019) found that lower parental sensitivity was associated with lower child OT, which in turn was marginally associated with more somatic symptoms (e.g., headaches, pain). Finally, Feldman, Gordon, Influs, Gutbir, and Ebstein (2013) found that reductions in parental caregiving were associated with lower child OT (when mothers were homozygous for the CD38 C allele), and that these children's lower OT predicted reduced social reciprocity. Although not all of these studies formally tested for mediation, the evidence suggests that OT may be a mechanism through which low parental support increases internalizing behaviors and reduces social engagement and connection. Given that the research reported here is all from one laboratory (Ruth Feldman's) and may not be replicable or generalizable, the proposed mediating role of OT should be considered a hypothesis rather than a conclusion. For the first step of the mediation model, the association between exposure (adversities) and outcome (basal OT), the meta-analytic results show a promising but not (yet) significant combined effect size, particularly in non-clinical studies and in studies that did not analyze OT analytes in urine. Thus, at this point in time, mediation is an attractive hypothesis in search of independent replications with more statistical power.

11.2. Effects of childhood adversity on endogenous OT in adult samples (Table 2)

This second meta-analysis aimed to evaluate the hypothesis that higher levels of early adversity are associated with lower levels of endogenous basal OT in adults. The meta-analysis was based on 34 publications (Table 2) reporting on $k = 31$ independent samples (see Figure 2 for a forest plot) with 98 effect sizes. The 31 samples included $N = 2495$ participants (with Ns ranging from 15 to 352). A multilevel random effects model was used again to test whether both the levels for within and between study variation were required. The model without the within-study level showed an equivalent fit compared to the full model (full model: df = 3, AICc = −83.36, loglik = 44.81; reduced model: df = 2, AICc = -.83.89, loglik = 44.01; LRT = 1.60, $p = .21$), allowing for analyses with the reduced model only including the between-study level. Results within studies were combined using a random effects model.

The combined effect size for the association between childhood adversity and OT levels in adults was $r = .048$ (95% CI: -.018, .113; $t = 1.49$, $p = .147$). The 95% PI was -.257, .352. The set of outcomes was heterogeneous: $Q(30) = 68.82$, $p < .001$. Eight effect sizes had to be estimated, but this did not affect the combined effect significantly, $Q(1) = 2.16$, $p = 0.142$. Because the combined effect size was non-significant, a test for the presence of publication bias was not conducted.

As shown in Table 2, the 31 samples included both non-clinical groups (community samples, which generally excluded participants with diagnoses for psychological disorders) and (partially) clinical groups (mostly case-control studies, in which cases had diagnoses for specific psychological disorders). The clinical samples involved mood disorders, borderline personality disorder, and traumatic stress-related disorders. Early adversity may play a role in the onset of these psychological disorders, which could in turn influence OT (Bakermans-Kranenburg & van IJzendoorn, 2013). We thus distinguished between non-clinical and (partially) clinical groups.

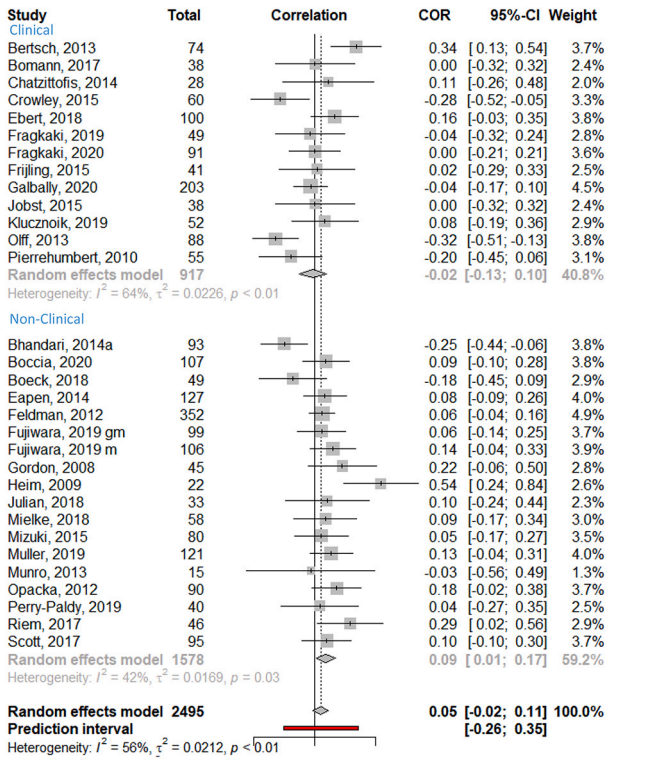

Fig. 2. Effect sizes for the association between childhood adversity and adult basal OT levels in non-clinical and clinical groups.
Note: In case of overlapping samples, one publication is referred in the figure but data from the various publications were included (i.e., the effect size for Boeck, Gumpp, et al., 2018, Boeck, Krause, et al., 2018 is also based on Krause et al., 2018; the effect size of Opacka-Juffry & Mohiyeddini, 2012 is also based on Mohiyeddini et al., 2014).

The set of $k = 13$ studies including (partially) clinical groups showed a combined effect size of $r = -0.016$ (95% CI −0.130, 0.096), $t = -0.31$, $p = .759$, whereas the set of $k = 18$ studies on non-clinical groups showed a significant combined effect size of $r = .091$ (95% CI 0.012, 0.170), $t = 2.43$, $p = .026$. The moderation test for clinical versus nonclinical groups showed a non-significant contrast, $Q(1) = 2.79$, $p = .095$, thus the difference between these two combined effect sizes was not significant. However, the effect size in the non-clinical groups suggests that greater childhood adversity is associated with lower OT in adults, while in the clinical samples this association is absent. Degree of adversity did not moderate the effect size, neither in the total set of studies, $Q(1) = 1.01$, $p = .316$, nor in the set of studies on non-clinical samples, $Q(1) = 0.12$, $p = 0.725$. Excluding the two studies with urine, the combined effect size for $k = 29$ studies was $r = .046$ (95% CI −0.024; 0.116), 95% PI −0.274, 0.366. Within this set of 29 studies, the moderation test for clinical versus nonclinical groups showed again a non-significant contrast, $Q(1) = 2.68$, $p = .101$. The set of $k = 16$ non-clinical, not urine-based studies showed a combined effect size of $r = .094$ (95% CI 0.003, 0.185), and in the set of $k = 13$ (partially) clinical studies the combined effect size remained $r = -0.016$ (95% CI −0.130, 0.098).

For descriptive purposes we computed the combined effect sizes for the two psychiatric disorders, borderline personality disorder (BPD) and mood disorders, for which there were multiple studies. For the three studies on BPD patients, the combined effect was r = .191 (95% CI −0.204, 0.586), and for the four studies on mood disorders the combined effect size was r = -.066 (95% CI -.309, 0.177). Borderline patients showed one of the largest point estimates for the association between adversity and lower basal OT. This is a promising hypothesis, but the number of studies is very small. With more and larger studies (hopefully done in the near future), a robust and significant effect might emerge.

In the total set of 31 studies, the use of extraction to assess OT levels ($Q(1)$ = 0.40, p =.530), the specimen (saliva, blood, urine, or CSF, moderator tested without sub-sets with $k < 4$ studies, $Q(1) = 0.05$, p = .818), and assay ($Q(1)$ = 0.02, p = .890) did not moderate the effect sizes. Within the various sub-sets of studies no combined effect size was significant. The continuous moderator sex (percentage of females in the samples) did not predict variation in effect sizes (p = .426), and the same was true of age at OT assessment (p = .272). Notably, virtually no study reported participant's age at experiencing adversity, so any potential effect of sensitive time windows on endogenous OT levels in adulthood could not be tested.

If the largest study's effect estimate is taken as a criterion, the study of Feldman et al. (2012; N = 352; r =.06 based on the two predictors reported in the study) might serve as a plausibility check for the meta-analytic result. Clearly the meta-analytic combined effect size for non-clinical groups, r = .091, converges with this estimate. Thus, there is some reason to believe that more adversity predicts lower OT levels but only in nonclinical participants.

11.3. Effects of childhood adversity on OXTR methylation (Table 3)

The third meta-analysis aimed to evaluate the hypothesis that higher levels of early adversity are associated with higher levels of *OXTRm*. This meta-analysis was based on 18 publications (Table 3) reporting on k = 15 independent samples (see Figure 3 for a forest plot) with 32 effect sizes.[2] Across these studies, there was little standardization of specific CpG sites within the *OXTR* CpG island targeted for methylation analyses, reflecting a lack of consensus in the field regarding which sites may be of functional significance. Studies ranged from targeting on one or two CpG sites (e.g., Gonzalez et al., 2020) to as many as 151 different CpG sites (Robakis et al., 2020), with each study further differing in how and if multiple CpG sites were clustered into methylation blocks for data analysis. This measurement variation resulted in an "apples and oranges" problem that constrained the current meta-analysis. For example, targeted CpG sites were too variable to group together for moderation analyses. Here we do not distinguish between different CpG sites targeted in different studies; instead, we analyze methylation density at whatever CpG sites were targeted, focusing on average methylation across those sites (e.g., if 18 CpG sites were separately analyzed, then we computed the average effect of early adversity on *OXTRm* across those 18 sites). The heterogeneity in CpG sites warrants caution in interpreting the results.

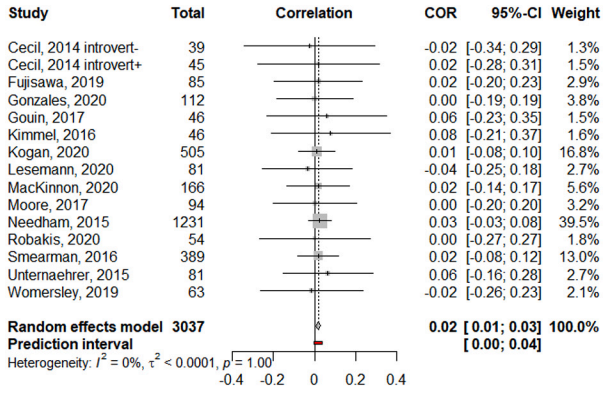

Fig. 3. Effect sizes for the association between childhood adversity and *OXTR* methylation.

Note: In case of overlapping samples, one publication is referred in the figure but data from the various publications were included (i.e., the effect size in the figure for MacKinnon et al., 2020 is also based on King et al., 2017). Kogan et al., 2020 overlaps with Kogan et al., 2019 and Brown et al., 2020.

The 15 samples included N = 3037 participants (with Ns ranging from 39 to 1231). Effect sizes were nested within studies. Thus, again, a multilevel random effects model was used to determine the levels required for the computation of the combined effect size and for moderator analyses. The model without the within-study level did show an equivalent fit compared to the full model (full model: df = 3, AICc = −55.47, loglik = 31.18; the reduced model: df = 2, AICc = -.57.93, loglik = 31.18; LRT = 0.00), so analyses were conducted using the reduced model with only the between-study level. Results within studies were combined using a random effects model. The combined effect size was r = .018 (95% CI .008, .028; t = 3.75, p = .002). The 95% PI was -.001, .037. The set of studies was homogeneous: $Q(14) = 0.94$, p = .99. Six effect sizes had to be estimated, but this did not affect the combined effect significantly, $Q(1) = 0.26$, $p = 0.614$. To examine publication bias, Eggers' test did not indicate the presence of funnel plot asymmetry (t = −0.637, p = 0.535).

Type of study design—whether childhood adversity was assessed in childhood (prospectively) or in adulthood (retrospectively)—showed a non-significant moderation effect, $Q(1)$ = 1.56, p = .212. The comparison of clinical versus non-clinical studies yielded a $Q(1) = 0.00$, p = .96. For the 11 non-clinical studies the combined effect size amounted to r = .018 (95% CI .006, .030), whereas the set of 4 clinical studies showed a combined effect of r = .017 (95% CI -.022, .057). Degree of childhood adversity did not moderate the effect size either, $Q(1) = 0.99$, p = .321. The continuous variables age at methylation assessment (p = .195) and sex distribution of samples (p = .656) were not significant moderators. Specimen (blood versus saliva or buccal cells) did significantly moderate methylation pattern, $Q(1) = 3.88$, p = .049. The ten studies using blood showed a combined effect size r = .023 (95% CI .010, .036), whereas the five studies using saliva or buccal cells showed a combined effect size r = .006 (95% CI -.013, .025). Assessed in blood, methylation was higher in participants with higher levels of childhood adversities.

Consistent with the results of the meta-analysis, several studies reported trend findings (documenting associations between childhood adversity exposures and heightened *OXTRm* in one or more target CpG sites) that, after correction for multiple testing, dropped below the threshold of statistical significance. For example, Smearman et al. (2016) detected increased methylation in 2 out of 18 CpG sites (analyzed as 5 methylation blocks), but the effect did not survive correction for multiple testing. The two CpG sites where the effect was detected closely aligned with the specific sites that were significant in another study (Unternaehrer et al., 2015). Both of these studies examined *OXTRm* in a similar region of exon 3 of the *OXTR*. Despite this convergence, it should be noted that each study in the meta-analysis operationalized *OXTRm* in different way, often without strong theoretical guidance, potentially opening the door to selective reporting and false positives. Having said that, a very small but statistically significant combined effect size emerged in the meta-analysis, indicating greater methylation among individuals with more childhood adversity.

Finally, several studies reported in Table 3 showed relations between *OXTRm* and relevant phenotypic outcomes (e.g., attachment insecurity,

[2] Note that Table 3 shows 20 publications. One study (Krause et al., 2018) assessed expression of the OT receptor protein, rather than OT receptor methylation. Another study (Krol et al., 2019) examined change in *OXTRm* over time. Neither of these studies were included in the meta-analysis.

developing supportive romantic relationships, experiences of depression and anxiety, theory of mind), which we were unable to meta-analyze. The studies highlight the potential role of *OXTRm* as an intervening mechanism through which early life adversity calibrates social and behavioral outcomes. However, the results of the current meta-analysis provide only modest support for such a mediation hypothesis because, to establish a mediating role between exposure and outcome, the first step from exposure to mediator needs to be substantial as mediation is the product of the two pathways. Our combined effect size for the first step was very small, but at least it was in support of the hypothesis that greater early adversity is associated with greater *OXTRm,* particularly in the set of studies that assessed DNA methylation in blood.

The largest sample in the set of methylation studies was Needham et al. (2015; $N = 1231$; see the forest plot in Figure 3), which found a significant beta of .025, which converges with the overall combined effect size in this set of *OXTRm* studies. Whereas Needham et al. (2015) studied a sample of middle-to-old age adults who had grown up under widely varying socioeconomic conditions (reported retrospectively), a recent cohort study (Dall 'Aglio et al., 2020; $N = 235$) employed a sample of 6-year old children living under less variable socioeconomic conditions in the Netherlands. Dall' Aglio et al. (2020), which was published after we finished our literature search, found no nominal or corrected significant *p*-value for the associations between prospectively observed parental (in-)sensitivity and methylation at 18 *OXTRm* loci.

11.4. Effects of early life stress on response to intranasal OT (Table 4)

The fourth and final meta-analysis aimed to evaluate the hypothesis that the positive effects of exogenously administered OT on biological and behavioral outcomes are reduced or absent in individuals with adverse childhood/caregiving experiences. This meta-analysis was based on 21 publications (Table 4) reporting on 13 independent samples. This group of studies employed mostly community samples ($k = 10$; i.e., healthy participants with a range of early life stress experiences), some clinical samples with diagnoses for psychological disorders ($k = 2$), and an institutionalized sample ($k = 1$). Although exogenous OT can be administered intravenously or intranasally, all of the studies included in the meta-analysis relied on intranasal administration. All studies further employed a randomized, placebo-controlled design, with varying dosages of OT. The outcome variables in this research ranged from physiological measures (e.g., heart rate variability, changes in cortisol) to neural measures (e.g., limbic deactivation, changes in functional connectivity between brain regions) to prosocial behavior (e.g., charitable donations, promoting social inclusion) to social skills (e.g., emotional recognition, mind-reading ability, ability to detect infidelity) to emotional symptoms (e.g., anxiety, anger/irritability).

For the meta-analysis, we determined, within each of the studies, the effects of OT administration in two subgroups: higher early adversity and lower early adversity (typically determined by a median split). This could be done in all but two studies (Ebert et al., 2013; Maier, Heinen-Ludwig, Güntürkün, Hurlemann, & Scheele, 2020); these two studies only reported early adversity as a continuous variable in the interaction with condition (OT or placebo), thus preventing the computation of effect sizes in two subgroups. For all other studies, including $k = 11$ independent samples (see Figure 4 for a forest plot) with 40 effect sizes, separate effects for the high- and low-adversity subgroups could be computed. The 11 studies included $N = 1164$ participants (*N*s ranging from 10 to 180). Because effect sizes were nested within subgroups within studies, a four-level multilevel random effects model was used to test whether the three levels for within and between study variance were required for a valid computation of the combined effect size and for moderator analyses (Pastor & Lazowski, 2018). The Hartung-Knapp adjustment of confidence intervals for random effects models was applied, and the method to estimate tau-square was the restricted maximum likelihood (REML) approach (see Assink & Wibbelink, 2016).

The model without the within-study *subgroup* level showed an equivalent fit compared to the full model with all levels (full model: df = 4, AICc = 4.350, loglik = 1.825; reduced model: df = 3, AICc = 4.358, loglik = 0.821; LRT = 2.008, $p = .157$). Therefore, it was not necessary to differentiate subgroups within studies, enabling us to test subgroups (adverse childhood experiences versus comparison) as a moderator. The model without the within-study *outcomes* level did however show a worse fit compared to the full model (reduced model: df = 3, AICc = 6.622, loglik = −0.311; LRT = 4.722, $p = .039$). The model without both the sub-group level and the study level did not show a worse fit compared to the full model (reduced model: df = 2, AICc = 2.770, loglik = o.694; LRT = 2.263, $p = .323$). Thus, only the level of outcomes had to be retained in further analyses. The combined effect size of the 80 effect sizes reported in the 11 independent studies was a significant $r = .064$ (95% CI: .007, .122; $t = 2.23$, $p = .029$). The 95% PI was -.445, .574. The set of studies was heterogeneous: $Q(79) = 5146.43$, $p < .001$.

Note however that this $r = .064$ is the combined effect size for the effect of OT administration on neural, hormonal, or behavioral outcomes independent of adverse childhood experiences. The main hypothesis for the administration studies focused on the moderating effect of childhood adversities. The moderator test revealed a nonsignificant $Q(1) = 3.62$, $p = .057$. For the set of outcomes in subgroups with higher childhood adversity, the combined effect size was $r = .011$ (95% CI -.067, .090, $p = .772$), whereas the comparison groups with lower childhood adversity showed a significant combined effect size of $r = .119$ (95% CI .036, .202, $p = .006$). As stated above, our general hypothesis was that low adversity would facilitate more positive intranasal OT effects. This seemed to be the case: lower (or absent) childhood adversity facilitated the positive effects of intranasal administration of OT, whereas in the high adversity participants such an effect could not be observed. That is, participants who reported relatively high levels of early life stress, usually operationalized as poor parental caregiving or a childhood history of abuse/neglect, either failed to show a positive response or displayed a negative response to intranasal OT. It should be noted, however, that the moderator—and thus the difference between the two effect sizes—was not statistically significant.

The following illustrates what is meant by failing to show a positive response or displaying a negative response to intranasal OT. After receiving exogenous OT, participants with a history of childhood/caregiving adversity: (1) did not behave in a more prosocial manner: no increase in charitable donations (Huffmeijer, Alink, Tops, Bakermans-Kranenburg, & van IJzendoorn, M. H., 2012; Van IJzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011) or money transfer to a recipient (Ebert et al., 2013), no increased effort to socially include an ostracized participant in a game (Riem, Bakermans-Kranenburg, Huffmeijer, & van IJzendoorn, M. H., 2013); (2) displayed equal or worse socioemotional skills: no increase in performance on an emotion recognition task (Feeser et al., 2014), reduced accuracy in remembering infant faces (Bhandari, van der Veen et al., 2014); (3) experienced more negative premenstrual emotional symptoms (Walsh et al., 2018); (4) maintained levels of negative social behavior: no decrease in interpersonal distance to a stranger (Riem et al., 2019), no decrease in handgrip force exerted in response to infant crying or laughter (Bakermans-Kranenburg, van IJzendoorn, Riem, Tops, & Alink, 2012); (5) did not downregulate activity of HPA axis: more attenuated cortisol decreases (Meinlschmidt & Heim, 2007), increased cortisol (Fan et al., 2015) and cortisol reactivity (Grimm et al., 2014); and (6) experienced less socially desirable neurobiological changes: reduced functional connectivity between brain regions (Fan et al., 2015; Riem et al., 2013), increased limbic deactivation (Grimm et al., 2014). All of these findings were in contrast to individuals who reported more supportive caregiving experiences in childhood and/or low levels of abuse/neglect.

It should be noted that for the total set of study outcomes, type of design (between- or within-subjects) or OT dose did not explain a significant part of the variance in effect sizes. Other variables might be important in moderating the effect of childhood adversity on the effects of OT administration on neural, hormonal, or behavioral outcomes. We

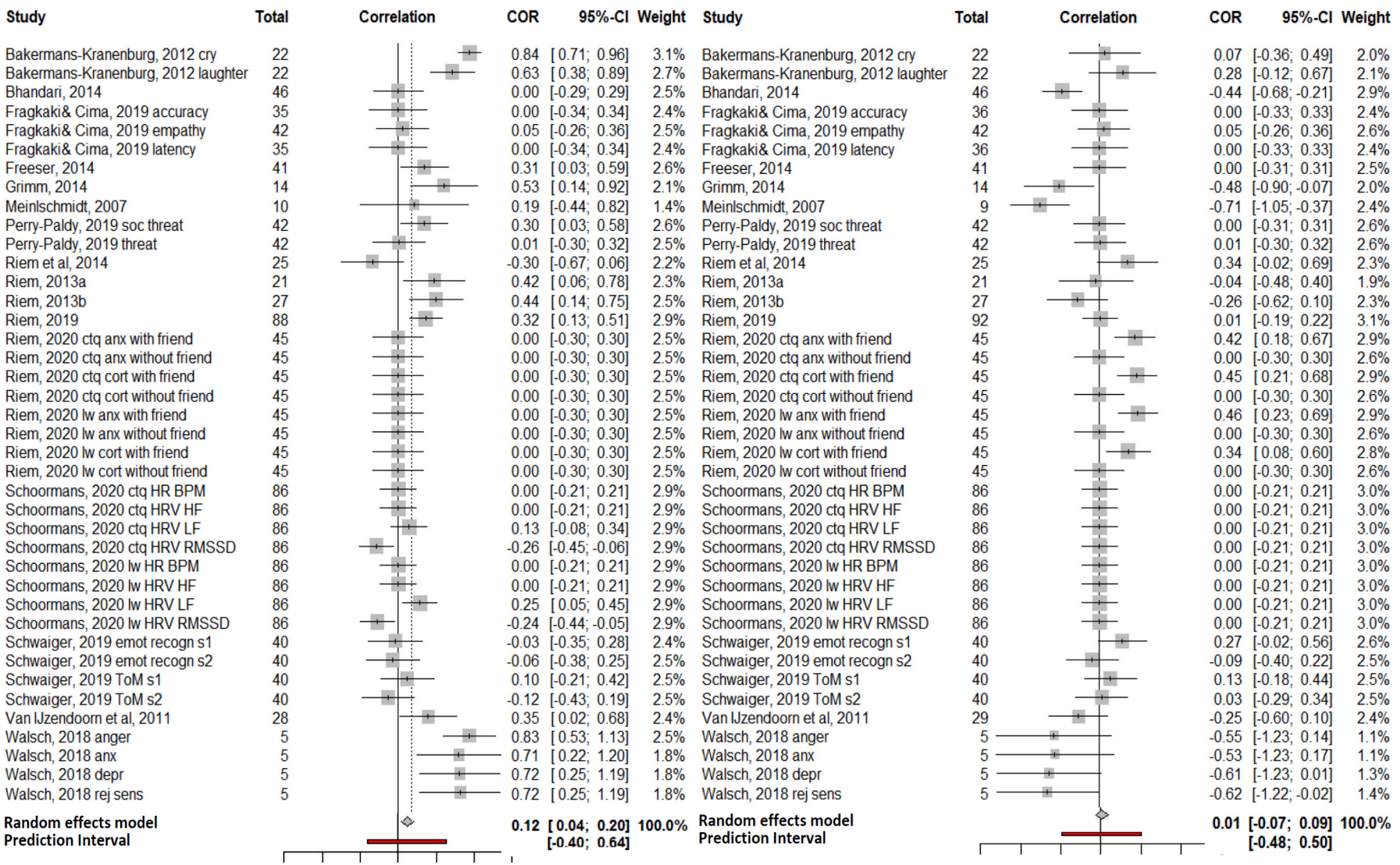

Fig. 4. Effects of oxytocin administration in groups with lower childhood adversity (left side of figure) and higher childhood adversity (right side of figure)

examined the potential moderating effects of the following variables: sex distribution, clinical status, and degree of childhood adversity. The moderators were included in a meta-regression together with the interactions of those moderators with the variable childhood adversity *versus* comparison subgroup. The meta-regression was not significant, F (7,72) = 1.080, $p = .386$, and none of the predictors or interaction effects were significant.

12. Discussion

Our review of human OT research focusing on early life stress was inspired by previous work on developmental programming of OT-AVP pathways in rodents (e.g., Kompier et al., 2019; Perkeybile et al., 2019). This animal work suggests regulatory effects of early adversity on the OT-AVP system with relations to life history-relevant traits, behaviors, and health outcomes. Here the central question was whether, in the human literature, individual differences in OT system parameters and sensitivity to intranasal OT administration would vary as a function of stressful developmental experience and environmental exposures—and thus might provide some support for the life history approach in general, and the adaptive calibration model (ACM) in particular.

The rodent literature suggests that *both* OT and AVP are involved in hypothesized adaptive calibration processes, with key sex differences in sensitivity and outcome. In contrast, the human literature is mainly absent of research linking AVP to early life experiences, but includes an emerging body of evidence relevant to understanding the role of OT and *OXTR* in adaptive calibration, with some studies relating variability in OT to life history-relevant developmental outcomes that can be interpreted within an evolutionary framework. Based on our review of published studies ($k = 86$) presented in Tables 1–4, including meta-analyses of $k = 66$ independent samples, we observed some associations between stressful childhood experiences and OT, especially in community samples. These suggestive findings make it plausible that hypotheses regarding the influence of early life stress on OT levels, methylation of *OXTR*, and biological and behavioral responses to exogenous OT are fruitful, to be tested and replicated in larger studies with better assessments of early adversity, OT and *OXTRm* mediators, and life history-relevant developmental outcomes, preferably in one mediational model.

12.1. Meta-analytic results

12.1.1. OT levels in children

A link between higher childhood adversity and lower OT levels was visible (albeit with a non-significant combined $r = .12$) in prospective studies of community samples of children (i.e., typical samples without substantiated child maltreatment). Children who had more stressful developmental experiences or environmental exposures while growing up tended to have lower endogenous basal levels of OT. However, the extant data on basal OT in children with documented histories of child maltreatment showed a lower association ($r = .05$). Consistent with research in rodents, the human developmental literature provided some evidence that lower levels of OT partially mediated the effects of stressful family and ecological conditions on the development of more anxious and less prosocial phenotypes. This support for a mediation model could only be discussed in the narrative review, as the research was too limited to be synthesized in a quantitative way.

The literature on early adversity and basal OT in children is still quite small, making the combined effect size in the meta-analysis more sensitive to the vagaries of individuals studies. Thus, conclusions should be considered tentative. For example, there are no studies of children with diagnoses for psychological disorders, and no studies employing a randomized design to study intervention effects on child OT. Only four studies examined children with documented histories of child maltreatment. Because these studies employed small sample sizes and involved very different ecological contexts (i.e., home vs. institutionalization), it is challenging to draw conclusions about the effects of severe adversity exposures on child OT. Nevertheless, a defensible hypothesis for further work is the potential presence of the expected association between more adversities and lower basal OT in community samples but the absence of such an association in samples with children who experienced severe adversities such as structural neglect in orphanages.

12.1.2. OT levels in adults

A fairly consistent signal emerged in retrospective studies of community samples of adults. Recalled experiences of low parental caregiving (in the typical range) and childhood abuse/neglect (in the severe range indicative of physical or emotional harm) were associated with reduced levels of basal OT, with a statistically significant combined effect size of r = .09, and somewhat higher when the two studies using urine samples for OT extraction were left out. More adversity predicts lower OT levels, but only in nonclinical participants. The set of studies including (partially) clinical groups showed a non-significant combined effect size of $r = -0.02$, even though the few studies of BPD patients showed a combined effect size of $r = .19$. Although the degree of early adversity did not moderate the effect sizes, type of early adversity might do so. However, this would involve a large number of studies and valid measures of different types of adversity, and comorbidity of adversities would need to be taken into account. Nevertheless, the theoretical importance of moving beyond the "early life stress" concept toward identifying what dimensions of the environment are being tracked by the OT system is undisputable (see further discussion below) and requires good measures in large samples.

12.1.3. OXTR methylation

Early adversity was associated with higher levels of *OXTRm*, but the effect size was small (r = .02), which was significant in nonclinical samples or when blood was the tissue of choice. Small effect sizes are not uncharacteristic of methylation studies. Although this finding is consistent with our hypothesis that early adversity causes higher levels of *OXTRm,* and thus might lead to lower *OXTR* protein expression, some caution is warranted. First, epigenomic differences have been shown to be partly heritable (Min et al., 2021), which in the applied and popular literature around epigenetics sometimes is overlooked. Non-experimental designs allowing for causal conclusions, such as Mendelian Randomization approaches, are still absent (Hamaker, Mulder, & van IJzendoorn, M. H., 2020; Mill & Heijmans, 2013). A possible alternative explanation is that levels of methylation may be a biomarker rather than a mediator. Second, we should be mindful of the recent history of candidate-genes studies in psychology and psychiatry, which were important sources of inspiration and heuristics for further work, but have also met with severe critiques and numerous failed replication attempts—lessons to be learned for epigenetics as well (Mill & Heijmans, 2013).

Replicated, large-scale epigenome-wide analysis with sufficient built-in protection against too many researcher degrees of freedom (e.g. large cohort studies such as Generation R [Dall' Aglio et al., 2020] or in the PACE consortium of cohort studies with epigenetic data [Felix et al., 2018]) would be a welcome addition to the existing research. One positive development is a movement within the epigenetics field toward development of best practices for choosing CpG sites (Lancaster et al., 2018). Nonetheless, it would be surprising if natural selection favored an epigenetic system in which adaptive functionality depended on one or a few loci in the whole epigenome. Distal (or trans) (epi-)genetic regulation of gene expression cannot be ignored (Mill & Heijmans, 2013; Min et al., 2021), and a primary focus on CpGs in or around *OXTR* might turn out to be misleading.

12.1.4. Response to intranasal OT

Our hypothesis was that low adversity would facilitate more positive intranasal OT effects, and that high levels of adversity would dampen

this intranasal OT effect. Indeed, participants who reported relatively high levels of early life stress either failed to show a positive response to intranasal OT (e.g., they did not behave in a more prosocial manner) or displayed a negative response to intranasal OT (e.g., displayed equal or worse socioemotional skills), the combined effect size was $r = .01$. That is in contrast to individuals who reported more supportive caregiving experiences in childhood and/or low levels of abuse/neglect. In these participants, the positive effects of intranasal administration of OT were facilitated ($r = .12$).

The studies on intranasal administration of OT might provide crucial information about the causality of OT levels for neurobiological or behavioral outcomes. Several studies used a placebo controlled within-subjects randomized controlled design in which each participant is exposed to a counter-balanced random order of placebo and OT and serves as his or her own control. Although this is a recommendable and statistically powerful approach (Quintana et al., 2021; for a computational example, see Van IJzendoorn & Bakermans-Kranenburg, 2016), even in such experiments causality is not guaranteed. First, randomizing placebo versus OT administration does not mean that the exposure to adversities is randomized (Hamaker et al., 2020). The causal conclusion that OT administration is more effective in one group compared to another is only valid if the participants had been randomly assigned to low versus high adversity environments. Such a design can be implemented in rodent studies but would pose ethical concerns in humans. Second, although the intranasal OT studies may provide a clear signal, the functional significance of that signal might be challenging to interpret because of the likely mismatch between what the OT system is evolved to do and what occurs when peripheral OT and AVP receptors are flooded by exogenous administration of the neuropeptide (Gangestad & Grebe, 2017).

12.2. General Limitations

The studies reviewed here have other limitations that suggest caution in interpreting and generalizing the findings. First, in the studies examining relations between early adversity and basal OT or *OXTRm*, the observed associations could be confounded. Population stratification in multi-ethnic samples and other potential confounders should be reckoned with as participants are not randomly assigned to lower and higher levels of childhood adversities. For example, genetics might be a confounder, as the same genetic factors might influence experiences of adversity and levels of basal OT or methylation. Second, our review did not address the effects of prenatal stress on OT, despite some evidence in both humans (Unternaehrer et al., 2016; but see Sammallahti et al., 2021) and non-human animals (de Souza et al., 2013) suggesting that maternal adversities during pregnancy may regulate development of the child's OT-AVP system. Third, our review did not address the interaction between developmental experiences/environmental exposures occurring early in life and those later in life (i.e., proximal to the OT assessment) (see Chatzittofis, Nordstrom, Uvnas-Moberg, Asberg, & Jokinen, 2014). Research on developmental programming of the OT-AVP system could benefit from including measures of recent stress exposures, to enable testing for (re)calibration of the system. Fourth, many studies relied on retrospective reports of early life stress (which do not correlate well with prospective measures). Fifth, much of the research reviewed here was limited by small samples sizes, and in some cases specialized study populations, thus limiting both statistical power and generalizability. A priori statistical power of the multilevel meta-analysis assuming an effect size of $r = .10$ amounts to 85% (at an alpha level of .05) only when the sample size is $N > 100$ (Harrer, Cuijpers, Furukawa, & Ebert, 2019). Less than half of the studies had sufficient power to find such an effect size. This underscores the importance of replications in larger samples, to increase confidence that we are dealing with robust findings in this complicated research field (Mulder et al., 2021; Rijlaarsdam et al., 2016). At the same time, from a meta-analytic perspective, a large number of studies is preferable to a small number of very large studies, since it takes the heterogeneity of effect sizes into account (see Kenny & Judd, 2019). Fifth, the studies reviewed here used peripheral measures of OT and *OXTRm* (with uncertain relations with central OT and *OXTRm*) that involved specimen, assay, and extraction choices (e.g., plasma vs. urine, immunoassay vs. mass spectrometry, extracted vs. unextracted samples) that remain under considerable debate (e.g., MacLean et al., 2019). Meta-analytically urine-based studies seemed to show deviating outcomes. Sixth, small sample sizes raise the possibility of selective publication of positive results, p-hacking, and risk of false positives (Head, Holman, Lanfear, Kahn, & Jennions, 2015; Leng & Ludwig, 2016). These issues could most effectively be addressed through preregistration and open sharing of data; unfortunately, none of the 86 publications in our review of the literature were preregistered. In the current series of meta-analyses, however, the replicability problems related to publication bias might be less prevalent because our central hypothesis often was different from that of the original papers.

13. The OT-AVP system as a mechanism of adaptive calibration of life history strategies

As discussed in the Introduction, the empirical literature reviewed in this paper was largely guided by the medical model. If this research had instead been conducted within an evolutionary-developmental framework, as guided by life history theory and the ACM, it would have looked different in at least four ways: How childhood adversity was measured, how oxytocinergic functioning was measured, what developmental outcomes were assessed, and how interrelationships between these variables were interpreted (focusing on adaptive calibration). We elaborate on each of these points below. As also discussed in the introduction, research on rodents has characterized the OT-AVP neurosecretory system as sensitive to early life stress and involved in calibrating a range of traits and behaviors related to life history strategies. The current review provides some convergent evidence in humans, though the literature is messy and conclusions need to be regarded as preliminary. Here we propose that incorporating an evolutionary-developmental perspective could help reveal a clearer signal in the noise—addressing some of the shortcomings of the current literature, leading to reinterpretation of some findings, stimulating new hypotheses and directions for research—that may ultimately facilitate greater integration of knowledge and alternative approaches to intervention.

The adaptive calibration model (ACM; Del Giudice et al., 2011) is a theory of individual differences in stress responsivity that builds on the concepts of life history theory and developmental plasticity. The central tenet of the ACM is that physiological stress response systems, including the autonomic nervous system and the HPA axis, the hypothalamic-pituitary-gonadal axis, and the serotonergic, dopaminergic, and OT-AVP systems, operate as mechanisms of conditional adaptation, with a key role in regulating the development of individual life history strategies. According to the ACM, the activation of autonomic and adrenocortical responses during childhood provides crucial information about threats and opportunities in the environment, their type, and their severity. Over time, this information becomes embedded in the parameters—recurring set points and reactivity patterns—of these physiological systems, which in turn provide the developing person with probabilistic summaries of key dimensions of the environment. For example, sustained activation of the HPA axis is generated by exposure to danger, unpredictable or uncontrollable contexts, and negative social evaluation, as well as by energetic stress (Dickerson & Kemeny, 2004); thus, the HPA axis apparently tracks the key environmental variables involved in regulation of alternative life history strategies (see Ellis et al., 2009). The current literature review suggests that the OT-AVP system, which has close bidirectional links with the HPA axis (Carter et al., 2020; Jurek & Neumann, 2018), may act in an analogous manner (at least in non-clinical community samples), tracking threats and opportunities in the developing organism's environment and biologically/

epigenetically embedding these experiences in the basal functioning and responsivity patterns of these peptides.

In the ACM, individual differences in the functioning of stress response systems regulate the coordinated development of a broad cluster of life history-related physiological and psychological traits, including growth and maturation, sexual and reproductive functioning, aggression, competition and risk taking, pair bonding, health over the life course, and related factors (Del Giudice et al., 2011; Ellis & Del Giudice, 2014). Consistent with the ACM, upregulation of OT pathways has been implicated in multiple traits expressed by individuals displaying slower life history strategies. Converging lines of evidence support a role for OT in maintaining the relatively high levels of human maternal (and paternal) care (reviewed in Feldman & Bakermans-Kranenburg, 2017; Scatliffe, Casavant, Vittner, & Cong, 2019; Szymanska, Schneider, Chateau-Smith, Nezelof, & Vulliez-Coady, 2017); in maternal protective behavior (reviewed in Bakermans-Kranenburg & van IJzendoorn, 2017), from human mothers actively protecting infants against strangers to rodent mothers carrying out offensive attacks against intruders; in supporting more cohesive and enduring sexual and romantic relationships and guarding them against threat (Aguilar-Raab et al., 2019; Gangestad & Grebe, 2017; Grebe et al., 2017); in enhancing ingroup, but not outgroup, trust (Van IJzendoorn & Bakermans-Kranenburg, 2012); and in supporting human longevity, health, and vitality (Carter et al., 2020), all of which are indicative of slower life history strategies (e.g., Belsky et al., 1991; Del Giudice, 2018; Ellis et al., 2012; Figueredo et al., 2006; Zhu, Lu, & Chang, 2021). These data, together with the tentative evidence from our literature review correlating early-life stress with down-regulation of OT-system parameters (e.g., methylation of the *OXTR* gene, blunted secretion of OT in peripheral fluids, reduced responsivity to exogenous OT), particularly in community-based samples, highlight the potential mediating role of OT in shifting individuals growing up under harsh, unpredictable conditions away from a slower life history strategy—and toward a faster one. This underscores the importance of more explicitly integrating the OT-AVP system into the ACM, to better understand how the developing organism regulates a broad range of life history-relevant traits and behaviors in relation to physical and psychosocial challenges encountered over ontogeny.

14. Implications of an evolutionary-developmental framework for studying adaptive calibration of the OT-AVP system

An evolutionary-developmental perspective guides research toward studying childhood adversity, oxytocinergic functioning, and developmental outcomes in particular ways, focusing on dimensions of adversity, OT responsivity to context, and adaptive variation in life history-related traits and behaviors.

14.1. Dimensions of adversity

A basic limitation of the medical model is that it provides little guidance for understanding what aspects of the childhood environment are important; i.e., it does not focus on or delineate basic dimensions of environmental experience that guide development of the OT-AVP system. Thus, studies included in the current review assessed early life stress in any number of ways, generally measuring the severity of childhood adversity (e.g., levels of maternal depression, maltreatment, trauma exposure), with little theoretical guidance on what dimensions of adversity matter or how different dimensions of adversity shape OT-AVP system parameters. In the small number of studies in the current review—too small in number to be meta-analyzed—that examined specific dimensions of abuse/neglect, recalled emotional abuse/neglect (as opposed to physical abuse/neglect) appeared to be most reliably associated with OT (Heim et al., 2009; Müller, Bertsch, Bülau, Herpertz, & Buchheim, 2019; Riem et al., 2017), suggesting an important hypothesis for future research.

Evolutionary-developmental models afford hypotheses about what aspects of the early environment should regulate the development of stress-sensitive neurobiological systems, especially in relation to variation in life history strategies. Research on different dimensions of adversity and their functional significance in relation to adaptive (and maladaptive) changes in biobehavioral development has become increasingly important in developmental science (e.g., McLaughlin, Sheridan, Humphreys, Belsky, & Ellis, 2021). Guided by life history models, the ACM distinguishes between early experiences that involve *harshness*, which encompasses extrinsic sources of morbidity and mortality, from those reflecting *unpredictability*, which involves stochastic variation in harshness (Ellis et al., 2009). Extrinsic refers to environmentally-mediated causes of morbidity and mortality that cannot generally be attenuated or prevented by the individual (e.g., community violence). An alternative framework, rooted in evolutionary-developmental concepts of experience-driven plasticity, distinguishes experiences involving *threat*, which encompasses harm or threat of harm to the child, from those reflecting *deprivation*, which involves an absence of expected inputs from the environment, such as cognitive and social stimulation during development (McLaughlin, Sheridan, & Lambert, 2014). We expect that our understanding of the effects of early adversity on OT system parameters, and especially our understanding of which adversities matter for what outcomes, could be substantially enhanced by systematically testing these theoretically guided dimensional models of adversity.

14.2. OT responsivity to context

The central focus of the ACM is on responsivity to context. Although the oxytocinergic system shows background activity even when the individual is not engaging in any specific task, individuals mount OT responses when external situations call for it (see the OT responsivity sections of Tables 1 and 2). OT responsivity may be especially important to study in adversity exposed people due to "sensitization effects" (Ellis, Bianchi, Griskevicius, & Frankenhuis, 2017). Adverse developmental experiences and environmental exposures may cause individuals to "maintain a smaller bank of resources—tangible, interpersonal, and intrapersonal—to deal with stressful events" (Gallo & Matthews, 2003, p. 34), as they experience more demands on their "resource bank" (e.g., exposures to violence) and thus are able to keep less in reserve. This lower reserve capacity may lead adversity-exposed people to conserve resources under basal conditions in order to more fully activate relevant biobehavioral processes in context. Thus, current OT profiles might best be understood as an interaction between early life and current conditions, whereby adversity-exposed people tend to mount OT responses primarily under current conditions or psychological states of stress/uncertainty (i.e., earlier-life experiences *sensitize* later biobehavioral responses to stress; see Mittal, Griskevicius, Simpson, Sung, & Young, 2015; Young, Griskevicius, Simpson, Waters, & Mittal, 2018). Only a small number of studies included in the current review— too few to evaluate through meta-analysis—tested for such sensitization effects (i.e., tested for the effects of early life stress on OT responsivity to current conditions or psychological states of stress/uncertainty). For example, two studies in the current review examined OT responses to the Trier Social Stress Test in girls or women with histories of child maltreatment (Pierrehumbert et al., 2010; Seltzer, Ziegler, Connolly, Prososki, & Pollak, 2014). Both studies documented heightened OT responses to the stressor followed by sharp reductions in OT (consistent with the notion of conserving resources). These intriguing results provide initial clues that underscore the potential value of studying OT responsivity to social stress in adversity-exposed people. Measuring OT responsivity to theoretically relevant environmental contexts should allow clearer signals to emerge in future research on the effects of developmental stress exposures.

14.3. Adaptive variation in developmental outcomes

Evolutionary-developmental scientists generally assume that different life history strategies are adaptive in context. This perspective moves us beyond value judgments about typical variation in family conditions, parenting, and child development. From a life history perspective, the child growing up under harsh, unpredictable conditions who develops insecure attachments, an exploitive interpersonal style, matures early, sustains early sexual debut, and engages in a range of antagonistic and risky social behaviors may be no less functional in her or his ecological niche than a child who grows up in a safe, stable environment and shows the opposite behaviors and dispositions. But this is not the perspective taken in much of the literature reviewed here and presented in Tables 1–4. Operating largely within a medical model, the current set of studies were mostly designed to measure how challenging early experiences disrupt or impair development. Thus, typical outcome variables included depression, anxiety, social-emotional difficulties, externalizing, problems, internalizing problems, Axis-I psychopathology, and so on. Only one study in the current review (Gonzalez et al., 2020) was guided by the ACM and thus focused on a biobehavioral outcome—neural reward sensitivity—that was theoretically linked to developmental adaptation to stress.

As noted in the Introduction, implicit in theory and research based on the medical model is the notion that there is an optimal level of OT or OT responsivity, and that levels falling outside of this range are deviations from the norm, putting individuals at risk for developmental dysregulation. This way of thinking, however, does not recognize adaptive individual differences. A widely held assumption in evolutionary biology is that, in most species, single "best" strategies for survival and reproduction are unlikely to evolve (Hinde, 1982, 1991). This is because the best strategy varies as a function of the physical, economic, and social parameters of one's environment, and thus a strategy that promotes success in some environmental contexts may lead to failure in others (Ellis & Del Giudice, 2019). Seemingly suboptimal levels of OT, detected among individuals who grow up under challenging circumstances, may reflect adaptive calibration of the system, with reduced OT functioning to regulate development toward faster life history strategies that are adaptive under harsh, unpredictable conditions, even if these strategies induce tradeoffs with considerable costs to physical or mental health over time. A more explicit focus on life history-relevant traits and behaviors is needed to investigate these issues.

15. Implications of an evolutionary-developmental perspective for preventive interventions and clinical treatment

From an evolutionary-developmental perspective, there are multiple approaches to intervention to address the sequelae of early adversity (Ellis et al., 2012; Ellis et al., 2020). The first involves altering causative environmental conditions involved in the regulation of life history strategies. This is a form of the more general intervention strategy of mitigating risk, but more specifically involves altering the social contexts of adversity-exposed children and adolescents in ways that, through changes in their experiences, induce an understanding that they can lead longer, healthier, more predictable lives (Ellis et al., 2012). For example, parenting interventions have been shown to facilitate more sensitive parenting (Juffer, Bakermans-Kranenburg, & Van Ijzendoorn, 2017), thus potentially altering the developmental context of the child in an evolutionarily meaningful way. Interventions with cash provisions and change of neighborhood (van IJzendoorn, Bakermans-Kranenburg, Coughlan, & Reijman, 2020) could potentially augment the effectiveness of parenting interventions. Given the central role of unpredictability in evolutionary models, interventions that focus on creating highly structured and predictable family environments (such as Multidimensional Treatment Foster Care), with fair and consistent limits and predictable consequences for rule breaking, as has been used with girls in the juvenile justice system randomly assigned to foster families or residential care (Chamberlain, Leve, & DeGarmo, 2007; Leve, Chamberlain, & Reid, 2005), may be especially relevant for shifting individuals away from faster life history strategies. Based on the current meta-analyses and narrative review, we hypothesize that such environmental effects are mediated, in part, by alterations of the OT-AVP system, at least in non-clinical populations.

Another approach is to attempt to directly target life history strategies, as opposed to environmental conditions. One tempting suggestion is to apply OT toward achieving this goal. Therapeutic use of OT may alter life history-relevant traits or behavior, such as increasing parental engagement or sensitivity (Naber, Poslawsky, Van Ijzendoorn, Van Engeland, & Bakermans-Kranenburg, 2013; Naber, van IJzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010), increasing trust of ingroup members (Van IJzendoorn & Bakermans-Kranenburg, 2012), altering fear conditioning (Gottschalk & Domschke, 2018), and down-regulating the HPA axis (Sharma et al., 2020). However, we have learned that OT interventions seem to be least effective for those who are most in need of such interventions (Bakermans-Kranenburg & van IJzendoorn, 2013), as also evident from the current meta-analytic work. Moreover, if we would assume for the moment that such therapeutic OT administration could be made successful in adversity-exposed people (i.e., that it exerts the same effects as in non-exposed people), the result could be equivalent to "declawing the cat": removing the psychological and behavioral weaponry necessary to survive and control resources in one's local ecology (Ellis et al., 2012). Consistent with the ACM, individual variations in the oxytocinergic system might be adaptively calibrated to childhood experiences and function to prepare individuals to successfully navigate such experiences in the future.

Another approach to addressing the sequelae of early adversity is to attempt to work with, rather than against, life history-relevant traits and behavior. For example, the "hidden talents" approach focuses on identifying and valuing specific skills that develop in the context of adversity, and using those skills to enhance intervention outcomes (Ellis et al., 2017; Ellis et al., 2020). However, even if neurobiological adaptations to stress can be harnessed in positive ways, they could still be costly to the individual, leading to a higher risks or morbidity and early mortality. Thus, the applied goal of an evolutionary-developmental perspective is *not* to reinforce fast life history strategies or better prepare stress-adapted people to live their lives in harsh, unpredictable environments. Indeed, there is a gap between "is and ought" that has to be bridged (Van IJzendoorn & Bakermans-Kranenburg, 2021). As stated above, changing underlying environmental conditions may be the preferred option, especially when this can be achieved early in life. But for people who have matured into harsh, unpredictable environments, one option may be to work with neurobiological adaptations to stress, such as by helping people who have experienced significant adversity to utilize their hidden talents in positive ways (Ellis et al., 2017, Ellis et al., 2020). The ACM calls for more attention to the demand characteristics of past and future environments in an individual life-course. The implication is that not only the individual, but also the environment, is variable, and both are potential targets for (preventive) interventions and treatment (Van IJzendoorn & Bakermans-Kranenburg, 2021).

16. Conclusion

Systematic literature reviews can be a powerful tool for revealing both the presence and absence of research. Conspicuously missing from the field is research on the role of the OT-AVP system in regulating the development of (potentially) costly but adaptive strategies that promote survival and reproduction under stressful conditions. Filling this gap could help move the field beyond its current focus on impairment and dysregulation toward an understanding of adaptation to context. The current meta-analyses provide tentative support for the hypothesis that the OT-AVP system is regulated by early life experiences, providing scope for developmental programming of the system to improve the fit between the organism and its environment. Variation in OT-AVP system

parameters may function as a mechanism of adaptive calibration through which developmental experiences and environmental exposures calibrate a range of traits and behaviors related to life history strategies. Human research on childhood adversity and OT remains steeped in a medical model focused on the harmful effects of early life stress. We argue that this medical model is incomplete because it fails to account for adaptive individual differences, and that knowledge could be advanced by shifting the focus toward a broader understanding of developmental adaptation to stress.

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CRediT authorship contribution statement

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Declaration of Competing Interest

We have no known conflict of interest to disclose.

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