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Review

Oxytocin: A Candidate Biomarker of Health Status During Early Childhood Development

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Abstract

The theoretical underpinnings and empirical data supporting oxytocin as a context-dependent biomarker of prosocial affiliation, bonding, attachment, emotional regulation, cognitive development, and the modulation of stress responses are summarized. We propose an interdisciplinary consensus against a backdrop of inconsistencies concerning behavioral and experimental findings for the oxytocinergic system. Current knowledge gaps demonstrating the inability to establish a hierarchy of findings are related to the following: (a) the theory and practice of oxytocinergic therapeutic interventions; (b) identification, characterization, and quantification of functional, mechanistic, and molecular biomarkers and matrices; (c) context- and time-dependent resilience factors associated with mind–brain–body development, (d) measures of intergenerational transmission, and (e) summative indicators of psychopathological co-morbidities. We analyze prospective objective measures of oxytocin against subjective caregiver reports of positive childhood experiences (PCEs, resulting from secure nurturing, established daily routines, pleasurable social interactions, opportunistic and spontaneous play, secure environments), which favor healthy developmental outcomes in preschool children. Few studies prospectively use the painless, noninvasive sampling of risk and resilience biomarker levels to index the health status, emotional regulation, and cognitive development in preschool children. We present the methodology for novel measures of risk (cortisol) and resilience (oxytocin) in human scalp hair. Future studies validating the therapeutic efficacy of oxytocin or the stress-mediating effects of oxytocin on socioemotional regulation and health status should systematically address these gaps.

Keywords: oxytocinergic system; oxytocin–arginine vasopressin pathway; stress pathway; positive childhood experiences; adverse childhood experiences; hypothalamic–pituitary–adrenal axis; hair biomarkers

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1. Introduction

Historically, many theories have been put forth to explain the effects of oxytocin in adaptive ecological and psychological resilience in the setting of a dysregulated stress pathway. This review is centered on the role of oxytocin in preverbal/preschool child development, attachment theory, resilience theory, theory of the mind, and self-identity theory as forerunners for the socially affiliative model of resilience. These are discussed in the context of the three childhood developmental domains, i.e., emotions, cognition, and behaviors, each of which cumulatively adds to child wellbeing and health outcomes.

Allostatic load is the common term assigned to the cumulative temporal experiences of chronic stress exposures that impinge upon the mind–brain–body connectome, leading to dysregulation of the central and peripheral nervous systems, poor health, impaired self-regulation, and identity disruption. This model proffers that parental/primary caregiver nurturing, followed by additional supportive relationships, activates oxytocin release for stress axis regulation, thereby curbing the long-term detrimental effects of allostatic load. Because many children have primary caregivers other than a parent, it is important to understand that the effects of oxytocinergic affiliative pathways apply equally to all primary caregivers. These effects occur within the limbic system of the brain at the level of the hypothalamic–pituitary–adrenal (HPA) axis (physiologic homeostasis), the amygdala (emotionality: fear, anxiety, etc.), and the prefrontal cortex (cognition: coping, planning, self-regulation). To fully comprehend the power of oxytocin to inhibit a deleterious cycle of allostatic loading with potential transmission across generations, we focus on advances in stress and resilience theory to address knowledge gaps centered upon early childhood–family adaptation and interventions designed to improve child well-being.

1.1. Current State of Oxytocin Research

1.1.1. Early Experiences and Neurodevelopment

Foundational neuronal pathways are shaped by both negative and positive experiences during sensitive periods of brain development [1]. Early childhood is a sensitive period when exposures to adverse childhood experiences (ACEs) or early life stress (ELS) in the presence or absence of positive childhood experiences (PCEs) may shape lifetime outcomes. ACEs can include events that affect children directly, such as physical abuse or neglect, and indirectly in their social environment, such as parent conflict, substance abuse, or mental illness [2]. Early life adversity (ELA) includes maternal cumulative lifetime exposures to stress, including childhood experiences with past or present insecure environments or relationships, community violence, household instability, and limited access to prenatal care. The four common domains of PCEs include nurturing, consistent child–family routines, access to extended networks providing pleasurable, enriching activities (e.g., play, green space), and provisions for safety [3]. The neural pathways most involved during early-stage affiliative child development are those of the limbic system, including the HPA axis [4].

1.1.2. HPA Axis Function and Toxic Stress

The HPA axis is the central node of the stress network that maintains body homeostasis through cortisol release and its negative feedback loop. This neuromodulatory system comprises pathways responsible for the release of neuroendocrine hormones, such as cortisol and oxytocin, among others, that modulate adaptive regulation of the sympathetic and parasympathetic nervous systems. Toxic stress, i.e., prolonged or repeated ELA experienced without the buffering presence of PCEs, affects neuroplasticity to perturb a child's emotional and cognitive development and health [5]. A myriad of mental and physical health disorders, such as anxiety, depression, cardiovascular disease, asthma, and

others, are consequential to toxic stress exposures, HPA axis dysregulation [6–8], and the pediatric onset of adult diseases [7].

Childhood trauma has been declared a worldwide public health crisis [9]. Children are particularly susceptible to creating maladaptive stress responses when faced with higher ACEs and few PCEs during critical periods of neuroplasticity in early life. Recent estimates show that 45.7 percent of U.S. children aged 2 to 17 have experienced two or more ACEs [10]. In a systematic review conducted by Hughes and colleagues, individuals experiencing four or more ACEs had increased negative health outcomes, inclusive of problematic drug use and interpersonal or self-directed harm [2]. Furthermore, individuals exposed to ACEs are at higher risk for adverse behavioral, neurobiological, and physical consequences [11].

1.1.3. Social and Behavioral Impacts

Beyond physiological effects, toxic stress has a profound impact on a child's social functioning [12–14]. A qualitative study conducted with kindergarten to 3rd-grade teachers focused on child behavioral observations in classrooms. Teachers reported that the children exposed to toxic stress lacked effective emotional regulation strategies and the ability to form and maintain social relationships with them and their peers [13]. A different study conducted a community-based intervention to mitigate the impact of toxic stress amongst youth at risk [14]. Interviews of these children revealed their inability to create and maintain meaningful relationships due to their home environments [14]. In this context, a potential mediator of the feelings of distrust and inability to build secure connections can be related to oxytocin's role in social bonding and modulating the stress response system [15–17].

1.1.4. Oxytocin Pathway Knowledge Gaps

There is a wealth of knowledge centered on the role of glucocorticoid response element (GRE) genes in fetal organ development, growth, tissue regeneration, and health maintenance through the lifespan [18]. In contrast, the roles of the greater than 150 genes associated with the oxytocin signaling pathway remains underexplored [19], particularly in preverbal children. No studies to date have analyzed oxytocin-related genes or factors regulating their gene expression in preschool children. Oxytocin mitigates cortisol synthesis primarily by dampening the HPA axis and stimulating parasympathetic nervous system activity. Thus, oxytocin downregulates physiological stress responses, promotes autonomic balance, and suppresses peak cortisol reactivity, returning the body to a restful, restorative state under conditions of caregiver warmth and responsiveness; consistent family routines; access to resources that give rise to enjoyment, competence, and social stimulation; and provisions for safety. Sartorius et al. (2024) conducted functional analyses to reveal the evolutionary timeline for the development of human oxytocin pathway genes [19]. They report that the function of "modern genes in the oxytocin pathway . . . primarily expressed in the brain and muscle tissue" is to guide parturition, lactation, metabolism, cardiovascular tone, social cognition, decision-making, and learning. They point to "a persistent knowledge gap regarding the function and purpose of the human oxytocin system and its treatment potential" in psychiatric disorders and conditions associated with dysfunctions in social behavior and cognition.

1.2. Theoretical Basis, Models/Frameworks of Social Cognition in Stress Resilience

1.2.1. Resilience Frameworks: Attachment, Biopsychosocial, and Synchrony Models

Attachment theory, resilience theory, the biopsychosocial framework, and affiliative neuroscience models explain how PCEs become physiologically embedded. Attachment theory describes how early caregiver relationships shape developmental and emotional outcomes in young children. The ecological resilience framework highlights environmen-

tal factors distinct from psychological resilience that contribute to progressive adaptive functioning. The biopsychosocial framework emphasizes interactions among biological, psychological, and social domains in determining the health status. The affiliative neuroscience model outlines the role of oxytocin in forming brain networks that promote prosocial attachment and stress regulation. Quintana and Guastella propose that oxytocin functions as an allostatic hormone due to its widespread developmental, social, and regulatory effects [20]. Instead of simply triggering fixed prosocial behaviors like empathy, oxytocin heightens sensory and cognitive awareness for both social and non-social cues. This allows an organism to respond flexibly—by prompting cooperation within a safe group or promoting defensive, protective behaviors (like maternal aggression) in a life-threatening environment [20]. Research demonstrates that attachment styles are linked to outcomes in child psychopathology, cognitive and emotional brain networks related to empathy and compassion, school readiness, and immune function [5].

Garmezy's early resilience work [21,22], later expanded by Masten and colleagues [23–25], demonstrated a shift in the focus on pathology towards competence-based developmental outcomes. Fleming and Ledogar described resilience as temporal and contextual, extending across individual, family, community, cultural, and ecosystem levels. Ruth Feldman integrated biological and behavioral plasticity, affiliative brain centers, and parent–child biobehavioral synchrony into a neuroscience-based resilience theory, connecting these processes to oxytocin pathways [26–30]. These concepts support Gottlieb's model of experience-guided brain development via behavioral canalization [31,32] with predictive epigenetic trajectories, which provides one explanation for behavioral patterns observed in the intergenerational transmission of toxic stress (ITTS).

Maternal calibration and entrainment of a child's neuroendocrine stress and prosocial pathways can be correlated with maternal and child ACE and PCE domain scores, although simple dose–response relationships may have limited value [5]. Assessing ELA including poverty, domestic or neighborhood violence, immigration-related stress, and acculturation is necessary to identify risks across the lifespan.

Together, these perspectives show that resilience is relational and dynamic. It results from the union of biological and social contours, exemplified in the synchronicity found between a baby and primary caregiver, as well as in the flexibility of families to adapt, which enables people to regulate their stress through human connection or bonding [5]. This perspective sees resilience as the capacity to employ a variety of social and biological processes to transmute contextual stressors into opportunities for growth, as opposed to simple stress reduction.

1.2.2. An Emerging Mechanistic Model: The Neurobiology of Oxytocin

The literature highlights an interdependence of oxytocin release, caregiver synchrony, and caregiver behaviors in shaping resilience capacities, as outlined in the affiliative neuroscience model of resilience [29]. Parent–child alignment in physiology and behavior offers recurring opportunities for co-regulation and contributes to the development of empathy, trust, and adaptive coping. Research on the theory of mind further shows how neural substrates supporting social cognition overlap with those involved in attachment, emotional understanding, and protection against psychopathology under conditions of toxic stress [33].

1.3. Oxytocin as a Biomarker of Stress Mediation, Development, and Health

Few studies exist for measures of oxytocin levels in young children. Oxytocin may be considered a biomarker when measuring actual physiological responses in individuals. Oxytocin is also a neuroendocrine hormone, responsible for parasympathetic regulation

in response to stress and prosocial affiliation or bonding. Because of its role as a neuromodulator, it is frequently identified as a therapy for symptom control in children with developmental disorders, such as autism spectrum disorders (ASDs), or attention deficit hyperactivity disorder (ADHD). Despite its study across many human subjects and healthcare settings, significant disagreements exist in both methodology and conceptualization regarding the role of oxytocin in therapeutic interventions. Questions remain about whether measured oxytocin levels reflect the synthesis and secretion of endogenous oxytocin or are influenced by the exogenous dosing of synthetic oxytocin. Variability across studies can stem from differences in the methodology used with sample-specific measurements (saliva, serum, CSF, urine, tissue, or hair), matrix-dependent extraction procedures, and assay platforms such as liquid chromatography/mass spectrometry, aptamers, or the enzyme-linked-immunosorbent assays (ELISAs) used for oxytocin quantification. The high level of temporal and context-sensitivity of central versus peripheral circulating oxytocin levels across various populations adds additional confusion to study results. The impact of oxytocin on behavior varies based upon an individual's developmental background, gender, mental health status, and social–emotional conditions; thus, generalizing across studies and varying populations is difficult [34–36]. See Table 1.

Table 1. A critical appraisal: inconsistencies, gaps, and future directions. This table identifies the primary issues with inconsistencies, gaps in empirical knowledge, and unanswered questions in the role of oxytocin in the development of preverbal/preschool children as discussed throughout this review. It provides a framework for understanding previous, divergent findings and developing research goals. Code for abbreviations: ACTH (adrenocorticotropic hormone), ASD (autism spectrum disorder), AVP (arginine vasopressin), AVP V1b (arginine vasopressin V1b receptor), CNS (central nervous system, CSF (cerebrospinal fluid), EEG (electroencephalogram), GWAS (genome-wide association studies), IV (intravenous), LC-MS/MS (liquid chromatography-tandem, mass spectrometry), OT (oxytocin), OXTR (oxytocin receptors), PK (pharmacokinetics), RCTs (research clinical trials), SNP (single-nucleotide polymorphism), ToM (theory of the mind), TPJ (temporoparietal junction).

Inconsistency	Conflicting Evidence	Potential Causes	Future Directions
Methodological Heterogeneity and Small-study Bias	Early positive findings often came from small, underpowered studies; meta-analyses and preregistered replications reveal publication bias and high heterogeneity [37,38].	Low power, selective reporting, inadequate analyses [37,38].	Need large, preregistered, harmonized consortia and open-source data.
Peripheral vs. Central Oxytocin (OT) Measurement	Modest correlation between peripheral (plasma/saliva) and central OT, which varies by assay/matrix [39,40].	Matrix, timing, extraction, and assay method strongly alter estimates [40].	Standardize sampling/assays and interpret peripheral levels cautiously.
Dose–Response, Therapeutic Half-life, and Route of Administration	Clinical dose–response is inconsistent: intravenous OT shows very short plasma half-life (1–6 min), intranasal OT produces variable plasma levels, delayed and uncertain CNS exposure [41,42].	Variable intranasal delivery (device/formulation/mucosa), rapid peripheral enzymatic clearance, and biphasic pharmacokinetics (PK).	Use dense early sampling, standardized delivery/devices and formulations, and CSF measures.
Intranasal OT Efficacy and Clinical Trials	Small trials report social benefits; larger preregistered RCTs and meta-analyses often show null or mixed results [43–45].	Dose, route, acute versus chronic administration, sex, baseline traits, and task selection moderate effects [44,45].	Require biomarker-guided, well-powered RCTs.
Genetics (OXTR, rs53576, AVPR1A)	Candidate–SNP links (e.g., rs53576) show early associations with empathy/ToM but often fail replication; small OXTR–ASD associations reported [37,46,47].	Ancestry, phenotype heterogeneity, polygenicity, and underpowered samples [37,46].	Favor multiethnic GWAS/meta-analyses and standardized phenotypes.

Table 1. *Cont.*

Inconsistency	Conflicting Evidence	Potential Causes	Future Directions
Adaptive Versus Maladaptive Toxic Stress	OT facilitates bonding/stress-buffering in safe contexts but amplifies vigilance, in-group bias, and trauma consolidation under threat [48–50].	Social context, early experiences, receptor distribution, and AVP co-signaling determine direction of effect [30,51].	Using OT as a context-sensitive neuromodulator.
Neuroimaging Effects (Amygdala/TPJ/ Mentalizing)	Meta-analyses find OT effects on amygdala and temporal/TPJ networks, but task/population heterogeneity yields inconsistent behavioral outcomes [52–54].	Task type, analytic choices, sample size, and sex/development moderate neural and behavioral links [52,53].	Use larger, preregistered pharmaco-imaging with shared unthresholded maps.
Perinatal/Obstetric OT Use and Long-term Outcomes	OT is essential in obstetrics; longitudinal links to neurodevelopment are mixed and confounded by indication [55,56].	Dose, timing, indication, maternal–infant interactions, and other confounders [55].	Need registry-linked longitudinal biomarker studies.
Circadian Expression of AVP and OT	AVP generally consistent nocturnal increases, whereas human OT findings are mixed: there reports of both nocturnal rises and no clear diurnal rhythm [57,58].	Sparse/low-frequency sampling, matrix differences (CSF vs plasma vs saliva), sex/hormonal state, and assay sensitivity [58,59].	Need 24 h high-frequency, multi-matrix sampling with validated assays (LC-MS/MS extraction).
Endogenous Circulating Half-life of AVP and OT	Reported OT plasma half-life 1–6 min; AVP reports are longer (commonly 5–15 min), but estimates vary by method and population [60,61].	Rapid enzymatic degradation/clearance, biphasic (distribution and elimination) kinetics, and assay vs. sample collection artifacts [62,63].	Development systematic, gold standard approach evaluating PK properties of OT (central vs exogenous)
AVP versus HPA axis (Temporal Ordering)	AVP (via the V1b receptor) can potentiate ACTH/cortisol release acutely, but chronic human data show cortisol dysregulation preceding AVP changes [64,65].	Acute vs chronic stress, central versus peripheral measures, and receptor specificity [64,65].	Require longitudinal, circuit-level investigations.
Sleep, Arousal, and Autonomic Effects	Some studies report OT promotes parasympathetic tone and improves sleep; others report increased alertness or sleep fragmentation depending on dose/route [66,67].	Administration route, dose–response, timing relative to sleep, and co-morbidities [66,68].	Include EEG and autonomic monitoring with timed dose–response studies.

2. Publication Search Strategy

We found no publications centered on early childhood development of the affiliative oxytocinergic system or the oxytocin–arginine vasopressin pathway. Interdisciplinary perspectives on the role of oxytocin typically focus on adolescents or adults, with frequent inconsistencies concerning the behavioral and observational findings on the oxytocinergic system. Systematic reviews, especially those offering meta-analysis of clinical trials, demonstrate a lack of studies conducted with young children below the age of 5 years. Thus, additional search terms included a combination of the following major themes: (a) theory and practice guiding oxytocinergic therapeutic interventions; (b) identification, characterization, and quantification of functional, mechanistic, and molecular biomarkers of the social affiliative pathway in its capacity to buffer chronic stress; (c) interactions of parental factors, child age- and sex-associated brain and behavioral development with or without intervention, (d) measures of intergenerational transmission of biopsychosocial factors; and (e) measures of psychopathological comorbidities.

Recent evidence linking risk and resilience factors to poor health outcomes with(out) oxytocin treatment comprise the largest number of references (52%), mostly published from 2020 to 2025, discussed in our narrative review. Concepts of the affiliative neuroendocrine

framework publications gained the greatest traction during 2017–2019 and comprise 16% of the references included in our review. The bulk of these studies did not test for or report the role of oxytocin in early childhood development. Seminal publications from animal and human research demonstrating the ability of oxytocin to modulate the cortisol feedback loop were most concentrated during 2000–2016 and constituted 25% of references under discussion. Early childhood is important because neuroplasticity and network formation, especially in the HPA axis, peak prior to a child's fourth birthday. Theoretical frameworks for interactions among stress, development, and poor health outcomes have progressed throughout the last century, providing 6% of our references. Research on the childhood onset of adult noncommunicable diseases, psychopathologies, and suicide is sharply increasing, yet these studies have not linked the socially affiliative role of oxytocin to health trajectories across the lifespan.

3. Biology and Regulation of the Oxytocinergic System

3.1. Oxytocin–Arginine Vasopressin Pathways and Brain Development

The oxytocin–arginine vasopressin (OT-AVP) system serves as a critical neurobiological network connecting early adversity, neural development, social–emotional functions, and stress-related outcomes. Genetic, epigenetic, and environmental factors converge on this system, supporting its potential as a biomarker for identifying children at risk for neurodevelopmental and psychiatric vulnerabilities [69,70]. Childhood stress exposure gives rise to dysregulation of the stress-response system, altered neuroimmune signaling, chronic inflammation (central and peripheral), and poor health [71]. Chronic childhood stress impairs the functioning of brain regions important for developing self-regulation and coping skills [72]. Clinical psychiatry emphasizes that stress exposures may manifest as risk-taking or resilience-building behaviors. Behavioral investigators describe stress adaptation as a balance between protective and vulnerable elements that influence recovery or worsening vulnerability [21,22]. Clinical evidence links oxytocin dysregulation to psychiatric disorders, including depression, anxiety, and post-traumatic stress disorder (PTSD) [70]. Recent syntheses that incorporate oxytocin into broader neurotransmitter systems linked to mental illness emphasize its multifaceted effects on social function and regulation [73]. Given that oxytocin and AVP coregulate social behavior and stress reactivity, the cooperative function of these neuropeptides is important for studies on neurodevelopmental psychopathology [74].

Neuroimaging studies reveal specific neural circuits that are especially susceptible to ELS, particularly in the salience network, responsible for detecting and filtering environmental stimuli, and the sensorimotor processing network, which integrates sensory input and coordinates motor responses [75]. Oxytocin and AVP are important for social and emotional development according to the brain underpinnings of affiliative behaviors [76]. A further understanding of how these networks function at various stages of child development is provided by evaluating parent–child neural synchrony in real-world contexts. Neural synchrony supports brain plasticity and adaptive socioemotional growth [77].

The OT-AVP system plays a key role in modulating stress responses and socioemotional behaviors. Oxytocin influences experiences of loneliness [78], grief [79], compassion [80], fear [16,78,81], anxiety and fear memory [82], reward and motivation [83], trust and cooperation [84], and symptoms of PTSD [85], primarily via its effects on limbic regions such as the amygdala [82]. Arginine vasopressin, in contrast, helps to modulate arousal, vigilance, and social communication, complementing oxytocin's anxiolytic and affiliative actions noted in neuropsychiatric disorders [74]. Genetic variations in OT-AVP signaling were also linked to differences in parental behaviors, such as emotional warmth or child intolerance [80].

Arginine vasopressin emerges as a modulator of stress-linked psychopathology from a risk-resilience perspective [21]. Its signaling through the V1b receptor (AVP V1B) enhances ACTH release and modifies HPA axis reactivity, proposed as a therapeutic target in stress-related disorders [64]. While daily oxytocin rhythms were associated with psychopathy traits and childhood trauma in high-risk youth [86], AVP linkages to arousal, vigilance, and heightened stress responsivity suggest that AVP-sensitive phenotypes may map onto externalizing risk profiles. Although AVP is less directly linked to psychiatric disorders than oxytocin, its role in HPA axis regulation suggests it may influence vulnerability to stress-related conditions, and targeting the AVP V1b receptor system has been proposed as a potential therapeutic approach [64]. Together, these data support a model in which AVP contributes to psychiatric vulnerability via HPA potentiation and social-affective tuning, with dysfunction shaped by the developmental history and context [64,74].

Maternal behaviors can induce epigenetic programming in their children [87], and any discussion of child developmental trajectories must include the potency of epigenetic mechanisms. Epigenetic mechanisms triggered by early-life experiences can have profound, lasting effects on early childhood development as described in Section 3.4.1.

The OT-AVP system and its brain circuits are critically sensitive to parental–child interactions during childhood. Comparative research in mammals demonstrates that receptor distributions for oxytocin and AVP are primarily located in limbic structures such as the amygdala, hypothalamus, and septum, as well as in the cortical regions involved with social cognition. These receptor distributions underlie social organization and affiliative behaviors, indicating conserved biological mechanisms across species [88]. Consistent maternal behaviors of positive (praise) and negative (criticism) feedback in early and middle childhood shape not only the brain but also sculpt the long-term socioemotional outcomes of children [89,90]. Low parental engagement with infants and early-life traumatic experiences have been linked to increased methylation of the oxytocin receptor [69,91].

3.2. Oxytocin Modulation of the Cortisol Feedback Loop

Oxytocin amelioration of the cortisol biofeedback loop has been studied for several decades [92,93]. The hypothalamic paraventricular nucleus (PVN) produces corticotropin-releasing hormone (CRH) in response to contextual stressors, which signals ACTH production from the anterior pituitary, to stimulate cortisol secretion from the adrenal cortex. Typically, plasma cortisol inhibits CRH and ACTH release for sustaining the diurnal pattern of physiologically healthy cortisol production (homeostasis), which is highest at 30 min after wakening, followed by an afternoon plateau, and ending with the lowest bedtime cortisol, which aids in sleep induction. As cortisol dips at night, oxytocin and AVP peak to promote restful sleep [94]. These opposing rhythms imply temporally distinct roles for cortisol and oxytocin. The second feedback mechanism for cortisol regulation is the OT-AVP pathway, prominently known for parental–infant bonding, sensory experience-induced neuroplasticity, and neuroendocrine entrainment in the infant [95] (see Figure 1).

Mechanistically, oxytocin acts at multiple points in the cortisol feedback loop: it modulates CRH neurons in the PVN, influences autonomic (vagal) tone and heart-rate variability linked to affect regulation and cognitive coping under stress, and thereby promotes allostatic recovery [36,96,97]. Parents may not be reliable historians and even if so, they cannot know with certainty the biological and physiological impact of chronic stress on their preverbal child. Consequently, any parental report concerning a child's development is purely subjective. The use of a child's hair biomarkers such as cortisol (measuring stress) and oxytocin (measuring social affiliation/bonding) is an objective, non-invasive measure of the child's mind–brain–body connectome in response to contextual experiences of ACEs/PCEs. Oxytocin effects may in part emerge after enzymatic degradation into

bioactive fragments that have more specific action profiles, a hypothesis that demands attention when linking peripheral measures to central functions [92]. The human hair shaft develops from the neuroectoderm [98]; therefore, hair may be optimal for measuring summative (up to 6 months) levels of circulating hormones with daily incorporation into hair. Hair oxytocin levels have been reported in adults reporting work-related burnout [99], across early childhood, and in their mothers [100–102]. Circulating oxytocin levels vary by age and by sex, with the highest levels present in females during their reproductive years [103].

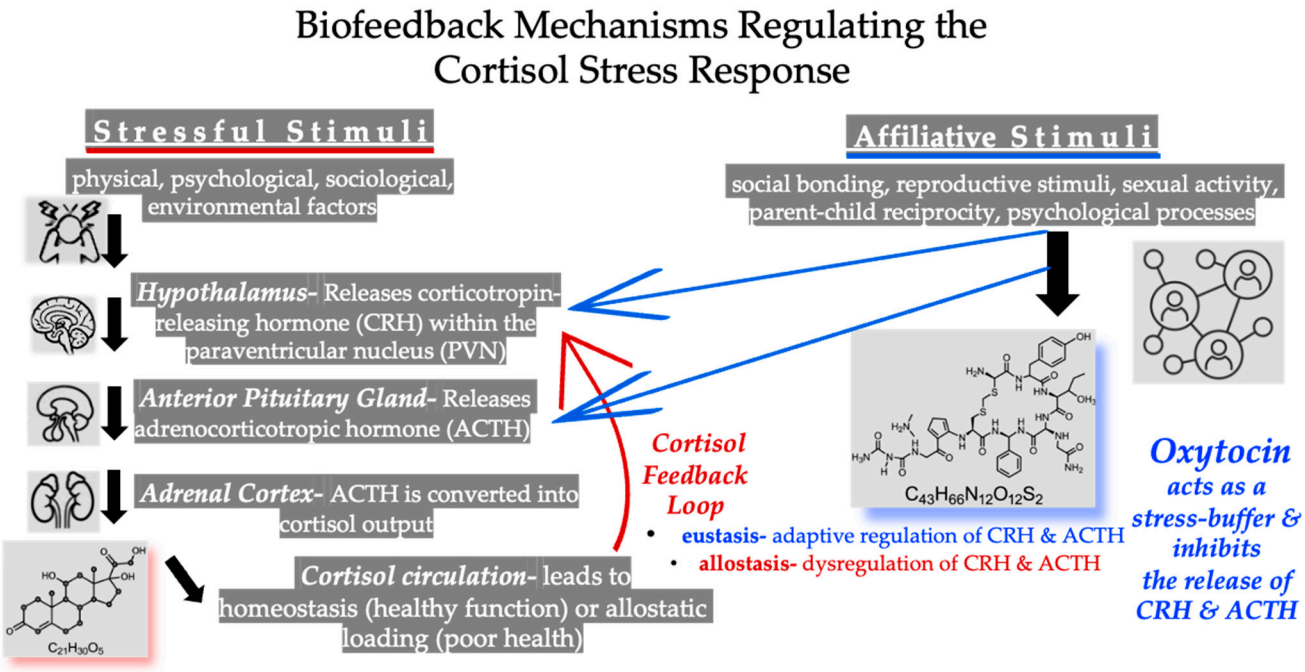


Figure 1. ACTH (adrenocorticotrophic stimulating hormone), CRH (corticotropin-releasing hormone), and PVN (paraventricular nucleus). The red font, arrow, and shadowing indicate the sympathetic action of the cortisol feedback loop in response to stressful stimuli. The blue font distinguishes the parasympathetic action of oxytocin in the regulation of the cortisol feedback loop in response to affiliative stimuli.

Oxytocin and AVP are structurally similar cyclic nonapeptides that differ by only two peptides at positions three and eight (OT: isoleucine/leucine; AVP: phenylalanine/arginine), changes that produce distinct receptor affinities and divergent physiological roles (e.g., the affiliative, anti-stress, anxiolytic oxytocin versus the antidiuretic, vasoconstrictive, and social activator AVP). This molecular proximity raises analytic and conceptual questions about fragment identity and specificity, notably whether measured peptides are functionally "oxytocin-like" or cross-reactive with AVP-related fragments.

The clinical and developmental context matters: early adversity and maltreatment are associated with altered oxytocin/cortisol dynamics and downstream social–emotional risk [86,104–106]. Rare oxytocin receptor (OXTR) variants link trauma exposure to cognitive and emotional processing differences (e.g., reduced perceptual organization, slower processing speeds, and changes in affect regulation and negative symptom severity) [107]. Because cortisol and oxytocin operate on different time scales and are subject to rapid clearance, protein binding, and fragment formation, single time-point sampling is insufficient. Integrative, longitudinal protocols that sample both hormones across circadian cycles, combine autonomic (vagal/heart-rate variability) and behavioral measures, and use fragment-sensitive assays are required to test how oxytocin mediates cortisol feedback,

promotes resilience, and strikes the balance between trauma and recovery. These considerations set the stage for examining how oxytocin–cortisol dynamics interface with the HPA–immune axis signaling in perinatal and caregiving contexts that impact maternal-child neuroplasticity [108–123] (see Figure 2).

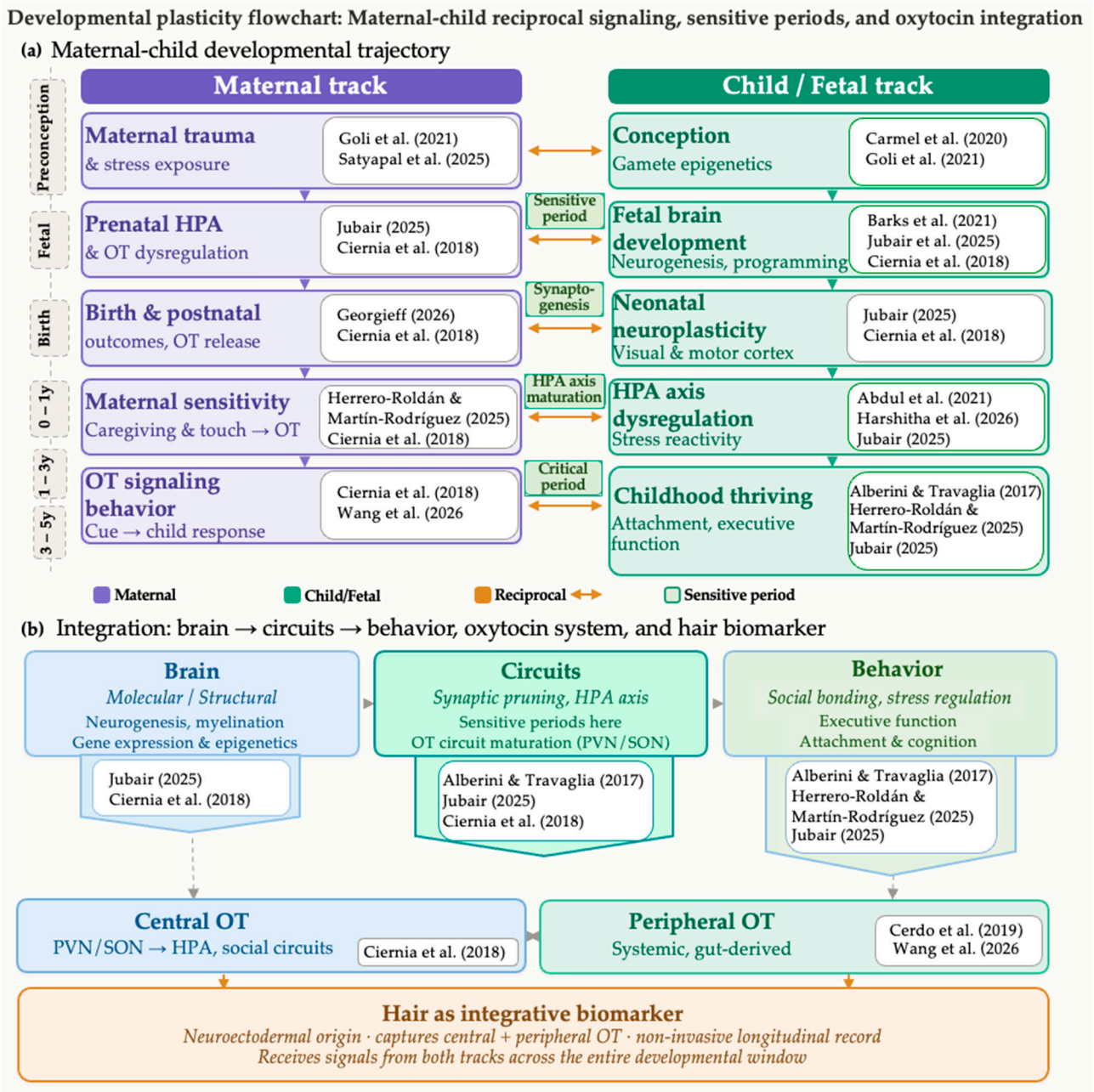


Figure 2. This figure integrates four bodies of evidence relevant to early development. First, work on neuroplasticity and sensitive periods establishes the timing of synaptic and neuronal pruning from the fetal period through early childhood. Second, studies of epigenetics, heredity, and transgenerational inheritance describe the mechanisms through which experience and ancestry shape neurodevelopment. Third, evidence on environmental, nutritional, and toxic stress exposures identifies common contributors to CNS dysregulation. Fourth, research on psychosocial factors and oxytocin signaling links the caregiving environment to stress-regulatory, social-emotional, and cognitive outcomes. Together, this evidence supports a reciprocal, developmentally timed model in which maternal–child interactions can be integrated and measured through hair oxytocin as a non-invasive biomarker [108–123].

3.3. HPA–Immune Axis

3.3.1. Maternal Psychiatric History and HPA Axis (Dys)Regulation

Maternal immunity and physical [124] and mental health [95] during the perinatal period play intricate, complex roles influencing her infant's HPA axis regulation and stress responsivity, setting a child's enduring health status and general sense of well-being. HPA axis (dys)regulation is cumulative during early life and becomes detectable closer to the child's age for HPA axis maturation (namely, 3-4 years of age). Maternal psychiatric disorders such as major depressive disorder (MDD), postpartum depression (PD), or postpartum psychosis (PP) are linked to severe morbidity for both the mother and infant [125]. Cattarinussi et al. found that mothers with psychiatric histories presented with worse executive functions and processing speeds across all cognitive domains, i.e., verbal learning, verbal memory, visual memory, executive function, verbal comprehension, and processing speed [126]. Children born to mothers with a psychiatric history display problematic internalizing and externalizing behaviors [95]. These outcomes unfold against a background of neuroendocrine–immune recalibration during late pregnancy and the postpartum period, with the HPA axis tightly coupled to OT-AVP-related processes that support lactation, bonding, and stress regulation [127,128].

3.3.2. Perinatal Adaptations and PD Risk

Adaptive changes in immunological setpoints, feedback sensitivity, and HPA axis tone are necessary during pregnancy and lactation [127,129]. PD risk increases when these adaptations are dysregulated. Reviews indicate perinatal HPA axis dysregulation as a likely cause of postpartum mood disorders [130]. Oxytocin is linked to HPA axis reactivity in postpartum women, with greater levels of oxytocin corresponding to decreased cortisol responses during mother–infant interactions [128,131]. Women with a childhood history of maltreatment are at greater risk for PD and long-term HPA axis dysregulation [132] detected by significant increases in hair cortisol concentration and stress reactivity that is amplified and sustained through middle life when experiencing new stressors [133]. Stress reactivity between mothers and children has been attributed to elevated maternal prenatal cortisol linked to mothers' childhood maltreatment, resulting in their children presenting with lower executive functioning [134].

High-risk mothers, based on their own childhood histories, experience a disconnect between the perception of their child's health, behavioral, and developmental status that is not consistent with their child's actual developmental outcomes [100–102].

3.3.3. Developmental Calibration of HPA Function

Physiological cortisol levels and stress-reactivity are calibrated by the quality of caregiving from early childhood through adolescence. In a large longitudinal cohort, higher maternal insensitivity and greater time spent in center-based care during the first three years of life predicted cumulative lower awakening cortisol at age 15 years [135]. Early psychological distress is linked to allostasis to explain vulnerability to chronic disease, with proposed behavioral and biological mechanisms connecting childhood stress exposures to immune and metabolic dysregulation in adulthood [136].

There is no clear consensus in the calculation of allostatic load. Investigators call for clearer, more standardized methods incorporating age, sex, race, and temporal exposures to ACEs and PCEs for determining loading scores [137]. HPA axis function and neurodevelopmental progression during early life can be influenced by vaginal vs. cesarean birth due to transfer of the maternal microbiome [138]. The vaginal microbiome modifies the mucosal immunity of an infant and communicates with central stress circuits via immunological and vagal pathways. Additionally, maternal breast milk contains oxytocin and secretory (s)-IgA

that provide a direct interface between the immunological and microbiological status of the mother, thereby regulating the newborn's physiology. The maternal influence of the child's gut–immune axis in child metabolism has not been fully explored [139]. Nonetheless, an allostatic algorithm revealed moderate inflammation and the earlier onset of childhood obesity following exposures to childhood adversity [139,140].

Postpartum women exposed to adversity show clustering between immune-cell mitochondrial oxygen consumption and alterations in cortisol and oxytocin, linking endocrine regulation to cellular energy metabolism [141]. These factors can influence the quality and quantity of milk production. Human breast milk oxytocin and s-IgA vary with maternal anxiety, suggesting that the maternal mood shapes immune signals available to the infant [139]. Breastfeeding mothers asymptomatic for anxiety or depression, but not symptomatic mothers, have higher circulating levels of oxytocin and lower cortisol in the postpartum period [128].

3.3.4. Social Buffering and Dyadic Biology

The social buffering properties of oxytocin discussed through this narrative review have addressed the ability of oxytocin to affect glucocorticoid gene activity driven by cortisol. GREs, short DNA sequences in immune-related genes, bind to the glucocorticoid receptor after cortisol-mediated activation. In adults, real-time partner dialogue increases interbrain synchrony between partners, which is associated with lower cortisol, higher oxytocin, and reductions in s-IgA, which suggest a coordinated adjustment of neuroendocrine and immune systems during affiliative exchange [142]. In romantic and co-parenting pairs, hyperscanning shows that social interactions and touch strengthen brain-to-brain coupling, and stronger coupling relates to better empathic accuracy and more coordinated behaviors [142–144]. Longitudinal work connects co-parental bonding with corticostriatal pathways that support coordinated caregiving and family formation, consistent with a partner-synchrony mechanism [145]. In youth, supportive friends show similar stress-buffering effects on physiology that engage the oxytocin system, which indicates that social context shapes HPA axis output across development [131]. Computational methods now incorporate parent–child interaction patterns with pediatric obsessive–compulsive disorder (OCD) cohorts to interpret how child oxytocin levels relate to their developmental stage and psychopathology [146,147].

3.3.5. Mechanistic Bridges Between Oxytocin and the HPA–Immune Axis

Immune dysregulation with altered pain perception and psychological distress are hallmark features of toxic stress (https://osg.ca.gov/wp-content/uploads/sites/266/2020/12/Part-I-3.-The-Biology-of-Toxic-Stress.pdf) (accessed on 23 June 2026) [148]. Several lines of evidence suggest that oxytocin directly interacts with immune pathways and microglial function [149,150]. Experimental data show that OXTR agonists can reduce perinatal brain injury by targeting microglia (macrophages of the brain and spinal cord), due to anti-inflammatory neuroprotective effects in early life [150]. Oxytocin can have varying results due to distinct astrocytic G-protein signaling in neuronal targets. Conceptually, oxytocin may support neuronal differentiation and curb inflammatory signaling by inhibiting glycogen synthase kinase-3β, a protein that regulates cell survival and inflammation. It may also function by modulating the Wnt/β-catenin pathway, which guides cell fate and tissue repair [151].

Complement signaling, a part of the innate immune system that serves as a bridge to adaptive immunity, enhancing the ability of antibodies to suppress inflammation and fight pathogens, can also influence oxytocin biology. In mice, C4a, a cleaved product in the classical complement pathway, binds to oxytocin, changes its circulating levels, and shifts

social behavior [152]. Yamamoto et al. (2025) conclude that innate immunity can fine-tune peptide availability and may influence coupling between oxytocin and the HPA–immune axis [152].

Emerging evidence also implicates mitochondria as a downstream effector of oxytocin signaling. In human postpartum groups, measures of mitochondrial oxidative metabolism vary with oxytocin under stress exposure. Preclinical studies suggest that oxytocin dosing can help restore mitochondrial function and limit oxidative/inflammatory damage, linking peptide signaling to cellular energy and redox balance [141,153].

In clinical settings, intranasal oxytocin has been associated with changes in cytokine profiles alongside social symptom outcomes in autism trials, again tying oxytocin to immune results [154]. At the systems level, hypothalamic circuits that integrate oxytocin and AVP support socioemotional behaviors from approach/affiliation to defensive responses, providing anatomical substrates for coordinated endocrine–immune adjustments during social interactions [155].

Testing clinical outcomes of oxytocin therapy to moderate stress–immune reactivity remains challenging due to the diurnal expression patterns of these hormones. The benefit of measuring neuroendocrine hormones and immune factors in hair is that hair stably binds circulating levels of these biomarkers to signify the cumulative average of physiological responses over weeks and months.

3.3.6. Cautions and Boundary Conditions

It is vital to operationalize the social context, the temporal or diurnal timing, the endogenous release, and synthetic oxytocin dosage in therapeutic interventions. Partner availability appears to be an important moderator of perinatal maternal physiology: when a co-parent is absent or unavailable during labor and the early postpartum period, the dyadic social buffering seen in partner hyperscanning studies is reduced, removing a natural brake on cortisol and coordinated affiliative responses, and may heighten maternal vulnerability to postpartum depression [142]. Exogenous oxytocin appears unlikely to substitute for partner-based synchrony and may have different effects in its absence [142,143].

An animal study revealed that giving high-dose intranasal oxytocin (50 µg) daily across three days in early life dysregulated the HPA axis and the formation of social behaviors as opposed to supporting neuroprotection [156]. Rault et al. (2013) acknowledged that their findings could be attributed to the dosage and age at dosing [156]. A recent study demonstrated that low concentrations (10 pmol/L) excite oxytocin neurons and higher concentrations (1 nmol/L) inhibit oxytocin neurons [149]. These animal studies illuminate how critical it is to establish a dose–response curve for appropriate therapeutic administration. Apart from the inconsistencies noted for oxytocin dosing regimens, it must be noted that problematic symptoms related to immune–neuroendocrine models of psychiatric disorders (i.e., PTSD) can be effectively modified via psychotherapy, as opposed to dosing with oxytocin [85].

Overall, findings summarized in this section support the idea that endogenous oxytocin and perhaps exogenous oxytocin optimizes prenatal stress and bonding by interacting with the HPA–immune axis. Future research could outline the ways in which social context, prior exposure, and the timing of intervention can affect these processes.

3.4. Genetics and Epigenetics of the Affiliative Brain Pathway

3.4.1. Epigenetic Mechanisms and Biological Embedding

Epigenetics is the study of biological embedding of positive and negative environmental factors capable of silencing protein expression. The phrase "biologically embedded" can be conceptualized as the adjustments made to bodily systems (e.g., endocrine, hormonal,

immune, and neuronal) under varying environmental and behavioral exposures [136]. Oxytocin, cortisol, their receptors, and their interactions with response element genes are susceptible to epigenetic modifications. ACEs and PCEs contribute to divergent neural networking during sensitive neuroplasticity periods in the fetal brain up to a child's fifth year of age. ACEs unbuffered by PCEs contribute to HPA axis dysregulation with the manifestation of cardiovascular and metabolic-associated diseases during later childhood. The association between HPA axis dysregulation and epigenetic factors must be explored to determine therapeutic means to reduce epigenetic transmission from parent to child. Expert opinions grounded in empirical studies suggest that epigenetic mechanisms are reversible and even preventable [157]. Processes involved in the reversal of these mechanisms that shape ITTS remain underexplored. A basic exploration requires the consideration of risk factors, measures, and interventions (see Figure 3) [132,133,158–178].

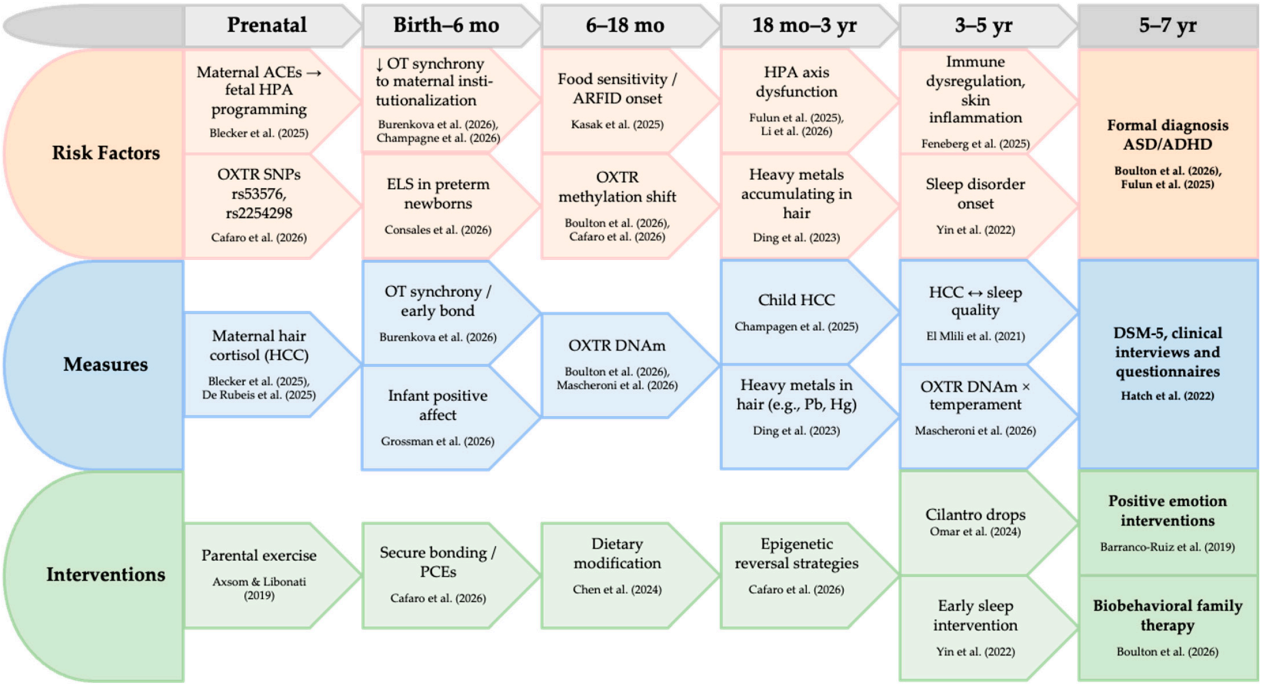


Figure 3. A cascade of neurodevelopmental risks, biomarkers, and interventions. This figure proposes a longitudinal, multifaceted framework of understanding and assessing neurodevelopmental conditions across six developmental time periods, ranging from the prenatal to ages 5–7. Content is organized in three rows representing distinct categories: risk factors (orange), the biological predispositions and environmental exposures that may promote atypical neurodevelopment; measures (blue), the biological and behavioral markers used to assess neurodevelopmental status at each stage; and interventions (green), the evidence-based strategies that may reduce or prevent symptom onset. This figure is grounded in the concept of cumulative allostatic loading: each developmental stage inherits the unresolved biological atypicalities of the previous one, such that a child's clinical presentation of symptoms at ages 5–7 represents years of biological compounding that cannot be as easily treated [132,133,158–178].

Parental histories of adversity shape their children's development and long-term wellness [157,179] via heritable epigenetic gene-silencing mechanisms. One study conducted by Leon et al. (2022) examined the extent to which ELS was inherited across mother–child dyads by identifying differentially methylated regions (DMRs) between children and their mothers [179]. Mothers and neglected children showed overlapping genome-wide DNA methylation patterns linked directly to the emotional intensity of ACEs the mother had faced. These findings help explain how ELS and dysfunctional parenting are biologically transmitted across generations [180,181]. A question remains as to whether maternal

treatments prior to or after childbirth may moderate sensitive DMR regions to prevent developmental disorders such as autism or ADHD in their children.

PCEs remain underexplored in preverbal and preschool children. A gradual shift in epigenetic healthcare practices over the last decade is gaining traction by focusing on health maintenance opposed to curing disease. For example, a recent review discusses the transgenerational benefits of parental physical activity and exercise training in mediating fetal metabolic and cardiac programming [182]. Nonetheless, the healthcare industry remains predominantly fixated on treating, as opposed to preventing, disease [183,184], often by administering synthetic (pharmaceutical and biotechnological) methods (Section 3.7).

The preclinical implications for oxytocin therapy surged when some began viewing oxytocin as a pharmacological "oasis" for psychiatric disorders [185]. Pharmaceuticals and biotechnological approaches to reverse the epigenetic mechanisms of DNA methylation, transcriptomic (i.e., microRNA), and/or histone modification are available. DNA methylation is the process of covalently binding a methyl group to effectively silence a heritable gene [186]. Histone modifications refer to the chemical alterations on lysine, arginine, and other residues, including methylation, acetylation, phosphorylation, and ubiquitination. ncRNAs, also known as microRNAs (miRNAs), bind to messenger RNA (mRNA) to cause its degradation, thereby blocking protein translation [187]. These changes occur at the level of the "chromosome rather than in the DNA sequence" [187]. Thus, epigenetic therapies are being investigated for the early onset of noncommunicable diseases: cancer [188,189], accelerated aging in MDD [190] and COVID-19 survivors [191], Parkinson's Disease [192,193], pulmonary tuberculosis [194], and osteoarthritis [195]. Current standard operating procedures guiding pharmaceutical dosing with oxytocin to treat the childhood onset of developmental disorders frequently fail to incorporate family or individual biobehavioral therapies that may sustain transgenerational remission. Positive emotion-based interventions are proven to "alleviate mood disorders, improve cognitive function, and enhance social and physiological health" [196], yet they remain underexplored.

3.4.2. OXTR Methylation and Social–Cognitive Function

Epigenetic mechanisms within the oxytocin pathway that regulate social cognition and behavior are largely unknown [197–199]. Although the oxytocinergic system is associated with social and behavioral development, there are very few direct links between epigenetic modifications and social cognition [197,198]. Puglia et al. (2015) investigated OXTR methylation as a link to amygdala activity when healthy, adult participants were presented with stimuli intended to produce fear and anger [199]. Results of the study showed that lower methylation led to increased endogenous oxytocin, which attenuated the perception of negative stimuli [199]. Adults with decreased OXTR methylation were less likely to have disordered social perceptions. Oxytocin has numerous functions in physiology, reproduction, parent–child bonding, and additional socioemotional and behavioral roles [200]. Distinctions should be drawn between epigenetic regulation of oxytocin synthesis in comparison to receptor turnover or the binding expression of oxytocin response element genes. Future research should continue to explore the links between the oxytocinergic system and social–cognitive functioning, particularly in pediatric populations.

Genetic variations in the OT-AVP pathway genes or the polymorphisms in the oxytocin receptor impact social behavior, stress, and psychiatric conditions such as autism, anxiety, and depression. Genetic factors affecting the oxytocin pathway involve polymorphisms in OXTR genes, the structural oxytocin gene, and the *CD38* gene. Pathway genes involved in psychiatric disorders are linked to an OXTR single-nucleotide polymorphism (SNP) related to autism, depression, and schizophrenia. Two specific SNPs are rs53576 and rs2254298 [27]. Figure 3 positions these genetic and epigenetic factors within the broader developmental

timeline, demonstrating how OXTR SNPs operating prenatally interact with early life stress, caregiver synchrony, and the accumulating allostatic load across early childhood, informing neurodevelopmental trajectories. As indicated in Figure 3, molecule-level variation in the *OXTR* gene, be it genetic or environmental, compounds over time, affecting immune, sleep, and HPA axis dysregulation by mid-childhood. The oxytocin receptor is a G-protein coupled receptor that mediates oxytocin effects in the periphery and brain through downstream intracellular signal transduction [130,201]. Intriguingly, the most studied OXTR polymorphism, rs53576, is associated with empathy, social behavior, and stress, where G alleles show increased emotional support seeking and sociability, whereas A alleles exhibit higher stress sensitivity with lower social tendencies [47,202]. OXTR polymorphisms vary by race and ethnic backgrounds [37]. Future research should combine epigenetic data with diverse populations to view how receptor expression and brain pathways mediate genotype-linked neural circuit behaviors. While OXTR polymorphisms represent fixed genetic variation, epigenetic modifications of this system (Figure 4) offer a potentially reversible pathway through which parental stress becomes biologically embedded and transmitted to offspring [132,133,158–168,178].

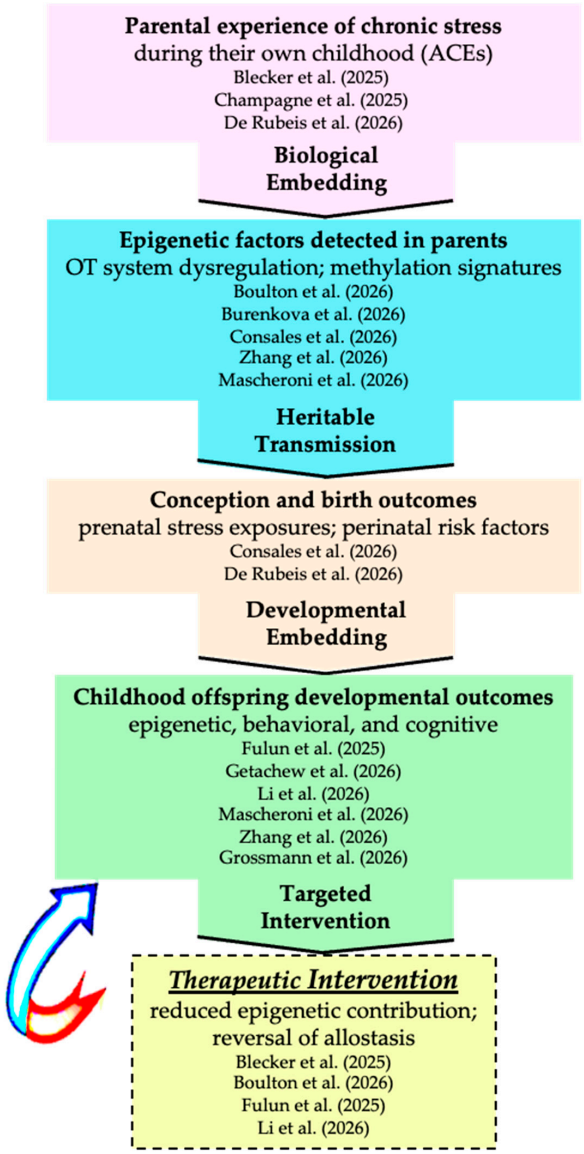


Figure 4. Pathways for intergenerational transmission. This figure proposes a pathway showing how parents' own childhood adversity (ACEs) may become biologically embedded and passed on to their

children through epigenetic mechanisms, including oxytocin system dysregulation and methylation changes. These factors can influence conception, pregnancy, and birth outcomes, which in turn shape children's developmental outcomes. The curved arrow indicates that targeted therapeutic interventions may help mitigate this intergenerational transmission by reducing or reversing epigenetic signatures [132,133,158–168,178].

3.5. The Power of Parenting and Interbrain Synchrony

3.5.1. Early Synchrony and Brain Plasticity

Many empirical studies clearly define the bi-directional role of parent–child behaviors that shape synchronous brain plasticity. The majority of these studies are based on neuroimaging and EEG technology measuring maternal–child interactions in real time.

Parenting functions as a behavioral system, as well as a neurobiological system, for regulating behavior. Neurobiologically, maternal endogenous oxytocin is highest during the perinatal period [103]. Behaviorally, oxytocin signals bidirectionally through the parent–child interactions. Through the interaction of the caregiver's and the infant's eye contact, voices, and touch, they can develop and create rhythmic patterns of multi-sensory synchrony with one another, thus affecting the infant's brain development and its ability to maintain emotional equilibrium. Inter-brain plasticity is defined as the process by which the infant's brain develops from repeated episodes of synchronization with the caregiver, and this process helps to refine the neural circuitry associated with empathy and the regulation of emotions [203]. Swain and colleagues expanded upon the previous research by identifying that parental attachment activates areas of the brain that are associated with emotional regulation, reward, and a motivation to care for others [204,205]. They also identified oxytocin as the primary neuromodulator responsible for maintaining these interactive processes [204,205]. While the research provides valuable information about how neural coupling in early life trains the brain's stress systems to recover, reorganize, and ultimately build resilience, it raises several questions. Parenting is therefore both experiential and neuroendocrine, operating as a dynamic system that organizes physiology, emotions, and meaning.

A central purpose for this comprehensive narrative review on oxytocin is to demonstrate the use of oxytocin as a measure of childhood outcomes to explain the potential for child flourishing. Flourishing is well established in the literature as the ability of an individual to thrive in the presence of positive experiences that are capable of buffering a multitude of stressful or adverse experiences [5]. Recent research on PCEs provides a lens to quantify relational processes. We proposed a PCE-Preschool scale to identify nurturing relationships, supportive environments, emotional safety, and opportunities for growth, each of which represents a different aspect of building resiliency in early life [5].

3.5.2. Biobehavioral Synchrony and Stress Regulation

The role of the parent is a biologically synchronized process that transmits regulatory control from one nervous system (the parent) to another (the child). The relationship of oxytocin-mediated attachment, daily routine consistency, and positive parental interactions in childhood all contribute to internalizing the models of regulation (balance and recovery) that contribute to a child's emotional resilience throughout their lifetime. These early relationships serve not only to protect against adverse events, but they also provide a foundation for the child to develop the skills necessary to be empathetic, self-regulate, and maintain good physical and mental health.

Feldman developed the biobehavioral synchrony framework that defined parent–infant synchrony as the coordination of physiological and behavioral rhythms, including gaze, affect, and vocalizations, which serve as the foundation of self-regulation [26,27]. According to Feldman, synchrony is not only the social, but also physiological training

of circadian biorhythms. Establishing consistent bedtime habits/routines (e.g., rocking, cuddling, singing, or reading for pre-verbal and preschool children) supports a rise in oxytocin for sleep induction and restful duration [58,94]. The concept of the sleep–social–oxytocin nexus illustrates how sleep quality, social interaction, and oxytocin signaling support the recovery of biological stress systems [68]. Together, these systems indicate that resilience is created through the biological dance between caregivers and young children.

The maternal stress and depression experienced during pregnancy program fetal regulatory systems, thus influencing how the infant will respond to future emotional challenges [206]. Early exposure to environmental toxins disrupts oxytocin and vasopressin pathways in the developing brain and indicates that biological stress regulation is active even before birth [207]. This potentially leads to dysregulation of the infant's stress physiology, which may persist throughout development due to neuronal network connectivity established during sensitive periods of brain neuroplasticity.

Together, these findings suggest a coherent pathway where parental stress and caregiver warmth become biologically embedded and transmitted to the offspring. Table 2 illustrates this pathway across five stages, from early-life parental stress through epigenetic and prenatal mechanisms, to childhood outcomes and potential points of therapeutic reversal [132–134,158–168,178].

Table 2. Intergenerational transmission of toxic stress. Proposes a five-step pathway linking parental early-life stress to offspring developmental outcomes and critical developmental windows as potential points for therapeutic intervention [132,133,158–168,178].

Pathway Step	Mechanisms	Key Finding
Step 1 Parental experience of chronic stress	• HPA axis dysregulation • Cortisol elevation • Biological embedding	A difficult childhood keeps the body's stress system overactive long term. Parents who experienced ACEs show higher cortisol levels years later, accentuated during pregnancy.
Step 2 Epigenetic factors detected in parents	• OT system dysregulation • OXTR methylation • Neural circuit disruption	Parental stress leaves biological marks, particularly on the oxytocin system and its receptor gene, that can be passed on to children [158–160,167,168].
Step 3 Conception and birth outcomes	• Prenatal cortisol exposure • Perinatal OT disruption • Heritable transmission	During pregnancy and at birth, the child is already being affected through elevated cortisol in the womb and disrupted oxytocin levels in newborns [134,161,162].
Step 4 Childhood offspring developmental outcomes	• HPA dysfunction • Behavioral outcomes • Cognitive outcomes • OT–affect disruption	Children show a range of outcomes tied to a dysregulated stress system, including ADHD [164], eating difficulties [165], lower positive affect [178], anxiety [166], and alterations in temperament [167].
Step 5 Therapeutic intervention	• OT administration • Epigenetic reversal • Biomarker considerations • Positive parenting techniques • Mindfulness training	Oxytocin treatment can reverse some effects of ELS in the brain [166] and targeted OT therapies show promise [158]. Accurate cortisol measurement is important for tracking whether interventions are working [132,163].

Following birth, the caregiver's attunement serves as a behavioral extension of the prenatal influences. Cardenas identified paternal sensitivity as a predictive factor of a child's attunement [208], while Moilanen and Rambo-Hernandez identified maternal relationship quality as predictive of self-regulatory growth in adolescents [209]. Boyer and Nelson further established the link between parental sensitivity and physiological outcomes, demonstrating that parental sensitivity mediated the relationship between social competence and cardiovascular health, evidence that the quality of a relationship can influence the child's allostatic load during development [210]. Together, these studies demonstrate that emotional safety and synchrony within the context of caregiving relationships provide the necessary mechanisms to regulate the child's biological stress systems throughout childhood and adolescence.

Oxytocin plays a dual role at the mechanistic level. It facilitates approach behaviors, increases sensitivity to social cues, and decreases HPA axis reactivity during stressful events [211]. Due to its presence in both the central and peripheral systems, oxytocin serves as a unique biomarker, allowing researchers to connect measurable physiological responses to subjective social experiences and vice versa. Thus, oxytocin is not only a correlate of human bonding, but rather a bridge connecting social experience to recovery. Further complexity is added by the influence of a family of genetic studies examining variants of OXTR rs53576 on how caregivers perceive and respond to their children's distress [212,213]. While gene–environment interactions were found to modulate the development of resilience using cellular aging markers (telomere length) as an indicator [214], it is also important to examine culturally- and contextually-based variables when examining the impact of genetic factors. In this way, Chander and group demonstrated that the relationship between OXTR-based empathy and the caregiver's culture was an important consideration [37].

3.5.3. Metaplasticity of Oxytocin Neuroendocrine Function

Oxytocin also plays a critical role in intra- and inter-individual neuroplasticity. Neuroplasticity research shows how experience-dependent changes within individual brain mechanisms has long-term potentiation with synaptic transmission and dendritic remodeling during the formation of new or the maturation of connected neural circuits [215]. Intra-individually, neuroplastic processes provide learning and adaptation through Hebbian (synaptic) plasticity. Homeostatic plasticity, on the other hand, serves to stabilize global network activity [216]. During pregnancy, oxytocin functions at the cellular and molecular level to induce neuroplasticity in mothers that is driven by synaptic remodeling, neurogenesis, and glial activity to prepare for caregiving and infant bonding [217]. Inter-brain plasticity is a curious phenomenon illuminating how socialization influences the neural synchronization observed during coupling interactions such as romantic relationships, co-parenting partners, or parent–child bonding [203,218].

During parental–infant socialization, neuroplasticity in the infant is driven at the network level for connectivity that is heightened by infants seeking and responding to familiar faces and facial expressions [219]. Early predispositions reveal innate neural detectors for social stimuli and substantial developmental variations in face and motion perception arising through early life [220]. Longitudinal studies exhibit that mother–child behavioral synchrony from infancy predicts the magnitude of neural activation to attachment cues, neuroendocrine systems involved in stress regulation, social bonding, and immunity [28]. Neural coordination, established by parent–child interactions developing through adolescence, becomes predominantly attuned to neural systems in social contexts, amplified sensitivity to social influence, and peer feedback [221].

3.6. Developmental Disorders

3.6.1. Internalizing and Externalizing Problems

Multiple factors, including the environment, parental background (e.g., histories of ACEs, PCEs, and mental health), and child temperament, can serve as risk factors for behavioral problems such as internalizing and externalizing behaviors. Familial dysfunction and the home environment have significant effects on child behavior. Family discord, violence, parental alcoholism, partner conflict, mental health concerns, and neuroticism [222] are common measures included in inventories. Parental mental health interacts with child temperament, and high parental psychopathology predicts greater child behavioral instability [222]. Even when parental psychopathology is low, children with temperament difficulties still show higher risk for externalizing problems such as aggression, defiance, and impulsivity [222].

Child psychopathology plays a major role in internalizing problems. High neuroticism is one of the strongest predictors of internalizing behaviors, whereas low extraversion and low agreeableness contribute to increased social anxiety and reduced emotional control [223]. Children who report deviations from typical Big Five profiles (openness, conscientiousness, extraversion, agreeableness, and neuroticism) show high levels of both externalizing and internalizing behaviors [224]. When a child's personality shifts away from developmental norms over time, they present a higher risk for both categories of problems [224]. Oxytocin-related pathways appear to underlie functions involved in the internalizing and externalizing symptoms in ways that intersect with environmental and temperamental factors.

Maternal depression (MDD and/or PD) is a major health concern associated with oxytocin pathway dysregulation. Low maternal oxytocin predicts children's internalizing problems in early childhood through age 6 [225]. Child maltreatment is also a significant risk factor consistently associated with oxytocin alterations. Children with a history of maltreatment show lower salivary oxytocin levels and reduced social cue recognition [226]. This study had limitations, including a broad age range (ages 2 to 15) and interindividual sample collection across an eight-hour period, both of which affect diurnal concentrations.

Child maltreatment has long been associated with HPA axis dysregulation. Maltreated adolescents, specifically girls with a history of abuse, have higher levels of urinary oxytocin and lower levels of salivary cortisol [227]. Given the biological mechanisms, dysregulation of the HPA axis, as indicated through these findings, can lead to externalizing problems (poor emotion regulation, impulsivity, oppositional behavior) and internalizing problems (anxiety and depression).

3.6.2. Neurodevelopmental and Psychiatric Disorders

New evidence indicates optimal intranasal oxytocin dosing capable of "rescuing" connectivity within salience and sensorimotor networks of adult males with autism [75]. Andari and colleagues concluded that the baseline/resting network strongly predicted individual responsiveness. Additionally, individuals with pre-existing connectivity patterns demonstrated greater oxytocin-induced changes, suggesting high heterogeneity in ASD [75]. This is also present at the genetic level in common OXTR polymorphisms, with rs53576 and rs2254298 associated with greater social impairment with ASD but also with fewer social deficits in ADHD [228]. Both findings suggest diagnosis-specific modifier alleles rather than uniform risk factors.

In comparison, peripheral biomarkers in plasma oxytocin concentrations have reported no reduction in ASD but rather correlate positively with symptom severity [229]. Broader social implications have been shown in mouse models of ASD as well, with probiotic treatments enhancing social behavior while also increasing oxytocin levels and improving

receptor signaling [230,231]. Empirical evidence from these models demonstrates the action of probiotics within the gut where there is a high concentration of oxytocin receptors. Greater than half of the cells present in the human body are microbial cells, most populous in the gut [232]. Therefore, it stands to reason that the rise in synthesized, secreted, circulating oxytocin occurs via microbial symbionts boosting oxytocin through vagus-nerve-dependent gut–brain–immune axis mechanisms [232]. These findings, as a whole show, how the oxytocin system in neurodevelopmental disorders can change and adapt based on genetic, neural, social, and microbial environmental factors.

ASD, ADHD, and schizophrenia manifest with impaired oxytocin and dopamine functions linked to faltering adaptive development of socialization skills [233]. It is important to note that investigators of ASD and ADHD focus primarily on the level of protein synthesis, whereas other psychiatric disorders tend to focus on receptor expression or methylation. Mice studies show an alignment with protein synthesis mechanisms with one study investigating mutations in the SHANK3 postsynaptic scaffold protein [234]. Naturally occurring forms of SHANK3 are responsible for synaptic development, brain function, and eye tracking. Knockout mouse ASD models for SHANK3 revealed increased global cerebral protein synthesis [234]. Knockout dog ASD models for SHANK3 demonstrated that exogenous oxytocin increases the eye gaze duration [235]. With schizophrenia, aberrant elevations in vasopressin (AVPR1a) and oxytocin (OXTR) receptor expression occur in the superior temporal sulcus and hypothalamus in humans with advancing age, perhaps as a compensatory mechanism for reduced vasopressin and oxytocin release [236]. Reductions in oxytocin are also confirmed in borderline personality disorder [237]. Schizophrenia studies have described schizophrenia as a condition of dopaminergic dysfunction with "dopamine system overdrive" [238]. Adolescent stress impairs socialization skills and is strongly associated with the emergence of schizophrenia [238] and borderline personality disorder during adolescence and early adulthood.

3.6.3. Sources of Therapeutic Oxytocin Preparations

The role of oxytocin as a central neuropeptide involved in the regulation of stress reactivity across systems (i.e., stress, affiliative, dopaminergic, acetylcholinergic), along with age- and sex-specific findings in humans, has been discussed. Much of this information has been gathered through in vivo and in vitro evidence, particularly in the arena preparing exogenous, synthetic oxytocin administration for preclinical and clinical trials. Other than pitocin or syntocinon for the induction of labor, it is unclear how and why certain preclinical and clinical trials have selected the synthetic formulations of oxytocin. See Table 3 for a list of suppliers.

Table 3. FDA-approved synthetic oxytocin manufacturers. Provides FDA Establishment Identifier (FEI) numbers and facility registration details obtained from the U.S. FDA Drug Establishment Registration & Listing Database and DailyMed FDA drug labels. Addresses were verified via company websites.

Manufacturer	**FEI/ID**	**Address**
Fresenius Kabi USA, LLC	FEI 840771732/023648251	3 Corporate Dr, Lake Zurich IL 60047
Par Sterile Products LLC (Pitocin®)	FEI 808402890	870 Parkdale Rd, Rochester MI 48307/6 Ram Ridge Rd, Chestnut Ridge NY 10977
Hospira Inc. (Pfizer)	FEI 3002802538	275 N Field Dr, Lake Forest IL 60045
Oxytocin Nasal Spray Vendors (Research and/or Clinical Use) 503A and 503B facilities		
Vendor	**FEI/Registration**	**Address**
Empower Pharmacy	FEI 3021758709 (503B)	7601 N Sam Houston Pkwy W, Ste 100, Houston TX 77064
Harbor Compounding	CA License PHY 50397 (503A)	3500 W Lake Center Dr, Unit B, Santa Ana CA 92704
Bayview Pharmacy	RI 503A License	3844 Post Rd, Warwick RI 02886
Fagron Sterile Services US	FEI 3010661617 (503B)	6611 W Hallett Rd, Latham NY 12110

3.6.4. Brief History of Synthetic Oxytocin Therapy

Synthetic oxytocin (pitocin or syntocinon) was first developed in 1954 by Vincent de Vigneaud, an American biochemist [239]. De Vigneaud and colleagues determined the structure of the neurohypophysial hormone oxytocin, which was the first peptide hormone to be synthesized [130,201]. Usage was focused on labor and childbirth, primarily on uterine contractions in labor [130,201]. Limited clinical trials began in the UK, with 31 labor patients being administered either synthetic oxytocin or purified natural oxytocin [240]. In comparing these two treatments, clinicians found synthetic oxytocin to be equal in efficacy to purified natural oxytocin produced in the body [240]. The ability to synthesize oxytocin served as a major milestone in peptide chemistry and pharmacology.

Apart from its longstanding clinical use for the induction of labor, animal studies show that oxytocin treatment reduces physiological responses to acute stress. In rodents, treatment via nasal cannula reduced pulmonary edema, neutrophil influx, and signs of oxidative stress following a heat challenge [241]. These findings suggest that oxytocin regulates systemic responses to environmental stress, such that recovery occurs through the coordinated inhibition of inflammation and reduction of oxidative stress via oxytocin and glucocorticoid response element genes [19]. Human preclinical and clinical trial studies provide parallel data within psychosocial contexts.

At the molecular level, oxytocin works together with vasopressin and the related receptors involved in empathy, pain perception, and social modulation [242–244]. Receptor dynamics may account for the variance in how children with neurodevelopmental disorders such as ASD, ADHD, and others process pain. Oxytocin receptor polymorphisms were associated with ELS experience as a pathway to psychiatric illness later in life, including schizophrenia [245]. Overall, the studies discussed indicate that oxytocin is both an immediate mediator of acute stress responses, as well as a long-term marker of psychiatric illness risk.

Adolescents who have experienced parental psychopathology (e.g., schizophrenia, bipolar disorder) have lower levels of serum oxytocin and heat shock protein HSP-70, a cellular stress-regulating protein [246]. Lower levels of these biomarkers may indicate increased stress reactivity and decreased resilience in youth at higher genetic and environmental risk. Overall, the evidence supports the idea that oxytocin and heat shock proteins may be biomarkers of ELS and mediate the subsequent long-term effects of ELS on emotional and physiological regulation.

3.6.5. Modern Clinical Usage

Childhood perinatal development is largely dependent on a mother's experience during parturition. All precautions should favor a mother's smooth birthing experience to benefit the child's birthing outcomes. The clinical usage of synthetic oxytocin spans a wide variety of procedures, including labor induction, uterine synchrony, control of post-partum hemorrhage, and adjunctive therapy for incomplete or inevitable abortion [62]. It is worth noting that oxytocin has a half-life of 3–5 min with continuous dosing required [62]. Since the 1950s, it is commonly used with labor and childbirth to favor positive maternal and neonatal outcomes, primarily with lactation ejection and stimulation of contractions [201]. Synthetic oxytocin is associated with a lower maternal PD risk when adjusted for history of depression and other risk factors [247]. A systematic review concluded that synthetic oxytocin raises maternal plasma concentrations during labor while fetal exposures show little to no increase [248]. Still, others point out that oxytocin induction, compared to spontaneous labor, especially with higher or prolonged dosing, increases perineal trauma and postpartum hemorrhage but appears to have no impact on lactation or breastfeeding [249].

3.6.6. Clinical Trials

Numerous clinical trials have investigated the use of intranasal synthetic oxytocin. Intravenous (IV) or intramuscular (IM) oxytocin is primarily aimed at labor and postpartum care. A meta-analysis of randomized controlled clinical trials to investigate high vs. low dosages in labor found that low-dose regimens tend to be as effective as high-dose regimens for labor augmentation and more effective in lowering rates of uterine tachysystole [250].

Meta-analyses warn that precautions are warranted during prophylactic labor induction because dosages and dosage timing play significant roles for favorable maternal and neonatal outcomes. One systematic review with a meta-analysis concluded that prophylactic administration post-vaginal delivery can reduce average postpartum blood loss [251]. Rapid IV administration can cause maternal hypotension and tachycardia, and dilution with an isotonic solution mitigates these adverse side effects [252]. In a separate meta-analysis, oxytocin administration, before or after placenta delivery, resulted in no significant change in postpartum hemorrhaging [253]. Additional randomized trials investigated the role of oxytocin in wound healing. Physical intimacy in relationships, along with administered oxytocin, resulted in a decrease in the cortisol response during wound healing [254]. Interestingly, intranasal oxytocin alone was not associated with wound healing, but the combination of physical intimacy resulted in faster recovery. This further illuminates the role of a supportive co-parent during maternal postpartum recovery.

3.6.7. Oxytocin and the Transdiagnostic Psychopathology Factor

Psychiatric research has shifted towards identifying transdiagnostic mechanisms underlying comorbidity across mental health disorders. The psychopathology factor (p-factor) model is a single unified dimension of mental illness that explains the shared variance across internalizing disorders, externalizing disorders, and thought disorders [255]. In pursuit of the p-factor, oxytocin has been identified as a possible molecular mechanism alongside other endocrine and inflammatory markers like cortisol, testosterone, and C-reactive protein [256,257]. Multiple modeling strategies demonstrated that neuroticism, impulsivity, and functional impairment were most highly correlated with elevated p-factor scores [258]. Family and twin studies support the notion of common genetic factors contributing to these patterns of a common biological risk process [259]. Given the known roles of oxytocin in regulating stress and in social functioning, testing oxytocin dysregulation may be a putative route by which transdiagnostic vulnerability may be evaluated.

Developmental studies have also attempted to refine the gold standard for measuring the p-factor. An approach using multiple quantitative models to determine the p-factor found that a total problem score (weighted equally) was the best clinical diagnostic tool [260]. Similarly, a neuroimaging analysis demonstrated that individuals with high p-factor scores had abnormal activation of the default mode and visual networks [261]. Brain regions where abnormal activation occurs overlap with oxytocin-sensitive circuitry and, therefore, provide evidence of a common biological substrate linking stress physiology to general psychiatric risk. Oxytocin is a strong candidate as the regulatory molecule that serves as a bridge between the domains of social behavior, stress adaptation, and transdiagnostic psychopathology. As a neuromodulator of resilience and perhaps a biomarker of vulnerability, a new theory harmonizing the mechanisms behind ITTS is warranted.

3.6.8. Current Gaps and Limitations

At a basic level, endogenous oxytocin is predominantly synthesized in the hypothalamus and to a lesser degree in other limbic structures. Oxytocin is also expressed through the ovaries, testes, mammary glands, kidneys, heart, pancreas, thymus [262] and the gut [232]. The synthesis of oxytocin in tissues other than the brain leads to complexity in interpret-

ing the effects of exogenous oxytocin observed in clinical trials. For example, oxytocin treatment of children with ASD have yielded mixed results.

Research conducted on ASD is a prime example of how a lack of data harmonization across disciplines impedes progress in effective oxytocin therapeutic designs to intervene in stress physiology and neurodevelopmental disorders. A randomized double-blind 4-week clinical trial showed an increase in social responsiveness in children with ASD who were treated with intranasal oxytocin [263]. Though these results differ from other RCTs showing no therapeutic effect, these inconsistencies may be partially explained by differences in the synthetic formulation, route of administration, or dose regimen. Another limitation causing discrepant findings may be due to under-powered trials including low sample sizes or broad age ranges. One well-designed 24-week-long RCT using daily intranasal oxytocin therapy aimed to address both underpowered and age-associated outcomes by enrolling 290 children aged 3–17 years equally split between placebo and treatment groups [264]. There were no significant differences found in social functioning between the groups pre- or post- dosing [264]. Smaller-scale RCTs have shown promise with combinations of applied behavioral analysis (ABA) and/or social skills training with intranasal oxytocin, albeit with a smaller sample size [265].

Several gaps and limitations remain within oxytocin research, specifically with endogenous oxytocin production in humans compared to current exogenous oxytocin formulations and their potential for fragmentation. Clinical trials have also focused on the effects of intranasal oxytocin in potentially mitigating stress responses. Schneider et al. (2025) recruited 80 heterosexual couples to receive daily intranasal oxytocin to test concurrent stress buffering under varying social, stress, and reproductive events [254]. Not all synthetic forms of oxytocin appear to replicate the full repertoire of natural signaling patterns of endogenous oxytocin most likely due to the route of administration. The chemical properties are thought to be identical; however, synthetic oxytocin administered peripherally via IV or IM during labor induction or postpartum hemorrhage control does not readily activate oxytocinergic brain centers. On the other hand, intranasal dosing is unique in that it has both peripheral and central action. Central action occurs via nose-to-brain pathways (i.e., olfactory/trigeminal nerves) and brain–gut pathways (i.e., vagal nerves).

3.7. Biologically Active Oxytocin Fragments as Biomarkers

Oxytocin released into the bloodstream and other body fluids does not remain as a complete nonapeptide; it may be broken down by peptidases into smaller pieces with different bioactivities and reactivities [39,266]. This biochemical heterogeneity is important, as many frequently used immunoassays cannot differentiate between intact oxytocin and its fragments. Hence, reported concentrations may be a mixture of forms rather than one analyte. Oxytocin fragments can have unique behavioral and physiological effects in animal models, different from oxytocin [266]. If humans experience similar fragment-specific actions, then these fragments may be helpful as informative biomarkers or confound attempts to interpret levels as a readout of central oxytocin release or intact-peptide signaling [267].

Measurement problems are numerous: immunoassays (e.g., ELISA, radioimmunoassay (RIA)) usually target peptide epitopes, and consequently, they cross-react with its metabolites. Laboratories also vary in their extraction procedures, the choice of antibody, and the timing, resulting in very low comparability across studies [39,267]. Currently, the best method for distinguishing between intact oxytocin and fragments is mass spectrometry (MS) or those immunoassays validated against MS. Only a handful of human studies have employed these techniques [267]. Pharmacokinetics make it even harder to interpret results: oxytocin attaches to plasma proteins and has a rapid clearance rate. Hence, plasma levels

reflect the dynamics of both binding and clearance, as well as release [268]. The rapid turnover implies that samples taken at a single time point are a poor representation of ongoing central activity.

The choice of biofluid is also relevant for the content and stability of fragments. Saliva and urine are very attractive for pediatric studies because they are semi-non-invasive methods, but the enzymatic activity in these matrices can degrade the peptides differently, so that the measured levels might be fragment-biased when compared with plasma [267,269]. Breast milk contains oxytocin along with many immune factors, and milk oxytocin varies depending on the maternal state and caregiving context, which is a potentially rich but complicated source of information [139]. Multi-fluid studies, e.g., Feldman. (2012), that link peripheral oxytocin to parent–infant synchrony are indeed valuable but should be interpreted with the understanding that assays may reflect fragments and that the assay choice influences outcomes [50].

Succinctly, to make the most of intact (and fragmented) oxytocin as a biomarker, future studies should give priority to LC–MS/MS or aptamer assays validated against MS and provide a detailed report of sample preparation. Only methodologically rigorous, fragment-aware measurements will make it possible to determine whether intact oxytocin or their specific fragments, or a combination of both, is the best indicator of caregiving, stress regulation, and child health.

3.8. Operational Challenges and Inconsistent Findings in Oxytocin Research

3.8.1. Genetic, Epigenetic, and Contextual Variability in Oxytocin Findings

Genetic changes and epigenetic modifications in the oxytocin system (mainly OXTR, OXT, and CD38) are among numerous reasons why humans vary significantly in their attachment styles, social cognitive skills, and responsiveness to care. The effect sizes are small and inconsistent across different studies and populations [37,73,270]. The literature on rs53576 is a classic example of the candidate-gene period: minor studies have reported links between empathy and prosocial traits, but meta-analyses and preregistered replications indicate only modest, domain-specific effects and great diversity concerning the ancestry and sample features [37,38]. These conflicting results demonstrate the risks of underpowered studies, publication bias, and culturally or ancestrally limited sampling. Thus, multiethnic, well-powered designs are indispensable for eliminating biased inference [37]. See Table 1.

Oxytocin's role in enhancing empathy and theory of mind has existed in limbo across decades of conflicting study results. Initially, several researchers were able to correlate various common OXTR rs53576 receptor gene mutations to increased empathic capacity and better social cognition performance [195,271]. However, subsequent attempts to confirm such results failed to yield statistically significant correlations [38]. Moreover, the failure to replicate results further contributed to a more general concern in behavioral genetics regarding the tendency for underpowered, small-scale studies to produce flawed but statistically significant results.

These contradictions are currently addressed with recent advances in the field. A large-scale meta-analytic study conducted by Chander et al. (2022) revealed that the role of oxytocin in empathy is not universal, but rather, will depend on who is being studied and the racial/cultural background of the participants [37]. Furthermore, the nature of the relationship between oxytocin and empathic behaviors (i.e., cognitive vs. emotional) was also shown to affect the size and direction of the correlation.

In addition to inconclusive results, the findings also indicate that early environmental exposures may influence an individual's responsiveness to oxytocin at a later point in time through epigenetic means [270].

3.8.2. Behavioral and Experimental Inconsistencies: Context, Tasks, and Reproducibility

The relationship between oxytocin and social behavior is equally intricate and context dependent. Different styles of interaction, such as touch, breastfeeding, and parent–child synchrony, increase peripheral oxytocin levels and are associated with bonding and regulation [30,272], but experimental manipulations (especially via intranasal oxytocin) show inconsistent results. Smaller studies usually reported social advantages, but larger and neuroimaging studies often encounter null or conflicting outcomes influenced by the subject's gender, baseline attributes, drug dosage, and experimental task performance [43,44]. Neuroimaging points to the amygdala and temporoparietal junction (TPJ) as regions involved in oxytocin-sensitive processes (e.g., emotion and mentalizing), which could be one reason why effects on "mind-reading" tasks are inconsistent [53,270].

Similarly, the intranasal administration of oxytocin has produced mixed results. While some studies have demonstrated improvement in the subjects' abilities to recognize emotions and to understand what another person is thinking [43], others conducting a large-scale, preregistered neuroimaging study have found no significant differences in either brain activity or behavior [44]. The one area of potential interest involves the temporoparietal junction (TPJ), which has been associated with the ability to take the perspective of another individual [53]. However, at present, there is insufficient evidence to conclude that oxytocin reliably modulates neural processes related to social reasoning.

Theoretical disagreements exist concerning how oxytocin can be conceptualized. Feldman (2021) views oxytocin as a transdiagnostic marker of resilience, shown to promote both social connection and stress recovery across all psychiatric disorders [30]. In contrast, Florea et al. (2022) argue that oxytocin is heavily modulated by multiple neurotransmitter systems, including dopamine and serotonin [73]. Therefore, the extent to which one can view the behavioral effects of oxytocin in isolation is limited. The interactions among these systems may help explain the variability of results seen across studies.

Methodological inconsistencies also pose a major obstacle to progress. Despite considerable variation in dosing, timing, and participant populations across studies, very few studies have sufficient sample sizes to detect subtle effects or culturally based variations. With the increasing focus on more stringent pre-registered methodology, the field is making progress towards standardization, although there is currently still no standardization in terms of study design or measurements. The same limitations are evident in attempts to define the p-factor, where overlapping symptoms and biological mechanisms make the differentiation between distinct diagnoses increasingly difficult.

Current data indicate that oxytocin plays a complex and context-dependent role in social behavior and psychopathology. While it appears to be an interesting candidate for use in transdiagnostic research, the mechanisms of action underlying the effects of oxytocin are still unclear. Further research will require the use of larger samples, more consistent task designs, and clearly defined operationalizations that connect molecular findings to real-world social outcomes.

3.8.3. Obstetric, Perinatal, and Postpartum Inconsistencies: Clinical and Developmental Contexts

Oxytocin is associated with uterine contractility and hemorrhage prevention, analgesia, lactation physiology, mother–infant synchronization, and stress management during the perinatal and postpartum window. Oxytocin administered during labor has analgesic and anti-hypersensitivity effects under a proper dosage, which may contribute to the low incidence of chronic post-cesarean pain [55]. Despite a dual role in neuropsychiatric and obstetric health, its clinical uses are still conceptually and methodologically fragmented. While oxytocin is frequently used in obstetrics to induce birth and prevent postpartum

hemorrhage [55,273], there is disagreement on its therapeutic scope because the FDA has not approved its intranasal administration for mental health or PD. Intranasal oxytocin has been tested in an RCT to discern if there were increases in oxytocin secreted in breast milk comparing mothers with and without PD [274]. This RCT found that mothers with PD given intranasal oxytocin remained at a baseline level of oxytocin in the breast milk, while mothers without PD had an increase in oxytocin in their breast milk.

As maternal oxytocin can prevent hypertension acquired in utero and improve baby immunological and social development, there is growing evidence linking breastfeeding-associated oxytocin to cardiovascular and developmental advantages [139,275]. Nevertheless, conflicting findings from meta-analyses evaluating neurodevelopmental outcomes after perinatal oxytocin exposure highlight the need for longitudinal biomarker validation, while also pointing to an inconsistent rise in the risk of neurodevelopmental disorders [56]. Oxytocin's role in maternal empathy and "mentalizing" networks, domains that may underpin resilience and postnatal adjustment [30], is highlighted by the neuroepigenetic dimension of oxytocin function [270] and temporoparietal modulation of self-other processing [53].

4. Discussion

This review depicts a strong emerging pattern for the role of oxytocin in the developing neurobiology and resilience of a child as it is influenced by the quality and stability of parent–child relationships partnered with temporal exposures to varying stressors. The foundations of stress and coping were established through work by Selye (1936), Lazarus (1974), and Lazarus and Folkman (1984) to understand how children experience and deal with chronic adversity [276–278]. Building on these foundational works, research on resilience has shown that stable, supportive caregiving can buffer children from these stressors, which helps to develop the ability of children to regulate their emotions and improve their overall long-term health [21,279,280]. Affiliative neuroscience research shows oxytocin to be one of the pathways connecting relational experiences with neurobiological adaptations [29] in response to stress. The central oxytocinergic system originates from the same embryonic neuroectoderm lineage as does the stress system. Therefore, the overlap of social and stress-regulatory processes makes oxytocin a compelling and methodologically challenging transdiagnostic tool in developmental research.

In addition to the previously mentioned sections regarding genetic, epigenetic, and environmental moderators, these sections also illustrate how variability in caregiving, synchrony, traumatic exposure, and family stress impacts oxytocin functions across childhood years [71,143,281]. Research focused on the allostatic load, parent/child attunement, and interbrain synchrony demonstrates that oxytocin should be considered not as a single, momentary measure, but as a system that develops over repeated interactions and across developmental periods. For this reason, cumulative biological measures are appropriate for assessing pre-verbal children who communicate via physiological and relational cues rather than verbally.

Collectively, these themes illustrate an increasing need for methods to assess oxytocin's long-term patterns of functioning versus its short-term fluctuation. Trimmed hair sampling represents a practical and theoretically consistent way to measure oxytocin, as hair is a matrix that integrates oxytocin and cortisol from the past several weeks or months, providing a chronology of biological activity that parallels the experiences that shape early development. In addition to being a minimally invasive procedure to collect data, hair is also less difficult to collect than blood samples and is suitable for infants and toddlers who cannot provide reliable biofluid samples. Given that human scalp hair is of neuroectodermal and mesodermal origin, it measures both central and peripheral

oxytocin. Hair oxytocin concentrations provide a reliable and ecologically valid window into the broader physiological context that influences caregiving, stress, and therapeutic dosing efficacy.

5. Future Directions

Future studies examining preverbal children will benefit from longitudinal designs that integrate hair-based oxytocin measurements with behavioral observations of the child, caregiver–child synchrony, environmental variables, and additional physiological indicators. Integrating hair oxytocin measurements within multi-system frameworks, including stress physiology, immune responses, PCEs, and resilience processes, will facilitate a clearer understanding of how early environments become biologically embedded. As the field moves toward more integrated and developmentally aligned methods, hair biomarkers may provide a means to address longstanding inconsistencies about measuring oxytocin and how early relational experiences influence long-term health outcomes. The Stanford Child Wellness Lab (CWL) is vetting a pediatric transdiagnostic clinical tool using biomarkers detected in the scalp hair of preverbal children to prospectively monitor the health status with advancing age, using validated and patented multi-omic methodology. Greater than 3000 nonstructural proteins were detected in the hair of mothers and their children, inclusive of cortisol, oxytocin, arginine vasopressin, HSP, histone-associated, and glucocorticoid response element proteins [282].

A dominant theme emerges through the integration of biological, developmental, and methodological concepts reviewed here. Oxytocin needs to be measured in a manner that captures the complex temporal nature of human development in early childhood. Painlessly trimmed hair shafts present a matrix for biomarker evaluation that is practical and developmentally relevant to support stable inferences and increase participation in early childhood research. Though challenges in standardizing and interpreting exist, the convergence of theoretical, developmental, and methodological perspectives suggests that hair oxytocin represents a viable means of improving the clarity of oxytocin research. As future studies continue to combine behavioral observations, the environmental context, and multi-system biological measures, developing research will be able to better clarify the role that early experiences play in becoming biologically embedded during critical windows in early childhood development.

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Abbreviations

The following abbreviations are used in this manuscript:

ACEs	adverse childhood experiences
ACTH	adrenocorticotropic hormone

ADHD	attention deficit hyperactivity disorder
ANS	autonomic nervous system
ASD	autism spectrum disorder
CNS	central nervous system
CRH	corticotropin-releasing hormone
CSF	cerebrospinal fluid
CWL	Child Wellness Laboratory
DNA	deoxyribonucleic acid
ELA	early life adversity
ELISA	enzyme-linked-immunosorbent assays
ELS	early life stress
FDA	Food and Drug Administration of the U.S.A.
FEI	FDA Establishment Identifier
GRE	glucocorticoid response element
G-protein	guanine nucleotide-binding protein
GWAS	genome wide association studies
HPA axis	hypothalamic-pituitary-adrenal axis
IV	intravenous
IM	intramuscular
LC-MS/MS	liquid chromatography-tandem, mass spectrometry
MDD	major depressive disorder
miRNA	micro ribonucleic amino acid
mRNA	messenger ribonucleic acid
MS	mass spectrometry
ncRNA	non-coding ribonucleic acid
OXTR	oxytocin receptor
OT-AVP	oxytocin-arginine vasopressin
PCEs	positive childhood experiences
PD	postpartum depression
PK	pharmacokinetics
PVN	paraventricular nucleus
RCT	randomized clinical trial
SNP	single nucleotide polymorphism
ToM	theory of the mind
ToNA	Theory of Neurogenesis Abruption
TPJ	temporoparietal junction

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