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Expanding Regulation Theory with Oxytocin: A Psychoneurobiological Model for Infant Development

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Abstract

Background—Oxytocin (OT), an affiliation hormone released during supportive social interactions, provides an exemplar of how social environments are reflected in our neurobiology from the beginning of life. A growing body of OT research has uncovered previously unknown functions of OT, including modulation of parenting behaviors, neuroprotection, affiliation, and bonding. Regulation theory provides a strong framework for describing how the maternal care environment affects infant neurodevelopment through a symphony of molecules that form the neurobiological milieu of the developing infant brain.

Objectives—The purpose of this paper is to expand on regulation theory by discussing how OT-based processes contribute to infant neurobiology and by proposing a new model for maternal–infant nursing practice and research.

Approach—We structure our discussion of the socially based, neurobiological processes of OT through its effects in the nested hierarches of genetic, epigenetic, molecular, cellular, neural circuit, multi-organ, and behavioral levels. Our discussion is also presented chronologically, as OT works through a positive feedback loop during infant neurodevelopment, beginning prenatally and continuing after birth.

Implications—Nurses are in a unique position to use innovative discoveries made by the biologic sciences to generate new nursing theories that inform clinical practice and inspire the development of innovative interventions that maximize the infant's exposure to supportive maternal care.

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Keywords

neonatal nursing; maternal-infant interaction; nursing interventions; nursing theory; regulation theory; oxytocin

From the beginning of life, our social environments influence the neurobiology of our brains and bodies. Oxytocin (OT), an affiliation hormone released during supportive social interactions, provides an exemplar of how social experiences shape the neurobiology of the developing infant brain. A growing body of OT research has uncovered previously unknown functions of OT during the early weeks of life, including modulation of parenting behaviors, neuroprotection, affiliation, and bonding (Feldman, Monakhov, Pratt, & Ebstein, 2016; Vargas-Martínez, Uvnäs-Moberg, Petersson, Olausson, & Jiménez-Estrada, 2014). Nurses have the most frequent interactions with infants and their families during this critical perinatal period, and have the power to shape the care environment of the neonate after birth. Through facilitating interventions that support OT systems, such as kangaroo care, breastfeeding, and sustained touch, the nurse is instrumental in providing families with the knowledge and resources to provide a socially supportive environment from the first moments of life. Table 1 presents examples of nursing diagnoses, potential interventions, and OT processes involved.

Incorporation of these nursing interventions into practice is inconsistent, perhaps due to the difficulty of quantifying the impact on infant outcomes. Consistent delivery of these supportive interventions depends on a deeper understanding of neurobiological processes that foster resilience and adaptation in the context of social environments. Improved understanding of OT function during neurodevelopment may allow researchers and clinicians to assess the immediate biological significance of psychosocial nursing interventions, thus motivating more consistent nursing care and development of novel interventions. In the current paper, we discuss how maternal care contributes to infant neurobiology and optimal neurodevelopment through OT-based processes.

Although strong nursing theories guide interventions based on behavioral responses, nursing theories focused on neurobiological and developmental effects of interventions are lacking. Psychologist Allan Schore (1996, 2001) brought together the work of numerous disciplines, including neurology, developmental psychology, social work, psychiatry, and nursing, to develop regulation theory. This complex theory serves as the framework for our discussion (Figure 1). The basic tenet of regulation theory is that maternal care affects infant neurodevelopment through the precise coordination of neurotransmitters and hormones that form the neurobiological environment of the developing infant brain. Regulation theory posits that early, consistent, and developmentally supportive maternal–infant interactions regulate infant brain biology and the subsequent affective states and social behaviors that emerge from that biology. The major principles of regulation theory are:

- Social context is critical to the development and function of the infant brain;
- Neurobiological processes that contribute to infant brain structure and function include genetic/epigenetic regulation, the mesocorticolimbic dopamine

pathways, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic-adrenal-medullary (SAM) system, and the parasympathetic nervous system;

- Infant neurodevelopment depends on the infant's experience, particularly with caregivers such as the mother; and
- Regulation of infant neurobiology by the sensitive caregiver supports infant emotion-regulation and self-regulation (Schore, 1996; Weber, Harrison, & Steward, 2012).

The regulation of infant brain biology, affective states, and behaviors by the mother not only promotes adaptation of key neurobiological systems during times of stress, but also augments maturation of the developing brain in a way that contributes to optimal neurodevelopment (Schore, 1996, 2001). OT is necessary for a variety of neural processes related to neurodevelopment—an umbrella term that refers to the generation, shaping, maturation, reshaping—and regeneration of the nervous system throughout life. The critical role of OT in infant neurodevelopment has been described in scientific discoveries within the last decade (Vargas-Martínez et al., 2014). The incorporation of OT, the "social hormone," into the next generation of nursing theory, practice, and research brings exciting opportunities to uncover the neurobiological roots of maternal–infant nursing interventions that facilitate affiliation, bonding, and infant neurodevelopment.

Purpose

In the following sections, we argue that OT release in the brain and body is a necessary and critical component for optimal neurodevelopment of all infants. We structure our discussion of neurobiological processes involving OT through nested hierarches of genetic, epigenetic, molecular, cellular, neural circuit, multi-organ, and behavioral levels (Figure 2). Our discussion is also presented chronologically, because the hormone OT influences neurodevelopment temporally through a positive feedback loop involving maternal–infant behaviors and neurobiological processes over time (Figure 3). While we present our argument in terms of positive relationships, we acknowledge that *regulation* of OT levels within the ideal range—for each brain region and within the context of the stimulus—is essential.

The Genetic Level: Oxytocin-based Genes in the Prenatal Period and Beyond

An integral component of nursing theory and research is the identification of biological risk factors that modify the way nurses provide person-centered nursing interventions (Conley & Tinkle, 2007). Human-based generational studies demonstrate that variations in maternal genes regulating the mother's OT system are not only associated with variations in infant genes, but also with maternal and infant peripheral OT levels, parenting behaviors, and the infant's socioemotional health (Feldman, Monakhov et al., 2016; Feldman, Zagoory-Sharon, et al., 2012). These generational studies provide evidence that the mother's OT genes are passed to the infant prenatally, and influence the behavioral phenotype of the infant postnatally. Genetic-based shaping (i.e., priming) of the dyad's OT systems begins during

pregnancy and has the potential to influence infant neurodevelopment through a positive feedback loop, consisting of repeated, synchronized, maternal–infant behaviors that begin at birth (Figure 3). Prenatal genetic priming of the dyad's OT systems means both mother and infant possess genetically mediated tendencies towards certain adaptive functions of the OT system and behaviors regulated by the OT system.

The genetic profile (i.e., characteristics of an individual's unique DNA) of the infant's OT system may modify the effect of nursing interventions that optimize attachment and socioemotional development in infants. Human genetic syndromes associated with OT dysregulation—such as Prader-Willi, Fragile X, and Williams Syndrome— produce profound deficits in socioemotional regulation and cognition, evidenced by the common symptoms of anxiety, emotional liability, hyperactivity, impulsivity, decreased "theory of mind," lack of empathy, and developmental delays (Francis et al., 2014). While genetic syndromes represent extreme cases of genetic risk for OT dysregulation, these syndromes serve as evidence that genes, which regulate OT system function, also have important influence on cognitive function. An infant's genetic profile will ultimately affect his/her socioemotional health and neurodevelopment. However, it is through modifiable infant epigenetics that nurses can provide supportive social interventions and promote best outcomes.

The Epigenetic Level: Maternal Behavior and Postnatal Effects

Regulation theory states that supportive maternal behaviors program development of the offspring neurobiological systems through epigenetic changes (Schore, 1996, 2001). Epigenetic changes are modifications of gene expression (i.e., whether the gene is active or inactive) that change an individual's phenotype but does not involve change to the DNA/genetic code (Conley & Tinkle, 2007). This concept has been demonstrated in the OT system with cross-fostering animal model studies, using high licking and grooming (HLG) and low licking and grooming (LLG) dams (i.e., female rats), their respective biological HLG/LLG pups, and HLG/LLG cross-fostered pups (Champagne, 2008). Compared to pups reared in LLG environments, all pups reared in HLG environments had greater expression of OT and oxytocin receptor (OTR) genes and displayed decreased anxiety, increased exploration, and greater response to novelty (Champagne, 2008). These researchers demonstrated that supportive maternal behaviors modify epigenetic regulation of the offspring OT system by decreasing methylation of infant OT/OTR genes, leading to changes in offspring social behaviors (Curley & Champagne, 2016; Meaney, 2001).

Researchers have not investigated associations between human maternal behaviors and epigenetic measures of infant OT. Researchers recently found significant associations in human adults between decreased methylation of the OT gene and better performance on sociocognitive tasks, such as recognizing facial expressions (Haas et al., 2016). Future research needs to address this key tenet of regulation theory, and confirm that the effect of human maternal influence on infant social behaviors occurs through epigenetic regulation of infant OT systems.

Priming: Maternal Care for the Infant's Developing OT System

According to regulation theory, the mother's developmentally appropriate sensory stimuli contribute to infant neurodevelopment (Schore, 2001). Sensory stimuli include a mother's touch, voice, gaze, facial expressions, scent, and breastmilk. New research is uncovering the ways in which OT facilitates the sensory processing of tactile, auditory, visual, olfactory, and gustatory stimuli. Researchers using animal models have shown that OT "mediates early experience-dependent cross-modal plasticity in the sensory cortices" (Zheng et al., 2014, p. 391). For example, OT underlies such sensory experiences as odor recognition (Wacker & Ludwig, 2012), attentiveness to facial expressions (Luo et al., 2015), and neuromodulation of the gustatory circuit (Beets, Temmerman, Janssen, & Schoofs, 2013). OT works in the prefrontal cortex to process signals from the olfactory bulb, auditory cortex, visual cortex, and gustatory circuit to facilitate high-order cognitive functions such as socially based learning and motivation (Bicks, Koike, Akbarian, & Morishita, 2015). OT enhances neural processing of facial stimuli by the orbitofrontal/visual cortices to attract the dyad to each other's social cues (Luo et al., 2015).

These biological discoveries are of critical importance to human infants, showing that sensory experience controls the production and release of OT (Freeman, Inoue, Smith, Goodman, & Young, 2014). Subsequently, OT in the brain and body enacts a variety of cognitive-based social functions, such as "modulating visual attention, processing auditory and multimodal sensory stimuli, and controlling orienting responses to visual stimuli" (Freeman et al., 2014, p. 128)—skills that are critical to an infant's socioemotional health. In the following sections, we review how the OT system, in coordination with other neurobiological systems, uses sensory experiences from the mother to shape the developing infant brain.

The Molecular Level: G-Proteins, Receptors, and OT

The breadth and depth of OT impact on shaping the developing infant brain is based in gene transcription and cell-signaling pathways required by neurons to synthesize the proteins necessary for key neural processes involved in neurodevelopment (Figure 4). OT is a nine amino acid peptide whose receptor is part of the G-protein-coupled receptor (GPCR) family, the body's largest class of membrane receptors. Once activated, GPCRs open ion channels on the cell membrane to influence enzymes and second messenger molecules that travel and communicate within the cell (Koehbach, Stockner, Bergmayr, Muttenthaler, & Gruber, 2013). These second messenger molecules can also open ion channels (e.g., calcium channels) inside the cell to further affect membrane charge. The influence of OT on intracellular and extracellular ion stores produces positive charge in the cell (i.e., depolarization), resulting in voltage changes on the cell membrane (an electric potential).

The Cellular Level: Electric Potentials and Development of Autoregulation

Electrical potentials are the primary mode of neuron-to-neuron communication (Vargas-Martínez et al., 2014). OT-induced potentials travel along the cell membrane, releasing OT-filled vesicles from the soma and dendrites into the extracellular space. In this way, OT

neurons control their own firing activity locally, with their own receptors and peptides—a property known as autoregulation (Philippe, Moos, Dayanithi, Gouzènes, & Sabatier, 1997). A single neuronal stimulus can "prime" OT neurons to autoregulate for long periods of time, (e.g., ~90 minutes), and in the presence of gonadal hormones like estrogen, this time can increase to several days (Tobin, Leng, & Ludwig, 2012). In this way, for example, a kangaroo care nursing intervention immediately after birth might prime and autoregulate OT neurons (Cong et al., 2015; Kommers et al., 2017).

OT is not only a neuromodulator (i.e., regulator of neuron groups) but also a neurotransmitter and neurohormone. Through somatodendritic release (Figure 4), OT can diffuse at such high concentrations from the hypothalamus that OT can regulate adjacent neural circuits. Axonal release of OT as a neurotransmitter adds localized, time-sensitive control of distant neural circuits. As a neurohormone, OT can diffuse into the third ventricle, and thus, the cerebral spinal fluid (Knobloch & Grinevich, 2014). OT is also released into the bloodstream by the pituitary. Through combinations of dendritic, somatic, axonal, and hormonal release, the OT neuron communicates by a peptide-induced "Morse code" (Figure 4), interpreted through the frequency, duration, timing, strength, and pattern of OT release (Vargas-Martínez et al., 2014).

Of critical importance are OT neuronal projections, which are abundant in the periphery and connect to the heart, kidneys, adrenal glands, pancreas, gastrointestinal tract, and reproductive organs. Many of these organs (e.g., the heart) can release OT independently and interdependently of OT signaling within the brain. Therefore, circulating OT released by the pituitary, vagal nerve, peripheral OT projections, and organs provide theoretical pathways for maternal stimuli to be received by the periphery and transmitted to OT neurons in the infant brain (Gutkowska, Jankowski, & Antunes-Rodrigues, 2014). These diverse OT release and signaling mechanisms allow for sophisticated communication with other neuromodulators, and facilitate the complex social behaviors produced during maternal–infant interaction (Harari-Dahan & Bernstein, 2014; Tobin et al., 2012; Vargas-Martínez et al., 2014; Viero et al., 2010).

The Neural Circuit Level: Neurotrophins and Establishment of Circuits

OT interacts with many neuromodulators that assist in the establishment of neural circuits, such as neurotrophins, cholecystokinin (CCK), γ-amino-butyric acid (GABA), and glutamate (Figure 4). OT significantly increases levels of neurotrophins; a group of proteins that act as growth factors to stimulate and control neurogenesis in the developing infant brain (Bakos, Zatkova, Bacova, & Ostatnikova, 2016). Neurotrophins can prevent excessive apoptosis and induce differentiation of progenitor cells into neurons. Researchers have shown that OT increases levels of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and CCK (Askvig, Leiphon, & Watt, 2012; Bakos, Lestanova, Strbak, Havranek, & Bacova, 2014; Havranek et al., 2015). These neurotrophins stimulate synthesis of neurotransmitters, formation of neuronal spines and synapses, and elongation of axons. They regulate neuron excitability, differentiation, connectivity, and survival (Bakos et al., 2014; Hill, Warren, & Roth, 2014).

OT communicates with GABA to augment these neural processes. An immature neuron's excitability, differentiation, connectivity, and electrical potential (i.e., whether it is excitatory, inhibitory, or both) determine its integration pattern within organized neural circuits (Ben-Ari, 2014). During early infant brain development, OT facilitates the shift of GABA's actions from excitatory to inhibitory (Ben-Ari, 2014), and consequently assists in determining the electrical potential of a neuron. This developmental shift of GABA is essential for the establishment and integration of the most fundamental neural circuits in the human brain. OT-GABA interactions within the brain produce giant depolarizing potentials (GDPs), which are synchronous depolarizations of a large group of neurons (Cherubini, Griguoli, Safiulina, & Lagostena, 2011). When groups of neurons are consistently and simultaneously depolarized, the number and strength of their synaptic connections increase in a structurally profound way, which leads to the formation of a neural circuit (Figure 4; Egorov & Draguhn, 2013). Thus GABA—facilitated by OT—influences neural plasticity through the activity of controlled, precise, and experience-dependent, electronic potentials within neural circuits (Cellot & Cherubini, 2013). In the next section, we discuss some of the critical neural circuits that are formed through the neurotrophic interactions and neural activity explained in this section.

The Multicircuit/Organ-System Level: Established Circuits and the OT System

Regulation theory states that a mother can regulate key neural circuits in the infant brain by providing stimuli sensitive to the infant's cues (Figure 1)—which indicate hunger, sleepiness, or need for social interaction. The primary site of OT synthesis is the supraoptic nuclei (SON) and the paraventricular nuclei (PVN) of the hypothalamus (Ferri & Flanagan-Cato, 2012), which regulate the physiologic functions driving infant sleep, arousal, and hunger. By providing stimuli that regulates infant sleep, arousal, and hunger, we hypothesize that the mother can regulate the infant's OT system. Regulation of basic infant behaviors is the cornerstone for synchronized, supportive interactions and mother–infant attachment—social functions regulated by the OT system (Feldman, 2006, 2015a, 2015b, 2015c). The following sections describe the OT system's interaction with infant neural circuits shaped by maternal stimuli and emphasized in regulation theory.

The Dopaminergic Reward Pathways

Projections of OT neurons from the center of the OT system are extensive (Figure 1), including hypothalamic projections to the nucleus accumbens, hippocampus, amygdala, and ventral tegmental area (VTA), crucial components of the dopaminergic reward system (Strathearn, 2011). The mesocorticolimbic dopamine pathways control responses to natural rewards, such as social interaction (Weber et al., 2012). Both dopamine and OT facilitate social behaviors, affiliation, bonding, and attachment (Feldman, 2015c). Relevant brain functions affected by OT/dopamine interactions include social recognition, preference, memory, desire for close proximity, salience to dyadic social cues, and approach/engagement behaviors (Coria-Avila et al., 2014). In healthy dyads, these brain functions are recruited to support behaviors that define sensitive and nurturing maternal–infant interaction. For mothers with high levels of OT and maternal–infant synchrony, greater brain activations

occur in the dopaminergic reward pathways when viewing their infants. These mothers also display increased functional connectivity among reward pathways, emotion circuits, and empathy networks (Atzil, Hendler, & Feldman, 2014).

Stress Response Systems

OT is released during eustress and distress (Figure 1), but has differential effects on the stress responses of the HPA axis and the SAM system, based on the severity, duration, and type of stressor (Harari-Dahan & Bernstein, 2014). The divergent effects of OT in stress systems produce approach/engagement or avoidance/aggressive behaviors in accordance with appropriate, adaptive anxiety responses to a stressor (Harari-Dahan & Bernstein, 2014). The ability of OT to decrease social anxiety in the dyad would facilitate socially based behaviors and emotions during maternal–infant interaction (Harari-Dahan & Bernstein, 2014; Neumann & Slattery, 2016). We hypothesize that supportive maternal stimuli arouses the infant to induce eustress, activating both the OT system and HPA axis. During infant distress, we hypothesize that supportive maternal stimuli release OT to suppress physiologic and psychologic stress reactivity, creating a social buffering of the stress response (Hostinar & Gunnar, 2015). Contextual and stress-specific interactions are a result of coordinated OT communication with either excitatory (e.g., glutamate, norepinephrine) or inhibitory (e.g., GABA, serotonin) neurotransmitters (MacDonald & Feifel, 2014).

OT modifies activity of sympathetic nerves, especially in the upper thoracic region of the spinal cord (Norman et al., 2011). Descending OT nerves projecting into the spine and peripheral nervous system can regulate the pain-related functions of the fight–flight stress response (Moreno-López, Martínez-Lorenzana, Condés-Lara, & Rojas-Piloni, 2013) of the SAM system (Figure 1). OT reduces pain thresholds and modulates pain perception (Uvnäs-Moberg, Handlin, & Petersson, 2015), which may explain why holding and breastfeeding are such powerful infant analgesics (Cong et al., 2012). Both skin-to-skin contact (Johnston et al., 2014) and breastfeeding (Shah, Herbozo, Aliwalas, & Shah, 2012) decrease infant pain response to heelstick. We suspect that in these maternally administered interventions, OT is responsible for social buffering of the infant's responses to pain and stress. Consistent with regulation theory, we hypothesize that maternal regulation of the infant's stress response assists with the emergence of emotion regulation during the first year of life (Maroun & Wagner, 2016), and the development of distinct and context-dependent social behaviors and emotions, such as trust, engagement, empathy, and cooperation (Bosch, 2011; Olff et al., 2013).

Autonomic Regulation of the Social Engagement System

OT heavily coordinates with the social engagement system (Figure 1), which produces the physiologic states, affective states, and engagement cues that encourage dyadic attachment (Nagasawa, Okabe, Mogi, & Kikusui, 2012). Developmentally supportive, maternal stimuli have the ability to create visceral signals in the periphery that can activate OTR on afferent vagal nerve fibers (Figure 1). OTR on the vagus transmit electric potentials to the infant brain; these potentials release hormones that stimulate processing of affective stimuli. Electrical potentials are then created and relayed back to the efferent vagus and motor neurons and transmitted peripherally into infant engagement cues, such as turning head

toward the mother, altering facial expression, and vocalizing (Iwasaki et al., 2015; Porges, 2003). After vagal stimulation, OT is released in the human brain and pituitary (Grippo, Trahanas, Zimmerman, Porges, & Carter, 2009; Gutkowska et al., 2014). When circulating OT reaches the atria of the heart, OTRs respond by releasing atrial natriuretic peptide (ANP), nitric oxide (NO), and more OT to regulate cardiovascular responses (Figure 1). Through ANP and NO, OT can regulate heart rate, blood pressure, metabolism, oxidation, and inflammation (Jankowski, Gonzalez-Reyes, Noiseux, & Gutkowska, 2012; Norman et al., 2010). Stimulation of the infant's vagus in response to supportive maternal behavior enables maternal regulation of the infant's physiology (e.g., heart rate, blood pressure) and behavior (e.g., arousal regulation), which promotes synchronous social interactions (Feldman, 2006, 2009; Feldman, Magori-Cohen, Galili, Singer, & Louzoun, 2011).

OT's coordination with the vagal nerve is critical for the foundation of infant socio-emotional regulation. Increases in sensitive parenting behaviors produce parallel increases in infant OT levels, vagal response, engagement, gaze, exploration, and reciprocity (Weisman, Zagoory-Sharon, & Feldman, 2012). Synchronized loops of interaction—based in synchronized vagal feedback—allow for coordinated release of OT in the dyad. In sum, the vagal nerve is not only an OT-based communication pathway for the brain and periphery, but also a biobehavioral pathway for autonomic regulation and affects synchrony in the dyad (Feldman, 2006).

The Behavioral Level: Emerging Social Interactions

An interesting phenomenon, based in bidirectional and positive feedback mechanisms, is the relationship among interaction behaviors, neurobiological processes involving OT, and infant neurodevelopment (Figure 3). OT levels across pregnancy and postpartum are not only associated with frequency of supportive maternal behaviors, but also with optimal coordination of interaction with the neonate's alert state (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Feldman, Gordon, & Zagoory-Sharon, 2011). These parenting behaviors include warmth, touch, speech, gaze, contingent responses, and high quality of affect (Bakermans-Kranenburg & van Ijzendoorn, 2008; Feldman, Monakhov, et al., 2016; Feldman, Zagoory-Sharon, et al., 2012). Parents with higher OT levels also provide more emotionally rich descriptions of their neonates (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). Parents who display more affectionate touch also show significantly greater increase in their OT levels after interaction (Feldman, Gordon, et al., 2010).

Human mothers demonstrating supportive maternal behaviors activate and enhance development of OT systems in their infants. Increases in parental OT levels produce parallel increases of OT in their infants and increase infant social engagement during parent–infant interaction (Weisman, Zagoory-Sharon, & Feldman, 2012), including parallel increases during kangaroo care (Cong et al., 2015; Kommers et al., 2017). Mothers with higher levels of supportive behaviors raise children who have higher OT levels, as well as higher levels of empathy, engagement, social reciprocity, and psychological wellness (Apter-Levy, Feldman, Vakart, Ebstein, & Feldman, 2013). Infants experiencing more supportive maternal behaviors have increased social cognition at 18 months, as well as increased affect

recognition, nonverbal skills, and pragmatic language skills as children (Wade, Hoffmann, Wigg, & Jenkins, 2014). Importantly, infants who experience developmentally supportive maternal care become children with more highly regulated OT systems and the best neurodevelopmental outcomes (Apter-Levy et al., 2013; Feldman 2015a, 2015b). These data suggest OT mediates the relationship between early, supportive social experiences, and social cognition; a key facet of infant development.

Clinical, Research, and Theoretical Implications

Nursing lacks an organizing model for both research and practice regarding its role in supporting infant neurodevelopment through supporting neurobiological processes, such as those discussed in this paper. We propose a new nursing model that links regulation theory (Schore, 1996) with maternal–infant interaction theory (Barnard & Eyres, 1979). The model (Figure 3) includes concepts central to nursing theory and practice, such as the health status, behaviors, and characteristics that mother and infant bring to the social interactions that form their relationship (Barnard & Eyres, 1979). For example, the mother's health status (e.g., preterm birth, gestational diabetes, hypertension, mood disorders, addiction) and genetic profile (e.g., estrogen receptor, OT/OTR genes) can impact the health status of her infant in utero (e.g., prematurity, congenital anomalies, brain injury, growth restriction), thus affecting birth timing and the behaviors and characteristics the infant exhibits postnatally (e.g., temperament, maturity, responsiveness to stimuli). The characteristics the mother brings to the interaction (e.g., her cultural background, personality, knowledge, beliefs, attitudes, and perception of her infant) can also affect her interaction behaviors (e.g., touch, gaze, voice, sensitive response to infant cues) and the interaction behaviors of her infant (e.g., grasping, gaze, vocalizations, cues). The model also includes concepts traditionally not found in nursing theory, such as maternal–infant neurobiological processes (Schore, 1996)—the chronological development of the infant brain over time—and the critical surge of OT in the mother and infant during birth.

Our model posits that nursing interventions supporting social engagement between mother and infant harnesses the dyad's natural OT systems to promote maturation of the infant brain. This model can be used as a framework for future research investigating a diverse array of clinical interventions that could improve infant outcomes through OT pathways, including programs to increase mother–infant contact, maternal knowledge of infant development, infant physiologic regulation, and dyadic resiliency to stress. Understanding the neurobiological mechanisms through which caregiver behavior is related to infant neurodevelopment can contribute to providing effective assessment and intervention services. Several existing interventions known to enhance the maternal–infant relationship, such as kangaroo care, breastfeeding, and sustained touch, are underutilized in high-risk infant populations. Identifying biomarkers that allow assessment of the immediate biological significance of our nursing interventions can provide the reinforcement needed to promote more consistent implementation. New interventions could also be developed and tested, using our model as a framework.

Multiple additional paths of research related to OT are needed. Currently, children targeted for OT research are primarily those with autism or attention deficient hyperactivity disorder.

OT has great potential as a distinctive biomarker of social interactions that provide neuroprotection and promote neuromaturation in high-risk neonates, especially those experiencing neonatal intensive care unit (NICU) hospitalization after birth. However, little is known about OT in human neonates. For example, normative values of OT levels have not been established for pediatric populations. Successful implementation of foundational, descriptive studies of normative values for measures of OT will pave the way for interventional research. Study of variation in OT levels could provide researchers and clinicians with a greater understanding of how interventions in the context of stressful social environments shape the trajectory of infant neurodevelopment, which is especially applicable to infants developing in the NICU. Few studies integrate measures of stressor exposure, the neurobiological milieu of the developing brain, structural neural circuit growth, and functional infant outcomes. The addition of OT to existing measures of neurobiological processes underlying development represents progress towards a more comprehensive, scientific investigation of human development.

We acknowledge that our scientific understanding of OT is still in its infancy, and measurement challenges exist. However, OT measurement methodologies have undergone considerable improvements over the past few decades, and continue to evolve to increase sensitivity and specificity, especially measurement of OT in peripheral body fluids (e.g., blood, urine, and saliva). In populations where peripheral OT levels are high (e.g., postpartum mothers and their infants), assays measuring OT are more likely to be sensitive and specific for OT. As researchers continue to investigate this critical biomarker, improvements in measurement and interpretation will continue, generating increased confidence in its reliability.

Conclusion

Interactions between infants and their parents serve as key events through which infant neurobiological systems are shaped by the OT system. Nurses are in a unique and privileged position to jumpstart the interaction feedback loop initiated at birth by exposing the neonate to an environment hallmarked by supportive maternal care. As we use the growing body of OT literature to understand the biological underpinnings of neurodevelopment during the perinatal period, nurses have the opportunity to apply these concepts to the care of vulnerable patient populations. The discipline of nursing has consistently promoted the use of psychosocial nursing interventions, therapeutic relationships, and community resources to facilitate healing and growth. As we look for nursing's place in the newly developing paradigm of healthcare delivery, OT is a critical hormone that biologically tells us where nursing should be: Present and socially supportive of our patients and their families when they need us the most.

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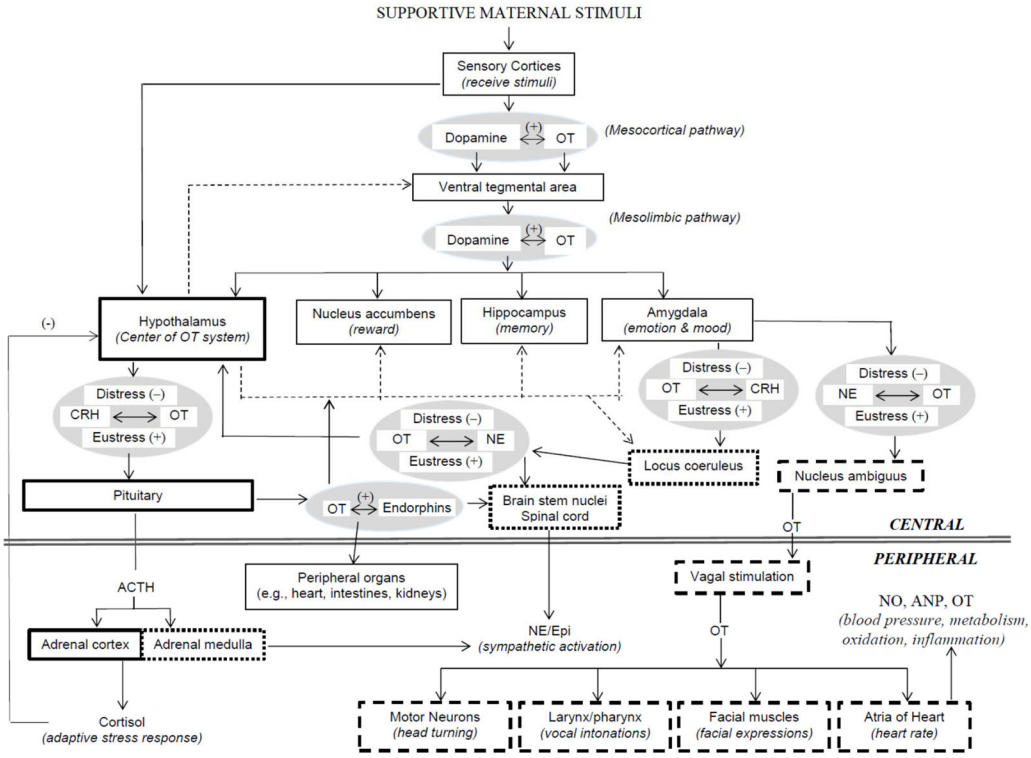

FIGURE 1.

OT-based Extension of regulation theory. OT = oxytocin, CRH = corticotropin-releasing hormone, NE = norepinephrine, Epi = epinephrine, ACTH = adrenocorticotropic hormone, ANP = atrial natriuretic peptide, NO = nitric oxide. Thick black-bordered boxes = hypothalamic-pituitary adrenal (HPA) axis. Dotted boxes = sympathetic-adrenal-medullary (SAM) axis. Dashed boxes = parasympathetic nervous system. Dashed lines = hypothalamic OT projections. Oval areas = OT/hormone interactions. Thick double line separates central and peripheral OT activity. Stimuli received by the infant's sensory cortices are relayed to the ventral tegmental area (VTA), then throughout the mesocorticolimbic dopamine pathway. Dopamine stimulates OT neurons, which co-express dopamine receptors, to release OT. OT stimulates dopamine release, forming a positive feedback loop. OT is released from the periventricular and supraoptic nucleus of the hypothalamus, the center of the OT system. During social buffering of infant distress, OT inhibits CRH neurons of the HPA axis within the hypothalamus, decreasing (1) ACTH from the pituitary, (2) cortisol from the adrenal cortex, (3) NE and Epi from the adrenal medulla, (4) CRH and NE from the amygdala, and (5) NE/Epi from the locus coeruleus, brain stem, and spinal cord. Infant eustress, experienced during supportive maternal stimulation, releases OT from the PVN to activate CRH neurons, increasing ACTH, cortisol, NE, and Epi. During eustress and social buffering, OT increases endogenous opioid release to enhance infant pleasure, interest, and motivation. The amygdala regulates the nucleus ambiguous, source of the right vagus. OT stimulates the vagus, a key component of the parasympathetic and social engagement systems. The social engagement system consists of the vagus, motor neurons in the cortex, and the muscles of the head, face, larynx, pharynx, and neck. Vagal regulation releases OT and changes infant vocal intonations, facial expressions, eyelid opening, head-turning, and eye contact seen

during maternal-infant interaction. Vagal regulation also changes heart rate, blood pressure, and energy balance through atrial release of OT, ANP, and NO.

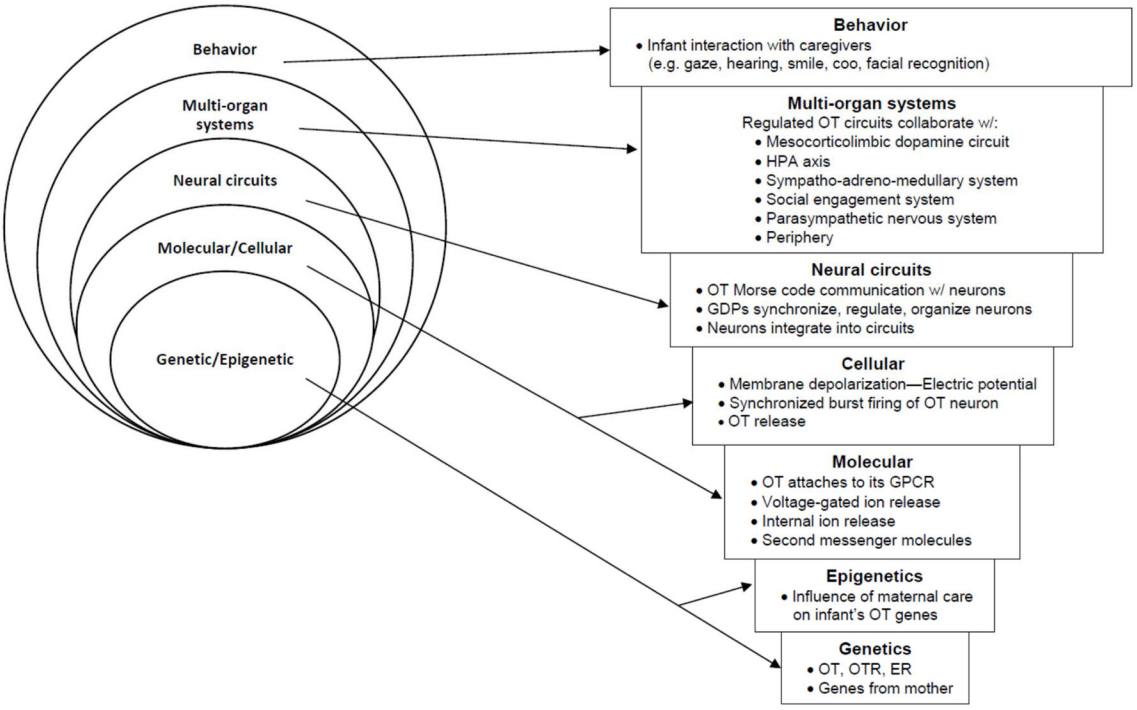

FIGURE 2.

Nested hierarchies of effects of oxytocin. OT = oxytocin, OTR = oxytocin receptors, ER = estrogen receptors, GPCR = G-protein-coupled receptor, GDP = giant depolarizing potentials, HPA = hypothalamic-pituitary-adrenal axis

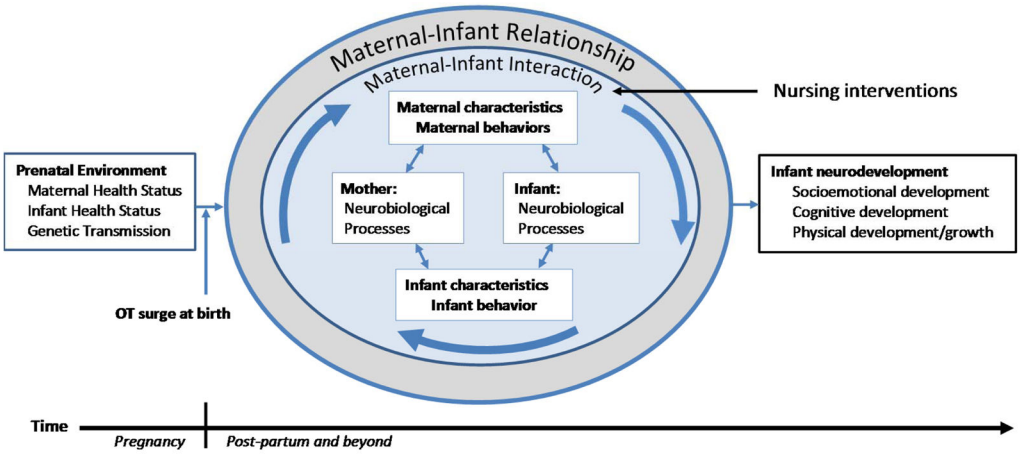

FIGURE 3.

A Psychoneurobiological Model of the Maternal-Infant Relationship Shaping Infant Neurodevelopment. A mother's genetic profile affects her neurobiological processes during pregnancy and after birth. Estrogen expression, heightened during pregnancy, is a powerful augmenter of maternal OT and OTR, and increases the expression and distribution of maternal OTR throughout pregnancy. Birth leads to a surge of OT release in the mother and subsequent initiation of supportive maternal behaviors toward her infant. The newborn infant is immediately exposed to supportive maternal care, spurring neurobiological processes (including OT-based processes) that are inherent within supportive maternal-infant interactions. Recurrent and consistently supportive interactions construct the maternal-infant relationship, which shapes infant development.

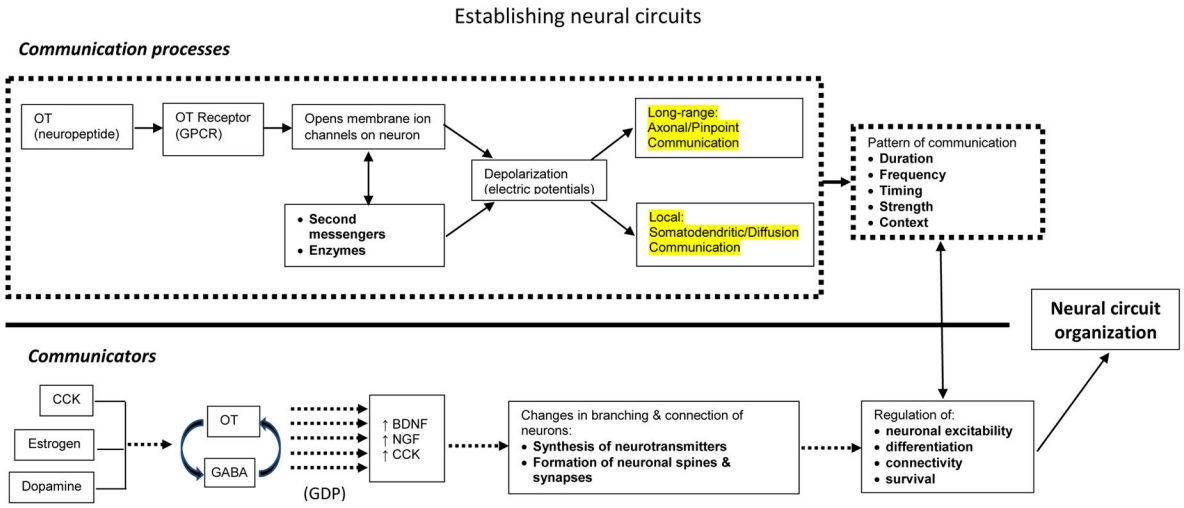

FIGURE 4.

Communication processes and communicators involved in establishing neural circuits. OTR = oxytocin receptors, GPCR = G-protein-coupled receptor; CCK = cholecystokinin; GABA = γ-amino-butyric acid; GDP = giant depolarizing potential; BDNF = brain-derived neurotrophic factor; NGF = nerve growth factor; Boxes below thick black line = neurotrophins involved in communication; boxes above thick black line = molecular/cellular communication processes. Communication processes occur in positions indicated by dashed arrows. Communication processes: The OT neuron communicates when its neuropeptide attaches to the OTR, a GPCR. Activated OTRs open the neuron's membrane ion channels to stimulate second messengers, enzymes, and intracellular ion stores. These molecules promote membrane depolarization and initiation of an electric potential. Through patterns of axonal and somatodendritic OT release, the OT neuron uses the duration, frequency, timing, strength, and context of OT release as a "Morse Code" communication. Communicators: CCK, estrogen, and dopamine augment OT/OTR levels. GABA, like OT, uses electric potentials for "Morse code" communication. GABA can either hyperpolarize or depolarize immature neurons. Differentiating and distinctive electric signals tell neurons when to "switch" potential (i.e., hyperpolarize or depolarize), and act as a conductor for integrating a neuron into its rightful circuit. Massive electric potentials produce GDPs (depicted by multiple stacked dotted lines), which regulate levels of BDNF, NGF, and CCK, and neurotrophins that facilitate neurotransmitter synthesis, neuronal spine and synapse formation, axon elongation, neuronal connectivity, and neuron survival. Neuronal changes, in turn, affect communication processes. Through this iterative process, neural circuits form, impacting infant neurodevelopment.

TABLE 1

Nursing Diagnoses and Interventions Related to Oxytocin Processes

Focus	Nursing diagnosis/nursing intervention	Underlying oxytocin-based process
Infant	Pain: chronic/acute • Assess pain using developmentally appropriate tools • Use nonpharmacologic interventions to reduce pain (e.g., non-nutritive sucking, breastfeeding, kangaroo care, facilitated tucking)	• OT nerves in spine, peripheral nervous system regulate pain[a] • OT reduces pain thresholds, pain perception[b]
	Disorganized behavior • Use consistent nurturing response • Assist parents: modify environment for appropriate stimulation (e.g., lighting, sound) • Model caregiving: support infant behavioral organization (e.g., hand containment, facilitated tucking, nonnutritive sucking)	• Physical contact increases OT release[c] • Infant sleep, arousal, & hunger regulate the OT system • Regulation of basic infant behaviors is cornerstone for supportive social interaction
	Delayed development: risk • Assess risk factors (e.g., prematurity, genetic disorders) • Identify/use educational resources to facilitate infant development • Implement neuroprotective interventions (e.g., kangaroo care, breastfeeding, stress-reduction, modification of environmental stimuli, minimize parent-infant separation)	• OT is necessary for neurodevelopmental processes[d] • We hypothesize that neuroprotective nursing interventions facilitate OT-based neurobiological processes in the infant
Mother	Anxiety • Assess level of and physical reactions to anxiety (heart racing, sleeplessness) • Encourage positive self-talk (e.g., “I can do this one step at a time,”) • Use empathy to validate feelings • Minimize the number of professionals with whom parents have contact. • Reduce parental-infant separation (which increases parental anxiety) • Provide anticipatory guidance on infant care plan	• Divergent effects of OT in stress response systems produce engagement or avoidance/aggression with appropriate anxiety responses to stress[e,f] • OT decreases social anxiety to facilitate socially-based behaviors during maternal-infant interaction[g,h]
	Powerlessness: risk • Assess parental satisfaction with the infant’s care • Encourage parents to participate in family-centered rounds • Assist parents in making decisions regarding infant treatment schedules • Encourage parents to fully-participate in the infant’s care • Establish a routine time for daily phone calls; initiate calls • Provide sense of control by having parents plan infant care/activities	• Mothers are at risk for alteration in parental role, ineffective parental performance, impaired parent-infant interaction, and impaired maternal-infant attachment, when they do not feel valuable and in control of infant care—which we theorize results in dysregulation of maternal OT system
	Role strain: parental/caregiver • Provide consistent, encouraging, nonjudgmental environment	• Empowering mothers to own their parental role results in sensitive parenting behaviors, higher levels of OT in mother

Focus	Nursing diagnosis/nursing intervention	Underlying oxytocin-based process
	• Involve in activities with the infant they can successfully achieve • Provide a "homelike" environment (e.g., family personalizes infant room/space) • Provide positive feedback for supportive parenting behaviors	and infant, and greater brain activation and connectivity in OT-based networks[i]
	Parental performance: ineffective • Use active listening: explore understanding of developmental needs, expectations • Examine parenting style, behaviors (e.g., psychosocial environment at home, attribution of negative traits to infant, involvement with infant care) • Assess maternal depression, stress, and anxiety • Plan education directed toward parental concerns • Model developmentally-appropriate caregiving skills (e.g., gentle touch, soft voice, containment, non-nutritive sucking, contingent responses to infant cues) • Acknowledge, praise parenting strengths • Initiate referrals to agencies (e.g., Help me Grow, March of Dimes), parent education programs, social support groups (e.g., NICU Peer Parent Support groups)	• Maternal OT is associated with supportive maternal behaviors and coordination of social interactions with the neonate's alert state[j,k] • Parenting behaviors that release infant OT include comforting touch, soft voice, gaze, contingent responses, high quality affect[l-m] • Parents who display more affectionate touch increase their OT levels after interaction with their infant[j]
Dyad	Breastfeeding: ineffective • Lactation counseling and breastfeeding assistance • Parent education • Infant nonnutritive sucking at breast	• OT levels are higher in breastfeeding than formula-feeding mothers[o] • Human milk OT levels are higher after breastfeeding[p]
	Family processes: interrupted • Assist parents in identifying and prioritizing family strengths and needs • Promote positive attitudes by communicating what skills parents already do well • Help parents identify appropriate support systems (e.g., extended family, friends, social worker), community resources (e.g., faith groups, volunteers, respite care) • Identify social services (e.g., transportation, finances, housing)	• Ensuring that family's needs are met relieves parental anxiety, allows parents to maximize time in the NICU • When family processes are restored, parents are less stressed, more likely to engage in supportive social interactions with their infants that release OT
	Parent-infant interaction: impaired • Assess parent-infant interactions, especially during feeding and care • Model consistent, nurturing behaviors when caring for, interacting with infant • Foster developmentally-appropriate parenting behaviors	• Early, consistent, developmentally-supportive interactions regulate infant OT brain biology, emotions and social behaviors that emerge from that biology
	Maternal infant attachment impaired: risk • Minimize parental-infant separation immediately after birth • Identify infant's strengths and vulnerabilities • Educate parents regarding infant growth and development, clarifying expectations	• Synchronized, supportive interactions foster attachment—which is facilitated by the OT system[q,r] • OT coordinates with the social engagement system, which produces the physiologic states, emotions, and engagement cues that encourage dyadic attachment[s]

Focus	Nursing diagnosis/nursing intervention	Underlying oxytocin-based process
	• Invite parents to spend the night (e.g., Ronald McDonald House, hospital room) • Provide infant photos, mementos, (e.g., outgrown blood pressure cuff, hat), journal developmental milestone reports to celebrate progress, promote normalcy • Suggest parents provide a photo and/or audiotape of themselves	

[a] Moreno-López, Martínez-Lorenzana, Condés-Lara, & Rojas-Piloni (2013).

[b] Uvnäs-Moberg, Handlin, & Petersson (2015).

[c] Weisman, Zagoory-Sharon, & Feldman (2012).

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