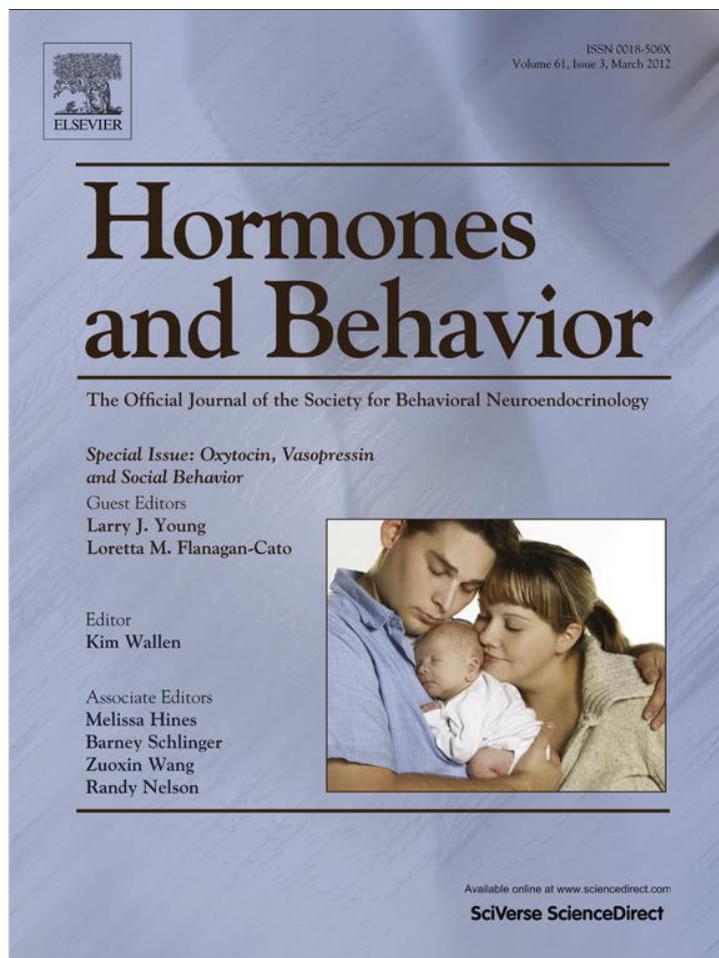


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Review

Oxytocin and social affiliation in humans

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ABSTRACT

A conceptual model detailing the process of *bio-behavioral synchrony* between the online physiological and behavioral responses of attachment partners during social contact is presented as a theoretical and empirical framework for the study of affiliative bonds. Guided by an ethological behavior-based approach, we suggest that micro-level social behaviors in the gaze, vocal, affective, and touch modalities are dynamically integrated with online physiological processes and hormonal response to create dyad-specific affiliations. Studies across multiple attachments throughout life are presented and demonstrate that the extended oxytocin (OT) system provides the neurohormonal substrate for parental, romantic, and filial attachment in humans; that the three prototypes of affiliation are expressed in similar constellations of social behavior; and that OT is stable over time within individuals, is mutually-influencing among partners, and that mechanisms of cross-generation and inter-couple transmission relate to coordinated social behavior. Research showing links between peripheral and genetic markers of OT with concurrent parenting and memories of parental care; between administration of OT to parent and infant's physiological readiness for social engagement; and between neuropeptides and the online synchrony of maternal and paternal brain response in social-cognitive and empathy networks support the hypothesis that human attachment develops within the matrix of biological attunement and close behavioral synchrony. The findings have conceptual implications for the study of inter-subjectivity as well as translational implications for the treatment of social disorders originating in early childhood, such as autism spectrum disorders, or those associated with disruptions to early bonding, such as postpartum depression or child abuse and neglect.

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"The roots of parenthood lie in the child's relations to his own parents in his earliest years. The love which a mother has for her children is a reflection of the love which she received when she was a little girl. The love which a father has for his children is a reflection of the love which he received when he was a little boy. It is in childhood that we learn to love"

John Bowlby, *The roots of parenthood*, 1953 (p. 15).

Affiliative bonds: a conceptual model

Behavior-based perspective on affiliation

Affiliation, from the Medieval Latin word *Affiliatus* – to adopt as a son – is defined as "to bring or receive into close connection" (Merriam-Webster Medical Dictionary, 2002) and appears to contain two elements; it refers to a close interpersonal bond, such as that between a parent and child, and it involves a process or action needed for that bond to take place. During the mid 20th century, authors such as Bowlby (1958), Harlow (1958), and Spitz (1946) began to draw attention to the primary role of love as a central motivating force of developmental progress and as a critical ingredient in the survival, safety, and well-being of the young. Affiliative bonds, defined as *selective* and *enduring* attachments, were conceptualized as providing the foundation for the infant's capacity to function competently within the eco-social niche, grow to form intimate bonds with non-kin members of society, and eventually nurture the next generation. This paradigm shift, which transformed "love" from the realm of the literary to the domain of hard core science, drew on several lines of concurrent inquiry in biology, philosophy, and the social sciences. These new fields not only introduced novel ideas but also advocated new methodologies as best practice for scientific progress. Most important were the works of the early Ethologists (Lorenz, 1950; Tinbergen, 1963) who underscored bonding as the central process supporting mammalian adaptation, highlighted behavior as the lens through which science should approach the study of social maturation, and suggested that the meticulous documentation of behaviors that emerge or intensify during periods of bond formation are necessary preconditions for any theory of human nature. By focusing on concrete bonding-related behaviors, these researchers advocated a bottom-up perspective of human development that is *behavior-based*, thus opposing the two central perspectives of the time: psychoanalysis, which outlined a theory-based rather than behavior-based viewpoint of human development, and Skinnerian behaviorism, which focused on the behavior of individuals, not of relational units. This new ethological-based approach altered the conceptualization of human affiliation in three key ways. First, it suggested that bonding is expressed through a set of species-specific stereotypic caregiving (and care-receiving) behaviors that appear immediately after birth and provide the foundation for the infant's neurobehavioral maturation, thereby advocating a critical-period viewpoint on attachment. Second, it indicated that bond formation is supported by unique neurohormonal systems and brain circuits, hence linking specific biology to specific behavior in the formation of affiliative bonds. Third, it underscored a lifetime perspective suggesting that (a) the three prototypes of affiliation in mammals – parental, pair, and filial – share underlying physiological mechanisms and overt behavioral expressions, and (b) bio-behavioral mechanisms formed in early infancy shape the way individuals function within their various attachments throughout life.

Several large-scales empirical programs and countless smaller studies over the past half-century lend support to the propositions forwarded by the attachment-ethological perspective and specified the biological basis of affiliation. Long-term human studies following

individuals from infancy to adulthood demonstrated that sensitive caregiving in infancy predicted better adult adaptation and more secure romantic relationships (Sroufe, 2005). The empirical work of Hofer, spanning 40 years of careful experimentations, teased apart the provisions embedded in the maternal physical proximity in mammals and demonstrated that the mother's physical presence includes a set of "bio-behavioral regulators" such as maternal touch, odor, movements, or body rhythms, each functions to regulate a specific physiological system in the pup, including autonomic functioning, thermoregulation, or attention (Hofer, 1995). Finally, the work of Meaney (2001; 2010; Zhang and Meaney, 2010) specified the relations between Oxytocin (OT) – a nine amino-acid neuropeptide synthesized in the hypothalamus – and patterns of maternal care. This research program showed that the amount of maternal caregiving, particularly the licking-and-grooming (LG) behaviors of rat dams, shaped the offspring's stress response and OT-mediated affiliation systems. Moreover, the generational transmission of OT and parental behavior was mediated by behavioral, rather than genetic mechanisms and was related to the amount of touch-and-contact the mother received as an infant (Champagne et al., 2001; Champagne, 2008).

Over the past decade, research at my lab followed these lines of inquiry in humans in an attempt to describe the role of OT in human social adaptation and the formation of affiliative bonds. We examined the links between OT and parenting behavior; the relations between brain structures implicated in parental care and their associations with OT; the cross-generation transmission of OT; the relations between peripheral indices of OT with allelic variations on the Oxytocin receptor (*OXTR*) and *CD38* genes; and the consistency in OT-related processes and relational behavior among the three prototypical forms of mammalian affiliations – parental, pair, and filial – which in humans refer to attachments with parents, romantic partners, and best friends. In several longitudinal studies, we assessed the combined effects of parenting and OT on children's social adaptation across childhood and up to adolescence in typical as well as atypical developmental conditions associated with disruptions to bonding processes, such as maternal post partum depression, preterm birth, and war-related PTSD. Following evolutionary models, we define social adaptation as the ability to function competently with non-kin members of society at both the level of global adaptation to the eco-social niche and the skills required to form and maintain intimate bonds with non-kin (Clutton-Brock, 1991; Davis and Daly, 1997; Eibl-Eibesfeldt, 1989).

Bio-behavioral synchrony

The work presented here is guided by our conceptual model on *bio-behavioral synchrony*, which utilizes the concept of synchrony and its emphasis on the temporal concordance of biological and social processes as a useful framework for the study of affiliative bonds (Feldman, 2007a, 2007b, 2007c, 2007d, *in pressa*, *in pressb*). Synchrony is a concept coined by the first researchers on parenting in social animals, beginning with research on the social insects nearly a century ago (Wheeler, 1928). Prompted by the question of what enables a group of ants to jointly carry a grain of wheat, or broadly speaking, collaborate to achieve a social goal, researchers described the process of *bio-behavioral synchrony*. Among members of a social group, such as flocks of birds synchronizing their journey toward warm climates or fish moving in perfect synchronous cycles to ward off a shark, there is a temporal concordance between the behavioral patterns of various members, between their online physiological processes, such as neural firing or hormonal release, and between the physiology of one member and the behavior of the other. Such synchronous process creates a time-locked ongoing relationship between the physiology and behavior of group members that is critical for the survival of the group as well as for the individual's adaptation to the

social milieu. Biobehavioral synchrony, therefore, is the process by which organisms become members of a social group and function collaboratively within it. The evolution of mammals implied that individual members of the eco-social niche are no longer initiated directly into large social groups but are ushered into the social milieu through intimate one-on-one reciprocal relationships with the caregiver. Hence, mammalian young receive their training for social reciprocity not within the large group but in the context of the nursing dyad by means of finely-tuned bio-behavioral adaptations between mother and child (Rosenblatt, 1965; Schneirla, 1946). Across mammalian species, dyad-specific maternal-infant bonds are built on repeatedly-experienced patterns of sensori, motor, and behavioral cues in each partner. Over time and repeated experience these discrete synchronized bio-behavioral events coordinate to form the unique bond that characterizes the rhythms, content, focus, and pace of the specific attachment relationship (Feldman, 2007a, 2012; Fleming et al., 1999). Studies in mammals and emerging data in humans suggest that the formation of these dyad-specific bio-behavioral bonds is underpinned by the extended OT system (Gimpl and Fahrenholz, 2001; Insel, 1997; Ross and Young, 2009). Yet, due to the fact that both the distribution of OT receptors in the brain and the links between maternal behaviors and OT expression show substantial between-species variations (Insel, 2010; Ross et al., 2009), it is critical that the specific associations between OT and processes of social bonding should be studied in humans, notwithstanding limitations of human neuroendocrine and molecular research.

Like other mammals, human mothers and infants engage in the species-typical repertoire of postpartum behaviors, which includes gaze at the infant's face or body, "motherese" high-pitched vocalizations, expression of positive affect, and affectionate touch, a behavior akin to the licking-and-grooming of other mammals (Feldman and Eidelman, 2007). Human mothers express these maternal behaviors already in the first postpartum day, but, moreover, mothers provide approximately 70% of their behaviors during the 7% of the time newborns spend in alert-scanning state, creating temporal contingencies between infant state and maternal social behavior already at the first post-birth hours (Feldman and Eidelman, 2007; Silberstein et al., 2009). These social contingencies are supported by physiological periodicities maturing in the fetus during the 3rd trimester of pregnancy, including the biological clock and cardiac pacemaker (Feldman, 2006; Groome et al., 1999; Mirmiran and Lunshof, 1996). Thus, as soon the human infant is born, he or she can experience a temporal match between their own state and the response of the social environment as mediated by the mother. Such early temporal concordance between maternal and infant readiness for social engagement is a critical human addition to the physiological provisions embedded in the maternal proximity in other mammals (Hofer, 1995) or the expression of maternal behavior in rodents (Meaney, 2010), and lays the foundation for the development of human-specific social, emotional, and cognitive competencies (Feldman, 2007a; Feldman and Eidelman, 2007; Feldman et al., 2004). At approximately 3 months, infants enter the social world as active partners and begin to engage in synchronous exchanges with their caregivers that contain coordinated sequences of gaze patterns, co-vocalizations, mutual expressions of positive affect, and loving touch (Feldman, 2003, 3007a). Synchrony experienced during the critical period between 3 and 9 months was found to promote children's self-regulation (Feldman et al., 1999), symbol use (Feldman, 2007b), the capacity for empathy across childhood and up to adolescence (Feldman, 2007c), as well as more optimal social adaptation and lower depression in adolescence (Feldman, 2010). These longitudinal findings support the sensitive period perspective suggested by Ethological models in the effects of early synchrony on children's neurobehavioral and social-emotional growth. From the end of the first year of life and on, with the emergence of children's symbolic competencies, interactions between close partners grow to contain

two parallel lines: a non-verbal line of synchrony between the partners' gaze, affective expression, vocal quality, body orientation, movements, and proximity position, and a verbal line of synchrony between levels of communicative intimacy, for instance between the degree of self-disclosure between close friends or romantic partners (Feldman, 2007d). Synchrony, therefore, describes a critical component of close relationships that builds on familiarity with the partner's style, manner, non-verbal patterns, personal rhythms, behavioral preferences, and pace of intimacy.

In this context, it is important to note that the construct of synchrony describes only the *temporal concordance* between processes that occur simultaneously or sequentially and postulates no heuristic system of symbols or a-prior assumptions. As such, synchrony provides an optimal framework for a bottom-up model that centers on discrete building blocks as they cohere into a theoretical model. Recent perspectives in neuroscience have underscored synchrony as the mechanism which underlies consciousness and supports the brain's capacity to form a unitary event out of the simultaneous activity of discrete brain regions (Edelman, 2004; 2006; Damasio, 2003), as stated by Lineas (2001, page 120): "timeness is consciousness". This transition from mechanisms of a "central organizer" to those of temporal synchrony highlight the importance of a bottom-up perspective and parallels the shift advocated by the early Ethologists. As such, the following review will focus specifically on studies that demonstrate *biobehavioral synchrony* in the relations of OT and matched dyadic behavior within attachment relationships: within each partner, among attachment partners, and between OT in one partner and social behavior in the other.

Oxytocin, affiliation, and biobehavioral synchrony

The exponential increase in empirical research on OT and social functioning in recent years raises the question as to what are the mechanisms mediating the effects of OT on human affiliation, apart from the obvious involvement of OT in the birth of the "mammalian dyad" by initiating uterine contraction and milk letdown, functions that were considered for decades as the sole tasks of this neuropeptide (Gimpl and Fahrenholz, 2001; Insel, 2010; Young, 2009). OT is a nonapeptide synthesized in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus, although the spinal cord, bed nucleus of the stria terminalis (BNST) and the anterior commissural nucleus also serve as central sources of OT (Carter, 1998). Brain regions receiving OT projections include the medial preoptic area (MPOA), the BNST, the lateral septum, the nucleus accumbens (NAcc), the amygdala, and the hippocampus as well as ventrally, the ventral tegmental area, solitary tract nuclei, and the spinal cord (Ross and Young, 2009). In addition, neurons in the PVN and SON release OT from their dendrite into the cerebral spinal fluid (Veening et al., 2010) and OT is also released at peripheral sites, including the heart, thymus, gastrointestinal tract, uterus, placenta, amnion, corpus luteum, and testes (Gordon et al., 2011), underscoring the widely-distributed and dynamic nature of OT production in body and brain. The OT system is reciprocally engaged with the hypothalamic-pituitary-adrenal axis (HPA) that mediates the stress response, and neuroanatomical evidence suggests that the HPA and OT systems are mutually regulated (Dabrowska et al., 2011). OT has shown to have significant anxiolytic and anti-stress effects (Neumann, 2008; Neumann and Landgraf, 2008), which are central for the initiation of breastfeeding and the formation of maternal-infant bonding (Uvnäs-Moberg, 1998).

In addition to anti-stress effects that induce a feeling of safety and support the approach behaviors required for bonding, OT plays a key role in the motivation to bond through its connectivity with the dopaminergic reward system. OT neurons are reciprocally connected with mesolimbic dopaminergic neurons and this interconnection serves an important role in both romantic and parental attachment by

initiating sexual behavior and forming sexual preferences (Melis and Argiolas, 2011) and by labeling the infant with an intuitive reinforcement and increasing the incentive value of the infant for its mother (Cardinal et al., 2002; Lee et al., 2000). Bos et al. (2011) suggest that gonadal steroids and neuropeptides jointly influence social bonding by increasing OT-dopamine interactions. In contexts perceived as safe, Estrogen and OT increase parasympathetic efference and inhibit amygdala output to the brainstem, leading to increased prefrontal activity and OT-dopamine interactions that enhance the motivation to bond. Recent data from our lab show that during the early stages of romantic attachment, levels of plasma OT and testosterone are inter-related and are associated with respiratory sinus arrhythmia (RSA), an index of parasympathetic influences over heart rate variability. Such hormonal-autonomic interactions were found to predict observed social reciprocity between new lovers, expressed in mutual gazing, matched affect, positive arousal, and affectionate touch.

Along the affiliation-supporting mechanisms of stress reduction and incentive motivation, recent findings linking OT to the immune system suggest that OT may enhance social affiliation through the sense of well-being associated with close bonds and the role of OT in promoting health (Hansenne, 2005; Macciò et al., 2010). For instance, administration of OT was found to increase the expression of both CD25 and CD95, proteins that mediate immune signaling (Gordon et al., 2011; Macciò et al., 2010). Similarly, Jin et al. (2007) showed that CD38, a transmembrane multi-functional molecule that combines enzymatic and receptor properties and is implicated in various physiological processes, including proliferation, differentiation, and migration, triggers OT release from soma and axon terminals of hypothalamic neurons through the mobilization of calcium. CD38 knockout mice showed lower plasma OT, disrupted maternal behavior in females, and social amnesia in males and similar links have been found in humans (see below). Preliminary data from our lab support the associations between OT and immune functioning. During periods of both parental and romantic bonding, we found an increase in plasma IL-6 and this increase was associated with the rise in OT during these periods.

Finally, OT is among the systems most open to environmental influences, mediates the epigenetic effects of maternal behavior (Szyf et al., 2008), and its generational transmission operates through patterns of maternal care (Francis et al., 2002). Naturally-occurring variations in maternal behavior, particularly maternal licking-and-grooming (LG), induce changes in the offspring's gene expression through a process of methylation, creating stable non-genomic alterations in DNA expression that are shaped by the affiliative components of the environment. These early maternal effects appear to involve up regulation of hypothalamic OT receptors and infants reared by high LG dams show elevated estrogen-primed OT receptors in the MPOA, which continue to be sensitive to social influences in the post-weaning period as seen in experiments involving both social isolation and social enrichment (Champagne, 2011). Maternal LG and the increased ER alpha expression in the MPOA increase OT receptor binding and activate the mesolimbic dopamine system and the release of dopamine in the NAcc (Cameron et al., 1992; Champagne et al., 2004). On the other hand, low LG mothering leads to elevation of cytosine methylation of ER associated with decreased ER alpha expression (Champagne et al., 2006). Maternal LG similarly induces epigenetic effects on stress reactivity by increasing glucocorticoid receptor expression within the hippocampus (Weaver, et al., 2004; Zhang and Meaney, 2010), underscoring the combined effects of OT and maternal behavior in shaping the offspring's long-term stress and reward pathways. Although very little research examined methylation of the Oxytocin receptor gene (OXTR) in humans, recent work points to the associations between DNA methylation on the OXTR rs2254298 SNP and autism spectrum disorder (ASD) (Gregory et al., 2009). Importantly, we found that

the GG risk alleles on the OXTR rs2254298 is associated with diminished parenting behavior (see below), highlighting the links between OT, epigenetic effects, parenting behavior, and neuropsychiatric disorders of early social dysfunctions.

Although much further research is required to chart the molecular, chemical, and neurological aspects of OT, it is clear that the OT system is among the most widely-distributed throughout body and brain and that OT is dynamically engaged with homeostatic, appetitive, reparatory, stress reduction, salience and reward, and perceptual systems in processes that involve ongoing transactions between the organism and its environment (Bos et al., 2011; Landgraf and Neumann, 2004; Veening, et al., 2010; Zhang and Meaney, 2010). Such widespread connectivity forms a multi-dimensional system that integrates the internal milieu in order to orient the organism to the social world. Indeed, human studies demonstrate that intranasal OT administration increases the salience of social cues and improves the capacity to read subtle non-verbal signals through which individuals understand the intentions and behaviors of social partners (Bartz et al., 2011). We suggest that such overarching behavior- and environment-sensitive system provides the neurobiological substrate for the process of *bio-behavioral synchrony* which binds members of a social unit into a unified time-locked event and affords ongoing physiological and behavioral support for the formation of finely-tuned dyad-specific attachments.

The role of oxytocin in affiliative bonds

OT and the parent–infant bond

OT and mothering

The mother-infant bond, with its intimacy of contact and dyadic unity, is not only part of our evolutionarily-based biology but is a central component of the human cultural heritage. Throughout human history and across cultural communities, images of maternal-infant proximity – in sculptures, drawings, carvings, and ink paintings – are deeply rooted in our collective unconscious and serve as the primary symbol for the human capacity to love. The behavioral building blocks of maternal affection – gaze, touch, voice, and affect – serve as the basic channels for the expression of love that underpin any form of human intimacy (Feldman, 2011a).

Much research has implicated OT in the expression of maternal behavior across a variety of species. OT-mediated maternal behaviors include the licking-and-grooming and arched-back nursing of rat dams (Francis et al., 2002), the sheep's olfactory-based recognition of her ewe (Kendrick et al., 1997), and the grooming and contact of Rhesus Macaques (Maestriperi, et al., 2009), as tested using peripheral measures, brain neurochemistry, OT knockout mice, and epigenetics (Szyf et al., 2008; Zhang and Meaney, 2010). Much less research examined the role of OT in human mothering, and such assessment is complicated by the inability to directly test OT at the brain neurochemical level and the need to rely on peripheral measures that are considered as proxies of brain activity (Rollins et al., 2010). To date, research on the role of OT in human parenting has relied on three methodologies: peripheral assessments of OT in plasma, saliva, urine, and CSF; a molecular genetic approach assessing variations in the OXTR in relation to parenting; and intranasal administration of OT to parents.

In the first study to evaluate OT and the development of maternal behavior in humans, we assessed maternal plasma OT and Cortisol (CT), a biomarker of the HPA-axis stress response, repeatedly from the first trimester of pregnancy and up to the first postpartum month. Postpartum mothers were observed interacting with their infants and were interviewed regarding their mothering-related thoughts and behaviors. As compared to single women not involved in a romantic relationship, plasma OT levels in pregnant and parturient women were significantly higher, pointing to increased activity of

the OT system during periods of bond formation (Gordon et al., 2008). OT levels were highly stable among individuals and women showing higher OT in early pregnancy also exhibited higher levels in late pregnancy and the postpartum. Finally, maternal OT levels in the first trimester predicted the amount of maternal postpartum behavior, including gaze, positive affect, “motherese” vocalizations, and affectionate touch, suggesting that OT across gestation functions to prime mothers for the expression of maternal behavior, consistent with the effects described in other mammals (Nelson and Panksepp, 1998). OT and CT were unrelated at each assessment but each charted an independent path to the prediction of maternal behavior, with higher OT associated with increased and higher CT with reduced maternal post-partum behavior (Feldman et al., 2007). Furthermore, maternal bonding to the fetus during the third trimester was predicted by the increase in plasma OT from the 1st to the 3rd trimester, indicating dynamic associations between OT and the evolving maternal-infant bond (Levine et al., 2007).

In addition to research directly assessing OT in mothers, two studies addressed the relations between breastfeeding, a proxy for OT production, with patterns of maternal care, brain activations, and infant outcome. In the first, we observed mothers of premature infants who expressed minimal, medium, and significant amounts of breastmilk in mother-infant interaction prior to hospital discharge and followed the infant's neuromaturation and cognitive development. Mothers who expressed more than 75% of the infant's nutrition exhibited more maternal postpartum behavior, particularly affectionate touch, and their infants showed better neuromaturation and cognitive growth at six months (Feldman and Eidelman, 2003). In an fMRI study, breastfeeding and formula feeding mothers were scanned in the postpartum and were observed interacting with their infants at 4 months. While listening to their own-infant cry, breastfeeding mothers showed greater activations in areas described in human and animal studies to play a key role in the expression of parenting, including the amygdala, striatum, superior frontal gyrus, and insula (Barrett and Fleming, 2011; Swain et al., 2007). Greater amygdala activations were correlated with higher observed maternal sensitivity, suggesting that the increase in brain activations triggered by breastfeeding may prepare for the expression of coordinated parenting at the stage when infants enter the social world (Kim et al., 2011).

Animal studies of maternal behavior have implicated OT-rich brain areas in the expression of maternal behavior. In particular, the NAcc, part of the mesolimbic dopaminergic reward circuit that receives OT projections, provides motivational drive to maternal behavior (Cardinal et al., 2002; Lee et al., 2000). Lesions and DA manipulations studies demonstrated that the NAcc is critical for maternal motivation to nest and retrieve pups (Champagne et al., 2004; Li and Fleming, 2003). The amygdala, a central node of the limbic affective system similarly receiving OT projections, has also been implicated in maternal attachment (Fleming and Korsmit, 1996; Lee et al., 2000; Oxley and Fleming, 2000). Lesions to the amygdala reduce maternal behavior (Toscano et al., 2009) and significant amygdala c-fos changes are observed following mother-pup interaction (Fleming and Korsmit, 1996). The NAcc and amygdala work in concert with several cortical areas, including the medial preoptic area, an OT-rich site that integrates infant sensory cues (Insel and Young, 2001; Lee et al., 2000; Oxley and Fleming, 2000), the anterior cingulate (ACC), and the dorso-medial prefrontal cortex (dmPFC) (MacLean and Newman, 1988; Murphy et al., 1981; Stamm, 1955). It thus appears that the neural basis of mothering integrates OT-rich sub-cortical motivational limbic areas with higher-level networks implicated in emotion modulation, social cognition, and empathy that allow the mother to read her infant's signals and plan adequate parenting.

Few studies examined OT in relation to attachment-based brain responses in humans. Strathearn et al. (2009) scanned secure and insecure mothers while viewing their own infant's happy and sad expressions. Secure mothers showed greater activations to their

infant's happy face in reward-related ventral striatum pathways and in OT-rich hypothalamic areas and these activations correlated with peripheral OT response to mother-infant contact. In contrast, insecure mothers showed greater insular activation to their infant's sad expression. In an OT administration study, Riem et al. (2011a) found that OT reduced amygdala activation to infant cry, consistent with its known anxiolytic effects, while increasing activations in empathy-related networks. In a second study of the same group (Riem et al., 2011b) assessing functional brain connectivity in response to infant laughter, OT was found to reduce amygdala activation and enhance functional connectivity between the amygdala and cortical and subcortical regions, pointing to enhanced salience of infant positive signals under OT.

In a recent study integrating brain, hormones, and behavior, we examined mothers' brain response to dynamic, ecologically-valid infant stimuli. Two groups of mothers were recruited on the basis of their social behavior during mother-infant interactions; synchronous mothers – mothers who coordinate their social behavior with the infant's signals, and intrusive mothers – those who provide excessive parenting when the infant signals a need for rest. Both the synchronous and the intrusive maternal styles are stable maternal styles from infancy to adolescence and bear important consequences for children's development (Feldman, 2010; Sroufe, 2005). Whole-brain analyses showed that synchronous mothers exhibited greater activations in the left NAcc, indicating that parenting in these mothers is underlaid by reward-related motivational mechanisms, whereas intrusive mothers activated the right amygdala, suggesting anxious and stress-related mechanisms underlying maternal care. Functional connectivity analysis showed that among the synchronous mothers, left NAcc and right amygdala were functionally correlated with emotion modulation, theory-of-mind, and empathy networks whereas among intrusive mothers, left NAcc and right amygdala were functionally correlated with pro-action areas. SPIN analysis, a technique measuring the temporal coherence of activity in a brain nucleus over time, indicated that in the synchronous group, left NAcc and right amygdala activations displayed clearer organization over time, whereas in the intrusive group activations were more disorganized. Finally, correlations between OT with NAcc and amygdala activations emerged in the synchronous group only. Overall, these findings suggest that optimal parenting is underlaid by reward-related motivational mechanisms, temporal organization of brain and behavior, and concordance between maternal brain, interactive behavior, and the functioning of the OT system (Atzil et al., 2011).

Finally, a new study examined associations between central and peripheral OT in humans by testing the links between plasma OT, variations in the *OXTR* and *CD38* genes, synchronous parenting, and memories of parental care in a large group of 352 mothers, fathers, and non-parents. Variations in *OXTR* have been associated with multiple social and emotional processes (Apicella et al., 2010; Israel et al., 2009; Kim et al., 2010; Rodrigues et al., 2009), and risk alleles on the *OXTR* rs2254298 and rs1042778 SNPs have been associated with increased risk for disorders characterized by social dysfunctions such as autism spectrum disorder (ASD, Lerer et al., 2008) and major depression (Thompson et al., 2011). In addition, we measured allelic variations on the *CD38* gene. In humans, the *CD38* rs3796863 risk allele has been associated with increased risk for ASD (Munesue et al., 2010). We found that individuals with high risk alleles on the *OXTR* rs2254298 or the *OXTR* rs1042778 SNPs or on the *CD38* rs3796863 SNP had lower levels of plasma OT and the effects were similar in mothers, fathers, and non-parents, demonstrating that peripheral levels of OT partially reflect OT neuropathways. Reduced plasma OT and risk alleles on the *OXTR* and *CD38* genes were each related to lower frequencies of parental affectionate touch during parent-infant interactions, similar to the findings in rodents (Meaney, 2010). Episodes of parent-infant gaze synchrony, moments in which parent

and infant share their social gaze, were the longest among parents who had both high levels of plasma OT and the low-risk *CD38* allele. These findings provide initial evidence that human attachment is mediated in part by the extended oxytocinergic system, including peripheral levels of plasma OT, the *CD38* gene, which is essential for OT release, and the *OXTR*, the single receptor encoding for this neuropeptide (Feldman et al., 2012).

OT and fathering

Paternal care is observed in only 3–5% of mammalian species, bi-parental species that exhibit active paternal involvement in childcare (Geary, 2000). Yet, whereas mammalian maternity is obligatory, mammalian paternity is facultative and functions to enhance infant endurance in the context of maternal care. Facultative fathering shows within-species variations that depend on social and ecological conditions, affords offspring a social competitiveness advantage (Clutton-Brock, 1991; MacDonald, 1988), and contributes to offspring endurance by means of both father-specific investments and mechanisms related to the co-evolution of mothering and fathering (Geary, 2000; Zigler, 2000). Across species, bi-parental mothers and fathers exhibit a gender-specific repertoire of parental behavior. Whereas the maternal repertoire involves licking, grooming, and the species-typical forms of touch-and-contact, paternal behavior is characterized by stimulatory activities, encouragement of exploration, and carrying the pups in space (Carter et al., 2005; Lonstein and DeVries, 2000). Human mothers and fathers similarly engage in gender-specific behaviors, with mothers preferring face-to-face positions and the maternal affectionate repertoire (Feldman et al., 2007), whereas fathers engaging in interactions that induce high positive arousal, exploratory focus, and rough-and-tumble contact (Lamb, 2010; Parke, 1996). Similarly, whereas mother-infant synchrony is rhythmic and socially-focused, father-infant synchrony is outward-oriented and contains quick and unpredictable peaks of positive arousal. It thus appears that mothers and fathers prepare infants to different elements embedded in attachment bonds: Mothers establish a sense of predictability and safety, while fathers prepare for novelty and excitement, and both components are needed for the formation of lasting attachments (Feldman, 2003).

Most animal studies on the neuropeptide basis of fathering examined the relations between paternal behavior and Arginine Vasopressin (AVP), a closely related neuropeptide to OT implicated in male bonding and aggressive and territorial behavior (Bielsky et al., 2005; Wang et al., 2000). Few studies in our lab examined OT in fathers and showed links between OT and the parent-specific repertoire as well as associations between AVP and paternal care.

In a study assessing OT in first-time fathers, we observed 160 mothers and fathers (80 couples) and their firstborn child, micro-coded maternal and paternal social behavior, and measured the parents' plasma OT and salivary CT in the first postpartum month and again six months later. Counter to expectations, we found comparable levels of baseline OT in fathers and mothers in the two time-points and both mothers and fathers showed higher levels of plasma OT compared to non-attached singles. Possibly, active paternal care provides one pathway to activate the OT system in bi-parental mammals, which in mothers is triggered by birth and lactation. OT in mothers and fathers showed *biological synchrony*, that is, maternal and paternal levels were inter-related at both the postpartum period and six months later, suggesting a process of endocrine fit in which partners shape each other's neuropeptide response through affiliative behavior and marital and coparental attachment. Finally, consistent with findings in biparental mammals, OT in mothers correlated with the social-affective repertoire, including maternal gaze, affect, vocalizations, and affectionate touch, whereas OT in fathers was associated with the object-oriented stimulatory play, consisting of positive arousal, object exploration, and stimulatory touch (Gordon et al., 2010a).

A second study of 112 mothers and fathers (not couples) and their 4–6 month old infants examined whether the parent-specific form of

touch functions to induce an OT response in the parent. OT functions as a bio-behavioral feedback loop and more touch and contact within attachment relationships increase OT levels and vice versa (Feldman et al., 2010b). Plasma and salivary OT were collected from mothers and fathers at baseline and following a 15 minute “play-and-touch” session, an experimental paradigm in which parents are asked to play freely with their infants and include any form of touch they typically use. Consistent with the typologies of high- and low licking-and-grooming rodents (Champagne, 2008; Zhang and Meaney, 2010), we found different profiles of OT response in the high-touch and low-touch groups. Mothers who provided high levels of affectionate touch (>66% of the time) showed an increase in salivary OT from pre- to post-interaction but such increase was not observed among mothers providing minimal touch (<33%). Consistent with the father-specific pattern of paternal care in mammals (Geary, 2000), fathers who provided high levels of stimulatory contact, such as moving the child's limbs, throwing the infant in the air, or moving the child across the room, increased their OT levels but not those engaging in minimal stimulatory touch (Feldman et al., 2010a). These findings have important translational implications and suggest that active parental touch can trigger an OT response in parents. Such findings can be used to devise touch-based interventions in cases where the OT system is dysfunctional, such as maternal post-partum depression.

Three studies examined OT and paternal behavior in combination with other hormones. Plasma OT and AVP and parenting behavior was measured in 144 mothers and fathers interacting with their six-month old infants. Interactions were micro-coded for the two behavioral constellations of mothers and fathers: social-oriented affiliative play and object-oriented stimulatory play. OT and AVP were not related and both showed comparable levels in mothers and fathers. However, OT was associated with the social-affective play in both mothers' and fathers' behavior, whereas AVP correlated with the object-directed stimulatory type of engagement. Interestingly, the infant's social and object play behaviors were also differentially related to the parent's OT and AVP, consistent with the model's predictions that attachment partners shape each other's physiology through joint interactive behavior within a social context. In a second study, OT and prolactin (PRL) were measured in the plasma of 43 fathers and their behavior during two play sessions – a social play session and an object-exploration toy session were micro-coded. OT and PRL were inter-related but were differentially associated with paternal behavior in the two play sessions. OT correlated with the father's behavior during the social play, whereas PRL was associated with his play during a session that called for introduction of specific toys and coordinating exploration with the infant (Gordon et al., 2010b). Consistent with much research on the links between OT and heightened social focus in humans (Bartz et al., 2011), it appears that OT is especially linked with early parental behavior that aims to engage infants socially and emphasizes non-verbal relational components infants must learn in order to become members of their social group. In addition to dyadic parent-child contexts, we measured parental OT and CT in relation to parents and infant's behavior during a triadic mother-father-infant interaction. Triadic synchrony – moments when parents and child are all in physical contact and coordinate their social gaze – were predicted by both mothers' and fathers' OT and were negatively related to the parents' CT (Gordon et al., 2010c). Finally, apart from the father-specific modes of play, we assessed plasma, salivary, and urinary OT in mothers and fathers interacting with their 6-month olds, we found that plasma and salivary OT were inter-related and both correlated with the degree of interactive synchrony between parent and child's affective expressions and with the number of positive communicative sequences observed during play (Feldman et al., 2011). Overall, these studies highlight the role of OT in supporting paternal behavior in both dyadic and triadic interactive contexts and as a hormone linked with the father-typical affiliative behavior.

Biological synchrony at the brain level among attachment partners was tested with an fMRI paradigm in which mothers and fathers were scanned while observing the same video of the attachment target—their own infant during solitary play. As suggested, fMRI studies of parenting point to the involvement of two neural networks underlying maternal care, a motivational-emotional limbic network, including the amygdala and NAcc, and a cortical social-attention network implicated in emotion modulation, social understanding, and empathy, including the medial prefrontal cortex (mPFC), Superior Temporal Sulcus (STS), insula, and inferior frontal gyrus (IFG), which integrate to support the mother's intuitive understanding of infant signals (Barrett and Fleming, 2011; Swain et al., 2007). Thirty mothers and fathers, comprising 15 married couples of young infants, were scanned while observing own-infant compared to standard-infant videos and online correlations between the voxel-by-voxel activations of mother's and father's brains were computed with a specifically-tailored algorithm. Online synchrony in brain activations between mothers' and fathers' brain emerged in social-cognitive cortical networks implicated in empathy, theory-of-mind, and mirror functions but not in limbic networks. Mothers showed greater limbic activations than fathers, and activations in limbic-motivational areas were correlated with maternal OT. Fathers showed greater activations in emotion-regulatory circuits, particularly in the mPFC, which were linked with paternal AVP. These findings are the first to show that parents synchronize online brain activity in social-cognitive networks that support intuitive understanding of the infant's communications and the planning of appropriate caregiving. These data provide evidence for the bio-behavioral synchrony model and suggest that such brain synchrony may support the emergence of human attachment within the matrix of neurobiological attunement between social partners (Atzil et al., 2011b).

Finally, an OT administration study to fathers provides further support to a neuro-peptide bio-behavioral synchrony model. Thirty-five fathers and their 6-month old infants participated in a double-blind placebo-controlled crossover study. Fathers inhaled either OT or placebo and salivary OT from both father and infant were measured four times — at baseline and in 20-minute intervals following administration. Respiratory sinus arrhythmia (RSA) was recorded from father and child during play and paternal and infant social behavior was micro-coded. Following OT administration, father's salivary OT increased dramatically and RSA was higher, pointing to a greater physiological readiness for social engagement (Porges, 2003). In addition, fathers showed more frequent touch and longer durations of engagement behavior in the OT condition. Moreover, consistent with the model's predictions, administration to father had a similar effect on the physiology and behavior of the infant. Infant salivary OT showed a similar dramatic rise in the OT condition, despite the fact that infants did not directly inhale OT. Similarly, infant RSA was higher and durations of infant social gaze and toy exploration were longer when fathers inhaled OT. Although the mechanisms of transmission are not entirely clear, these findings are the first to demonstrate that OT administration to a parent can lead to alterations in the physiology and behavior of the infant in ways that induce greater readiness for social contact. These findings have important translational implications for a potential neuropeptide treatment of infants at risk for social dysfunctions, such as siblings of children with ASD, without the actual risk of administering drug to a young infant (Weisman et al., 2011).

The cross generation transmission of OT in humans

Research in animal models indicates that the generational transmission of OT operates through parenting behavior (Francis et al., 2002; Champagne, 2008, 2011) and similar mechanisms may be expected in humans. Assessing cross-generation transmission of OT as mediated by parenting behavior, we measured salivary OT in mothers and fathers and in their 6-month old infants at baseline

and following the “play-and-touch” paradigm and micro-coded the partners' interaction synchrony. Already at this young age, parent and infant's OT levels were inter-related at both the baseline and reactivity assessments and the degree of OT increase following contact was correlated as well. Parent–infant synchrony was found to moderate the inter-generational effect. In the context of high parent–infant synchrony, the degree of concordance between the parent and infant's OT was high whereas no associations emerged between parent and infant's OT when synchrony was low. These data suggest that behavioral coordination provides one channel through which parental OT shapes the infant's emerging neuropeptide organization and its ensuing life-time effects on social affiliation (Feldman et al., 2010a).

A different line of research on the generational transmission of OT examined adults' retrospective accounts of parental care in their childhood in relation to OT. Heim et al. (2009) found lower levels of OT in the CSF of women with a history of child abuse. Gordon et al. (2008) showed that adult memories of the warmth and care they received as children were related to higher plasma OT. Bartz et al. (2011) demonstrated that the effects of OT administration on memories of maternal closeness in childhood were mediated by the individual's history of reported attachment security and the beneficial effects of OT inhaling were observed only among securely attached individuals. Finally, Feldman et al. (2011) found that mothers' and fathers' plasma and salivary OT were related to more positive memories of parental care as well as to more secure attachment to romantic partners. Finally, in the aforementioned study of plasma OT and genetic variability (Feldman et al., 2012), memories of parental care were examined in relation to the parent's actual behavior toward his or her infant. Among both parents and non parents, more positive memories of parental care were associated with higher plasma OT and the low risk alleles on the *CD38* rs3796863 SNP. Furthermore, mothers and fathers who reported more positive care in their own childhood provided more affectionate touch to their infants, consistent with the generational transmission of optimal parenting through patterns of maternal touch described for other mammals.

OT and mothering in atypical development

Emerging research suggests that disorders associated with disruptions to maternal–infant bonding are marked by disordered functioning of the OT system. Mothers with high symptoms of antenatal and post-partum depression had lower plasma OT (Skrandz et al., 2011). Lower levels of OT and AVP were found among adopted children with a history of disrupted early attachment (Fries et al., 2005). Foster mothers who expressed more joy during interactions with their infants also showed greater OT response and greater ERP activation of the P3 component, implying greater focused attention to their infant's pictures (Bick and Dozier, 2010). In a longitudinal study of 155 clinically depressed and non-depressed mothers and their children followed from birth to six years, we found that nearly 60% of the children growing up in the context of chronic maternal depression suffered a psychiatric disorder, mostly anxiety or conduct disorders, and showed lower emotional self-regulatory skills, reduced empathy to the distress of others, and disruptions to social engagement behavior, expressed in social withdrawal, minimal eye contact, diminished arousal, enthusiasm, and creativity, and lower symbolic play. Depressed mothers had significantly lower salivary OT, but consistent with expectations, lower levels of peripheral OT were also observed in the children as well as in the fathers and were related to the diminished reciprocity between parent and child. Moreover, we found that functioning of the OT system provided a buffer against the effects of chronic maternal depression on infant social growth and psychopathology. Chronically depressed mothers, as well as their children, were four times more likely to be homozygous for the G risk allele on the *OXTR* rs2254298, consistent with previous research pointing to associations between this allele and

greater risk for major depression (Thompson et al., 2011). Yet, children of depressed with the A low risk allele on the *OXTR* rs2254298, had higher levels of salivary OT, significantly lower levels of psychopathology and their expressed empathy was comparable to that of controls. These findings suggest that in the context of risk associated with maternal-infant bonding, more optimal functioning of the OT system may promote resilience and provide a buffer that mitigates some of the effects of maternal depression on children's social competence, empathy, and proneness to psychopathology (Feldman, 2011b). Taken together, these findings highlight the lifetime risk imposed by early disruptions to the parent-infant bond that preclude the experience of bio-behavioral attunement between maternal and infant's physiology and behavior, whether by risk related to infant biological conditions, such as ASD or prematurity, maternal disorder, such as postpartum depression, or contextual risk, such as abuse and neglect.

OT and romantic attachment: pair bonding in humans

Romantic relationships have a profound effect on adult life and have been associated with well-being and health, whereas the inability to form and maintain intimate bonds is linked with much psychological distress (Burman and Margolin, 1992; Bloom et al., 1978). Yet, very little research addressed the neuroendocrine basis of pair bonding in humans.

Animal studies point to the role of OT in pair bonding in mammals (Carter, 1998). OT plays a critical role in the regulation of pair-bond formation in monogamous prairie voles (Insel and Hulihan, 1995): intracerebroventricular infusion of OT facilitates partner's attachment in female prairie voles (Williams et al., 1994), blockade of OT receptors impairs bond formation (Cho et al., 1999), and peripheral levels of OT correlate with partners' affiliative behavior (Snowdon et al., 2010). Human studies similarly highlight the involvement of OT in pair bonding. OT administration increased couples' positive communication (Ditzen et al., 2009) and plasma OT was related to positive communication, affiliation, and emotional support between partners (Gonzaga et al., 2006; Grewen et al., 2005). Yet, results are mixed and few studies found correlations between OT and negative emotions, anxiety, and distress in romantic couples (Holt-Lunstad et al., 2008; Tabak et al., 2010; Taylor et al., 2010).

In addition to direct measurement of OT, imaging studies of romantic partners showed greater activations in OT- and dopamine-rich brain areas, such as greater neural activity in the left posterior cingulate cortex and caudate regions, in the initial stages of romantic attachment, whereas activations of the cortical regions including anterior cingulate, insular cortex, and ventral pallidum was increased in long-term pair-bonds (Aron et al., 2005; Bartels and Zeki, 2004; Kim et al., 2009). Both the initial period of romantic love and long-term relationships are associated with neural activity in dopamine-rich reward and basal ganglia systems, such as the ventral tegmental area (VTA) and dorsal striatum (Aron et al., 2005; Acevedo et al., 2011; Bartels and Zeki, 2004). These findings underscore the OT-dopamine associations proposed as one mechanism that mediates the effects of OT on bond formation. Consistent with the OT-dopamine model, an increase in parasympathetic activity, as measured by RSA response to negative and positive emotions, was also found during the first period of falling in love (Schneiderman et al., 2011). Interestingly, brain regions implicated in maternal attachment were also shown to be activated in prolonged romantic relationships as assessed by both fMRI (Acevedo et al., 2011) and ERP (Weisman et al., *in press*), consistent with the position that parental and romantic attachment share underlying mechanisms (Feldman, *in press*, *in press*).

In a recent study, we assessed the role of OT in romantic attachment in a group of 163 young adults, including 120 new lovers (60 couples) three months after the initiation of a romantic

relationship and 43 non-attached singles. Twenty-five of the 36 couples who stayed together were seen again six months later to evaluate dynamic changes in OT during the period of pair bonding in humans. Similar to our research in parents, couples were observed in dyadic interactions and were each interviewed regarding relationship-related preoccupations, thoughts, worries, and typical attachment behaviors. Results showed that plasma OT levels were significantly higher in new lovers as compared to singles, suggesting increased activity of the OT system when falling in love. Interestingly, comparing OT in new parents, new lovers, and singles, levels among the new lovers were the highest, significantly higher than those observed in parents, highlighting the first period of romantic attachment and its accompanied euphoria as the one associated with greatest increase in OT production. During the six months between the first and second assessments, these high OT levels did not drop and were stable within individuals. Plasma OT correlated with the couple's interactive synchrony, including behaviors such as social focus, positive affect, affectionate touch, and synchronized dyadic states, as well as with new lovers' preoccupations and worries regarding the partner and the relationship. These findings show remarkable similarity to those observed in parents and lend support to our model that proposes consistency between the three prototypes of attachment in humans. The findings further corroborate our proposition that both parental and romantic attachment is supported by similar OT-based neuroendocrine mechanisms and is expressed in a similar behavioral repertoire including gaze, touch, affect, and vocalizations and their online coordination (Schneiderman et al., 2012).

OT and filial attachment; our best friends

The TV series *Friends* captured the imagination of an entire generation, possibly as filial attachment represents a deep human need that is often left unmet in today's technological society. Any random stretch from the long-running series demonstrates with remarkable precision that close friendship is expressed by intimate familiarity with the pace, rhythms, jokes, movements, behavioral mannerisms, and verbal idiosyncrasies of each member of the clan. However, although close friendships are important components of well being and social adaptation, in contrast to the extant research on the parent-infant bond and, to a lesser extent, on romantic attachment, nearly no research has focused on the long-term attachments individuals form with their best friends, their physiological correlates, and mental health sequelae. Research has documented children's entry into social groups at the preschool years and described the development of children's friendships across middle childhood (Asher and Gottman, 1981; Hartup, 1989; Schneider et al., 1989), yet, we are aware of no study that examined best-friend relationships from an "affiliation" perspective, observing interactions between close friends and assessing the reciprocity, engagement, and interpersonal sensitivity between children and their intimate friends and their neurohormonal correlates.

In two longitudinal studies we examined children's interactions with their best friends and their links with the synchrony children experienced within the mother-child and father-child relationship in infancy, thereby addressing the consistency between parental and filial attachment. In one of these studies, OT was also assessed.

The first study was a longitudinal follow-up of the cohort of mothers and fathers and their firstborn child described above (Gordon et al., 2010a). We re-visited these families when the children were 3 years, the age when children first show selective attachment to a "best friend" (Asher and Gottman, 1981). Mothers' and father's plasma OT and interactive synchrony were measured when infants were one and six months. At 3 years, children were videotaped interacting with mother, father, and best friend and baseline and reactivity assessments of salivary OT were collected before and after

play. Consistent with the model's predictions, we found that children experiencing more synchronous parenting in infancy and more sensitive and responsive concurrent interactions with their parents transferred these positive internalized relationships to their first "filial affiliation" and their interactions with best friends were marked by greater reciprocity, rudimentary concern for the friend's needs (e.g., "you can have the toy"), greater emotional involvement, and higher affective attunement, as has been long suggested by Bowlby (1969). OT showed individual stability in each parent. These data describe a three-year stability in peripheral OT in humans and suggest that OT production may be set in early childhood through experiences within the mother-infant relationship and continues to function in a relatively consistent manner throughout life. Consistent with our previously described findings for the cross generation transmission of OT in infants and children of depressed mothers, child OT correlated with parents' OT and was predicted by the level of synchrony the child experienced in the first months of life. These longitudinal findings suggest a mutually influencing bio-behavioral process where child OT is shaped by the parents' early behavior, the parents' postpartum behavior is predicted by their OT levels, and the parents' early behavior and neuroendocrine response predict more reciprocal dialog and greater empathy between children and their close friends at the time when children make their first attachments to non-kin members of society.

In the second study, we followed children's multiple affiliative bonds and social adaptation longitudinally from infancy to adolescence. Children were observed at 5 months, 3 years, and 13 years during interactions with mother and father. At 3 years, children were also observed in lengthy ecological observations at childcare to assess social competence and aggression in the peer group. At 13 years, children were observed interacting with same-sex best friend in a positive (planning a school activity) and conflict (dialoging a conflict in their relationship) interactions. We found that the degree of reciprocity children formed with mother and father were individually stable across the 13-year period and were mutually-influencing between couples so that maternal and paternal reciprocity were inter-related at each stage. Children reared in contexts of high parental reciprocity throughout infancy showed greater social adaptation at childcare, that is, they were more friendly, cooperative, interacted with ease with adults and peers, were able to show both leadership and participation, were self-regulated, maintained social involvement, and were able to find more prosocial solutions to conflicts with peers (e.g., "you take the red color first and then I take"). Adolescents whose parents were more reciprocal throughout childhood showed better dialogical skills during interactions with best friends. Dialogical abilities imply the capacity to acknowledge the other's needs, opinions, and emotions; view oneself in someone else's position; discuss disagreements with empathy while maintaining positive affect and involvement; and engage in a give-and-take, fluent, and non-constricted exchange while maintaining an autonomous stance (Feldman and Bamberger, 2011). Dialogical skills are thought to provide the basis of the individual's empathic, prosocial, and moral orientation (Batson, 1991; Day and Tappan, 1996). Although OT was not measured in this study, previous studies showed that OT administration increases both trust and empathy (Bartz et al., 2011). This suggests that the capacity for empathy develops within close attachment bonds in early infancy, develops to include the first non-kin members of the social group children encounter, continue with intimate friends in early adolescence, an age when children often consolidate life-long friendships (Hartup, 1989), and culminate in the capacity to form and maintain romantic bonds and eventually provide nurturance to the next generation. Overall, these findings demonstrate the consistency between the three types of affiliative bonds humans form throughout life – with parents, partners, and best friends – and demonstrate that both behavioral expressions and neurohormonal substrates play an important and mutually-influencing role in the formation and maintenance of affiliative bonds.

Conclusions and implications

Our capacity to form, maintain, and conduct our lives in the context of close affiliative bonds marks, at least according to some perspectives, the apex of the human condition. This review offers a behavior-based neuroendocrine perspective on affiliation in humans within an evolutionary framework. The *biobehavioral synchrony* model highlights the behavioral building blocks of social bonding, including gaze, touch, vocal, body, and affective expressions; considers the ways in which these micro-social behaviors coalesce into unique affiliative bonds with specific pace, rhythm, patterns, and interpersonal focus starting from the first day of life; and describes how early social bonds transform yet maintain their consistent expression and underlying neurobiology across multiple relationships throughout life. The theoretical model and empirical findings presented here resonate with two types of conclusions, conceptual conclusions and translational conclusions, and each is discussed in turn.

Conceptual implications

Gerald Edelman, among the well-known theoreticians in neuroscience, argues in his latest book *Second nature* (2006) that the central unresolved issue in current neuroscience is that of *subjectivity*. After countless of studies, models, dollars, and effort resulting in great advances in the study of the brain and its workings, knowledge of the human brain remains external to the experiencing individual. There is still no way science can bridge the "subjectivity gap" and measure how perceptions, thoughts, emotions, and physiological states are felt by the living self-aware person. This, Edelman maintains, is not merely a problem to be resolved by more sophisticated machines but may represent an inherently unsolvable gap. While acknowledging the gravity of the subjectivity dilemma, we tentatively suggest that one way to approach the issue of *subjectivity* is through the lens of *inter-subjectivity*. According to the phenomenological philosophy of Husserl, detailed in his famous *Philosophy as a rigorous science* (Husserl, 1911), the human capacity to "know" about "things" in the outside world is never categorical but always involves a *relationship*, a relationship between the perceiving self and the external object. Consistent with this perspective, our biobehavioral synchrony model suggests that the human capacity to perceive such relationships between the self and the external world, perceptions which provides the basis for any knowledge, is formed within the matrix of the "nursing dyad". The human infant's capacity to engage in the world and learn its signals is supported online by neurohormonal and brain systems that maintain the infant's involvement with close attachment partners. The role of these attachment partners is to become intimately familiar with the infant's social signals and escort the child into the world in a step-by-step manner that resonates with the infant's subjectivity at both the biological and behavioral levels. Within such finely-tuned attachments, the human infant can send signals that are reciprocated and turn into interpersonal events that transform subjectivity into inter-subjectivity. These mutually-regulated bio-behavioral cycles keep the child's focus on the social world and provide the basis for exploration, sharing, and meaning-making. It can thus be suggested that these moments of inter-subjectivity lie at the mid-range between Edelman's closed brain that is available only to the experiencing individual and the external material brain that is accessible to scientific research. Such conceptualization echoes the "intermediate area" of play, love, and creativity described by Winnicott (1971), in which the internal and the objective are mutually influenced and co-constructed. Synchronous processes, through their online integration of physiology and behavior between attachment partners within a social context, can transform the intra-psychic into an interpersonal event that is open to objective measurement while still preserving its personal qualities. Synchrony, therefore, may offer a

unique venue for the external observation of a private brain experience, as seen by the findings which show parallel response in one partner to the physiological changes in the other, whether involving brain activations or alterations in peripheral hormones and autonomic activity following OT administration. As such, the current model offers a framework for future theory and research on the ongoing co-construction of brain activations, hormonal response, and behavioral expressions between attachment partners that may tap the issue of subjectivity by objectively describing shared “private” processes at the hormonal, brain, and behavioral levels.

Translational implications

The potential for neuropeptide therapy to treat disorders of social functioning has been recently suggested, triggered by the marked and consistent effects of intranasal administration of OT on improving social and emotional functioning in healthy individuals and in remedying some key features of the disorder in high-risk populations (Meyer-Lindenberg et al., 2011). OT therapy has been suggested, and in some cases studied, in conditions such as ASD, depression, schizophrenia, and social anxiety. The current findings provide a detailed description of the reciprocal relations between OT and attachment-related social behaviors beginning in the neonatal period with the parents, and continuing through children's close friendships, young adults' romantic attachment, and adults' parental and co-parental processes. These rich micro-level behavioral observations may highlight several translational directions. First, results indicating associations between OT increase and high levels of parental touch may help devise interventions for mothers suffering from post-partum depression, a condition affecting nearly 18% of women in industrial societies (Serretti et al., 2006), or following premature birth, a condition occurring in approximately 12% of births (March of Dimes, 2006). Depressed mothers tend to show minimal levels of affectionate touch (Feldman et al., 2009) and maternal touch following premature birth is similarly reduced (Feldman and Eidelman, 2007). This diminished maternal contact may mediate the low levels of OT in their children. Interventions that induce maternal touch, educate mothers on the importance of tactile contact for infant development, and teach mothers concrete techniques for more optimal touch may help trigger the OT system in depressed mothers. Such techniques may also be important following premature birth, when the OT system has often not been initiated properly due to C section, difficulties in breastfeeding, incubation, and the physical separation between mother and child. Due to the mutual effects of maternal and paternal OT on each other and on the child, fathers' touch may also be important in cases of maternal postpartum depression and premature birth. Emerging data from our lab point to the positive effects of OT on emotional functioning and well-being in combat-related PTSD, and such techniques may ease the often lifetime negative effects of the disorder on the veteran and his family. The dramatic increase in OT during the initial stages of romantic attachment and its relation to couple reciprocity may suggest that OT therapy can be used in conjunction with concrete behavioral-relational intervention for couples in distress. The intriguing findings showing that OT administration to parent and have parallel effects on the infant's hormonal and autonomic systems that support social engagement may open new opportunities to treat young children who are at high risk for social dysfunctions, such as children growing in abusive contexts of siblings of ASD children, without the ethical difficulties of administering drug to a very young infant. Finally, the associations described between allelic variations on the *OXTR* and *CD38* genes suggest that integrating a molecular genetic approach into the study of OT intervention may specify treatment to those most at need on the basis of their genetic make-up. Yet, it is important to remember that although advances in translational OT research may open new and exciting vistas, it is critical that such advances should be integrated with effort directed

to parental training, re-evaluation of social priorities, and policy making. Nearly 60 years ago Bowlby (1953) advocated for the well-being of children with the plea that “it is in childhood that we learn to love”. Our responsibility as caregivers, scientists, policy makers, mental health professionals, and concerned citizens is that every young child should be given the opportunity to learn how to love and every young parent should receive the guidance to make it happen.

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