Title: Neurobiology and Evolution: Mechanisms, Mediators, and Adaptive Consequences of Caregiving

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Glossary:

AVP - arginine vasopressin
BNST - bed nucleus of the stria terminalis,
CORT - cortisol or corticosterone
CRF - corticotropin releasing factor
DVC - dorsal vagal complex.
HPA - hypothalamic-pituitary-adrenal axis
HRV - heart rate variability.
5-HT – 5-hydroxytryptamine (aka serotonin)
NA – nucleus ambiguus
NE - norepinephrine
OT - oxytocin
PTSD - post traumatic stress disorder.
PVN - paraventricular nucleus of the hypothalamus
RSA - respiratory sinus arrhythmia
VVC - ventral vagal complex
Introduction and Perspective

The authors of this chapter are married to each other. We began our academic careers in different research fields. Porges was trained in experimental psychology, and was studying the psychophysiology of human “attention.” Carter was a zoologist, working in the field of animal behavior and neuroendocrinology. Sometime in the late 1990s it became apparent that although we were asking different questions and using different scientific models, we were in fact studying components of the same neural systems. After decades of marriage, we had become professionally re-acquainted in the brainstem. It is in the brainstem that the circuits regulating the autonomic nervous system and endocrine function, interact, and communicate to manage the physiology of social behavior. Through our almost daily intellectual dialog, we developed and now share a “brainstem-centric” model of social behavior. Our model, as applied in this chapter, examines the neurobiology of caregiving in light of the bidirectionality between peripheral structures involved in the autonomic and endocrine systems (e.g., heart, lungs, adrenals, and gut) and brainstem nuclei. The model also incorporates an appreciation for evolutionary changes in the regulation of these structures, as well as those of higher centers in the brain.

The defining features of our view of a social nervous system focus on several brainstem structures that are regulated by ancient neurochemicals (Carter, et al., 2008; Landgraf and Neumann, 2004). Thus, a necessary context for understanding the biology of sociality includes evolution and phylogeny. We will argue that like other forms of positive social behaviors, caregiving is an emergent property of the evolution of the mammalian nervous system (Porges, 1997). Knowledge of the processes that have sculpted the mammalian nervous system provides an integrated point of view on the costs and benefits of caregiving. The elements of these systems are not unique to caregiving. However, awareness of the neurophysiological systems that underlie caregiving and the related concept of social support, are essential to an understanding of the mechanisms through which both “giving and receiving” can influence health and well-being.

Positive social behaviors, and their neural underpinnings, are essential for both reproduction and survival. Positive social behaviors also are usually reciprocal and symbiotic. Social engagement and caregiving are most readily expressed in a context of safety. Among the novel adaptations of the mammalian nervous system is an evolved “social engagement system,” which permits social behavior and social communication. The social engagement system also serves to inhibit even more primitive systems responsible for the defensive reactions to threat and danger (Porges, 2001; 2003).

Understanding of the neurochemistry of the social engagement system is aided by an acknowledgement that the biology of the mother-infant interaction provides a neuroendocrine prototype for mammalian sociality. Neuropeptide hormones, such as oxytocin and vasopressin, involved in birth and lactation, as well as in the regulation of the autonomic nervous system, probably evolved from primitive molecules necessary for water conservation and homeostasis. Many of the same neural and endocrine systems that permit birth, lactation and maternal behavior, have been implicated in the giving and receiving of positive experiences (Carter, 1998). However, the processes that underlie positive sociality are not limited to mother-infant interactions or to biological parent-infant relationships. Biologically unrelated individuals may express or experience caregiving (Hrdy, 2008). Knowledge of the shared neural and endocrine systems responsible for mammalian caregiving offers an important perspective on the more general nature of the causes and consequences of mammalian sociality.

Defining features of caregiving include symbiosis and reciprocity.
Caregiving includes providing food, protection or other resources. However, caregiving also may extend beyond these physical elements to include emotional support for the need for affiliation and perceived safety. Most mammals, including humans and rodents, are altricial at birth, and caregiving is necessary to compensate for the infant’s undeveloped motor and autonomic nervous systems. Due to an immature cortico-spinal motor system, the infant is incapable of independently obtaining food or protecting itself from a predator. Due to an immature autonomic nervous system the infant is incapable of independently thermoregulating or ingesting and digesting certain foods. Thus, the mature nervous system of the caregiver becomes intertwined with the undeveloped nervous system of the infant to create a model of “symbiotic regulation.” The caregiver becomes part of a complex feedback system supporting the biological and behavioral needs of the infant. Within this model of “symbiotic regulation” the caregiver is not solely giving to the infant. The behaviors of the infant also trigger specific physiological processes (e.g., autonomic and endocrine feedback circuits) that help establish strong bonds, provide emotional comfort for the caregiver, and stimulate neural systems that support the health of the caregiver.

Through the process of maturation, motor and autonomic systems change. As the infant matures, there is a transition from a dependence on the caregiver for the regulation of biobehavioral processes to a greater degree of self-regulation. However, throughout the lifespan most mammals will continue to be dependent on others to maintain optimal well-being and state regulation (Hrdy, 2008). In some, but not all mammalian species, caregiving is based on or induces selective and reinforcing emotional social relationships and bonds (Carter, 1998; Porges, 1998). When enduring bonds are present, devastating reactions to separation or loss are to be expected (Bowlby, 1988).

Caregiving may or may not be reciprocal. However, reciprocity and the spontaneous reversal of the roles of giving and receiving are positive features of strong relationships and are the optimal features of “symbiotic-regulation.” Conversely, a lack of reciprocity often signals distressed and vulnerable relationships. The inability of an individual to enter and maintain reciprocal social relations is a feature of several psychiatric disorders (Teicher, et al., 2003).

When a mammalian mother initially interacts with her offspring, usually she has just given birth and must provide milk to nurture the newborn. The onset of maternal caregiving is normally closely associated with birth and lactation. The physical events of birth and lactation provide endocrine windows of opportunity for the establishment of strong social bonds. The hormones of birth and lactation are plausible candidates to explain the causes and beneficial effects of caregiving (Carter, 1998; Numan, 2007).

The evolution of a caregiving system: the transition from “self-regulation” to “other-regulation.”

Evolutionary theories attempting to explain between- and within-species variation in social behavior tend to focus on ultimate causes and assumed selection pressures. These theories are based on ancient historical events and are limited to the fossil record. Thus, it can be difficult to test evolutionary theories within the context of the expressed behavior or physiology of contemporary animals. However, a phylogenetic perspective that investigates the biological and behavioral shifts from reptiles to mammals bypasses the need to focus on ancient events and may be used to illustrate several neurobiological features underlying sociality, some of which may bear on evolutionary hypotheses. For example, most behaviors associated with caregiving and prosociality in humans are seen in other mammals, but are not evident in reptiles. Differences among mammalian species, individual variation, and developmental changes in social contact and caregiving are common. Analyses of these variations provide experiments of nature, which cast a new light on the neurobiology of sociality.
In part, the phylogenetic transition from reptiles to mammals appears to be a shift from an organism capable of “self-regulation” to an organism that is dependent at certain points in development on “other-regulation.” It is within this phylogenetic transition, in which regulation by “other” becomes adaptive, that the neurobiology of sociality emerges. The defining feature of the “other” in the mammalian model of regulation requires adaptive consequences, including support and protection of the vulnerable infant.

Of course, we are not suggesting that regulation of homeostasis in humans is strictly accomplished by “other-regulation”. For most mammals, and especially humans, a developmental increase in self-regulation capacity parallels the development of specific features of the nervous system. With physical maturation, neural pathways from the cortex to the brainstem exhibit a greater efficiency in regulating the autonomic nervous system and enable the maintenance of physiological homeostasis in both safe and dangerous situations (Porges, 2001). These maturational changes provide greater abilities to self-regulate and reduce dependence on others. However, it is important to note that developmental trends in self-regulation occur in a context of giving and receiving throughout the lifespan and thus may often involve some level physiological dependence between individuals.

The phylogeny of the mammalian nervous system and communication systems.

The phylogeny of the mammalian nervous system offers important clues to social behavior. In the transition from aquatic to terrestrial life, ancient gill (branchial) arches were co-opted to form the face and head in many species, which has implications for how and why features of the central nervous system are inextricably linked to features of the face and the head. Taken together in modern mammals, including humans, these interconnections permit social engagement and social communication, including sucking, swallowing, facial expressions and the production and receipt of airborne vocalizations (Porges 2001; 2007). Below we describe our work on the polyvagal theory, which uses insights from phylogeny to advance hypotheses about how positive social behaviors are connected to the regulation of autonomic states.

The Polyvagal Theory.

Overview

In essence, polyvagal theory reveals the intimate connection between social behavior and the autonomic nervous system (Porges, 2007). The mammalian nervous system cannot function without the support of visceral organs supplying oxygen and energy. The autonomic nervous system, via bidirectional pathways, regulates the viscera and conveys information upward to the hypothalamus, amygdala and neocortex. Sensory information from the viscera contributes to what humans experience as "emotion" or "emotional states." These emotional states, in turn, are components of the "motivational" systems that stimulate social engagement and allow sociality to be experienced as reinforcing. Often these emotional and motivational states involve other brain systems, including those that rely on dopamine and endogenous opioids (Numan, 2007).

Traditional views of the mammalian autonomic nervous system have divided the system into two neural circuits including a sympathetic response that involves mobilizing energy or arousal for task demands (e.g., the fight-or-flight stress response) and a parasympathetic response that directs energy for use in restorative physiological functions (e.g., promoting immune function, digestion, cellular repair, etc). Polyvagal theory challenges this view by suggesting that the mammalian autonomic nervous system actually retains three (and not two) neural circuits that are hierarchically organized (Porges, 1995, 1998, 2001, 2003, 2007). These three circuits include the sympathetic fight-
or-flight response, but subdivide parasympathetic activation into (a) a vagal circuit that coordinates activity in the face and head while also promoting the regulation of restorative autonomic states above the diaphragm and (b) an evolutionarily ancient vagal circuit that regulates autonomic states below the diaphragm and permits an immobilization response to cues that the organism is in mortal danger. These three neural circuits are expressed in a phylogenetically organized hierarchy (Table 1). In this hierarchy of adaptive responses, the newest circuit is the branch of the parasympathetic nervous system that coordinates activity in the face and head, permitting social communication. This newer circuit is used first in response to challenges to the organism. If the newest circuit fails to provide safety, older survival-oriented circuits are recruited sequentially, with the defensive fight-or-flight response preceding the use of an immobilization response. It is important to note that social behavior, social communication, and visceral homeostasis, as promoted by the newest circuit, are largely incompatible with neurophysiological states and behaviors that are regulated by circuits that support the defense strategies of both “flight and fight” and immobilization. Inhibition of systems that are in general defensive or protective is necessary to initiate social engagement, and to allow positive social behaviors. Conversely, positive social behaviors may be inhibited during prolonged periods of adversity. However, systems that support sociality, because they are intertwined with restorative physiological states, also may be protective against the costly or destructive effects of chronic fear or stress. Below we expand on the mechanics of these three distinct neural circuits, which are described in the polyvagal theory.

**The Vagus Nerve**

Of particular importance to mammalian social behavior, and to polyvagal theory is the parasympathetic component of the autonomic nervous system, especially the vagus (10th cranial) nerve, which consists of afferent (sensory) and efferent (motor) components. The afferent component transmits information concerning the status of visceral organs (e.g., heart, lungs, gut) to the brain. The efferent component consists of two branches that influence the activities of these organs. The unmyelinated vagus primarily regulates organs below the diaphragm (e.g., gut), while the myelinated vagus regulates organs located above the diaphragm (e.g., heart and lungs). However, both branches of the vagus influence the heart, although the pacemaker (i.e., sino-atrial node) is predominantly regulated by the myelinated vagus. The neural regulation of the pacemaker by the myelinated vagal circuit functions as a rapid neural mechanism to coordinate metabolic resources with the behavioral demands of a rapidly changing physical and social environment (Porges, 1996).

The unmyelinated component of the vagus, which permits slowing of the heart (bradycardia), originates in the dorsal motor nucleus of the vagus (also known as the dorsal vagal complex, DVC). The unmyelinated vagus is shared by mammals with other vertebrates (i.e., reptiles, amphibia, and fish). The phylogenetically more recent myelinated branch originates in the nucleus ambiguus (NA) of the ventral vagal complex (VVC), allowing rapid interaction between the brain and viscera. The myelinated vagus stabilizes cardiovascular function and is responsible for respiratory sinus arrhythmia (RSA), a rise and fall in heart rate is associated with phases of breathing: usually heart rate increases with inspiration and decreases with expiration. RSA, sometimes called *vagal tone* or *cardiac vagal tone*, is an index of the dynamic influence of the myelinated vagus on the heart. The term *vagal tone* might be misleading, since there may be vagal influences to the heart via the unmyelinated vagus that would not be reflected in RSA. When RSA is depressed, since it reflects reduced influences of “myelinated” vagus on the heart, heart rate quickly accelerates. Recovery of RSA reflects the re-establishment of influence of the “myelinated” vagus on the heart (see Porges, 1996) and reflects a physiological state that would promote social behavior. RSA, reflecting the dynamic influence of the myelinated vagus, is cardioprotective, and directly implicated in cortical
oxygenation. Measures of RSA (vagal tone) are predictive and probably permissive for health and longevity in humans. For example, RSA predicts mortality after a heart attack (Kleiger, et al., 1987).

Of particular importance to mammalian social behavior, the myelinated vagus is associated in the brainstem with cranial nerves that innervate the face and head. Thus, the myelinated vagal functions are coordinated with the neural regulation of the larynx and pharynx to coordinate sucking, swallowing, and breathing with vocalizations. The muscles of the human face, especially of the upper face involved in subtle emotional expressions, have projections from this system, which may be particularly important in social communication during face-to-face interactions.

**Neuroanatomical evolution and social cognition.**

The comparatively modern processes that supplied oxygen to the large primate cortex co-evolved with the emergence of higher levels of cognitive functions (Porges, 2001; 2007). The expanding mammalian cortex in general, and specific sensory and neuroanatomical changes in particular, set the stage for human cognition, speech, and more elaborate forms of caregiving beyond the maternal–infant interaction. For example, in contrast to their reptilian ancestors, mammals evolved auditory systems that enabled them to respond to airborne acoustic signals, an important requisite for increasingly complex modes of social interaction. And, phylogenetic transitions in brainstem areas that regulate the vagus intertwined with areas that regulate the striated muscles of the face and head. The result of this transition was the emergence of a capability for a dynamic social engagement system with social communication features [e.g., head movements, production of vocalizations, and a selective ability to hear conspecific (same species) vocal communication.] Concurrently and in support of these anatomical changes, the new mammalian myelinated vagus emerged. The myelinated vagus could inhibit the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, effectively making it possible to inhibit mobilization (fight—flight) responses. This inhibitory feature of the autonomic nervous system allowed animals to engage in high levels of social interaction, including nurturance of the young and an ability to engage other conspecifics in a prosocial manner without trigger defensive behaviors, while maintaining a calm physiological and behavioral state.

The phylogenetic transition from reptiles to mammals also resulted in a face-heart connection, in which the striated muscles of the face and head were regulated in the same brainstem areas that evoked the calming influence of the myelinated vagus. The striated muscles of the face and head are involved in social cueing (e.g., facial expressions, vocalizations, listening, head gesture, etc). These systems serve as “trigger” stimuli to the feature detectors in the nervous system that detect risk and safety in the environment (see neuroception below). The expanded mammalian cortex also demands high levels of oxygen. Oxygenation of the cortex in mammals is accomplished in part through the same adaptations of the autonomic nervous system that permit elaborate forms of reciprocal sociality. These systems, including terrestrial lungs and a four-chamber heart, that support the oxygenation of the neocortex, also are regulated in part by the myelinated branch of vagus nerve.

This synergism of neural mechanisms in mammals down regulated defensive systems and promoted proximity by providing social cues (e.g., intonation of vocalization, facial expressivity, posture and head gesture) that the organism was not in a physiological state that promoted aggressive and dangerous behaviors. Detection of these social cues allowed for symbiotic regulation of behavior, and the elaboration of reciprocal caregiving. These same systems provided setting conditions under which social behaviors could have a significant impact on cognition and health. In the human nervous system specific features of person-to-person interactions are innate triggers of adaptive biobehavioral systems, which in turn can support health and healing. In the absence of social interactions, or under conditions of social adversity, various forms of maladaptive behaviors and illness may be expressed.
Neuroception and the social management of threat and danger.

The integrated functions of the myelinated vagus permit the expression of positive emotions and social communication. However, the nervous system also is constantly assessing the environment as safe, dangerous, or life threatening. For example, components of the autonomic nervous system also regulate the muscles of the middle ear, permitting the extraction of human voice from background noises that may include the very high or very low frequency sounds that signal danger. Under conditions of threat or fear RSA is reduced, heart rate increases and social communication is compromised. Through a process of “neuroception” specific neural circuits are triggered that may support defensive strategies.

As we discussed above, defensive strategies may involve either active coping (i.e., “fight-or-flight” responses) or passive coping (i.e., “immobilization” responses). The fight/flight system allows mobilization and permits the organism to engage in active or instrumental behaviors that facilitate coping. This system is supported by the sympathoadrenal systems, including the release of catecholamines and glucocorticoids, which increase available energy. Under some conditions such as inescapable danger or other forms of extreme stress, mobilization strategies may be inhibited. These defensive strategies are characterized by passive coping, including immobility. Under more severe conditions many systems may be shut down, including those dependent on the neocortex. In these circumstances animals may show death-feigning or "helplessness" behaviors.

The unmyelinated vagus tends to slow the heart, consistent with a reptilian adaptive strategy of freezing and conserving energy in the face of danger. However, mammals, with their large cortex, cannot maintain clear cognition and consciousness without relatively high concentrations of oxygen. Thus, prolonged decelerations of the heart can lead to unconsciousness and eventually death. Mechanisms exist for protecting the heart and brain from “shutting down” at several levels within the body. As described below, among these are the neural effects of peptide hormones.

Neurochemistry and the social nervous system.

Neuropeptides regulate sociality, emotion and the autonomic nervous system. Social behaviors are supported and coordinated by both endocrine and autonomic processes. The complex networks of biochemical systems necessary for reproduction and homeostasis also are implicated in social behavior (Carter, et al., 2008). Given the energetic demands of social interactions, it is not surprising that the same neurotransmitters that are involved in social behavior also regulate the autonomic nervous system. Two mammalian hormones/neuromodulators - oxytocin (OT) and arginine vasopressin (AVP) - have been shown to be of particular importance to mammalian birth, lactation and maternal behavior, as well as sociality. There is increasing evidence that the functions of these same molecules, and especially OT, are central to the causes and consequences of positive social behaviors, including sensitivity to social cues in others, and constructs such as trust, and caregiving (Heinrichs, et al., 2008).

OT and AVP are small neuropeptides that differ from each other in only two of nine amino acids (Landgraf and Neumann, 2004). OT is produced primarily in hypothalamic nuclei, including the supraoptic (SON) and paraventricular nuclei (PVN). AVP is synthesized in the PVN and SON as well as other brain regions implicated in the regulation of emotional behaviors, as well as circadian rhythms. In addition, and especially in males, AVP also is abundant in the amygdala, bed nucleus of the stria terminalis and lateral septum, brain regions of particular importance to social and emotional regulation and self-defense (DeVries and Panzica, 2006).
OT and AVP are transported from the hypothalamus (SON and PVN) to the mammalian posterior pituitary where they are released into the blood stream, acting as hormones on peripheral target tissues, such as the uterus or mammary tissue. Within the brain, these same chemicals also serve as neuromodulators, affecting a broad range of neural processes (Landgraf and Neumann, 2004). Both OT and AVP are capable of moving throughout the central nervous system, probably by passive diffusion.

Receptors for these molecules (OTR and AVPV1aR) are found in various brain areas implicated in social behavior (Gimpl and Fahrenholz, 2001). In contrast to most biologically active compounds, OT appears to have only one form of receptor. AVP has at least three distinct receptors subtypes with separable functions. However, the OT peptide also may affect the AVP receptors and vice versa.

The neuroanatomy of the OT system allows a coordinated effect on behavior, autonomic functions and peripheral tissues. In some, but not all cases, AVP and OT have opposite functions, possibly because they are capable of acting as antagonists to each other’s receptors, while in other cases these peptides have similar effects. Dynamic interactions between OT and AVP may in turn regulate physiology and behavior, allowing shifts between positive social behaviors and defensive states (Viviani and Stoop, 2008).

Evolution of oxytocin and vasopressin.

It is likely that the essential elements upon which sociality are based arose from physiological processes fundamental to the need to conserve water and minerals. Among these are adaptations allowing the transition from aquatic to terrestrial life, including internal fertilization and eventually pregnancy and placental reproduction. Although AVP is also known as the “anti-diuretic hormone,” both OT and AVP influence kidney function in adults, in general conserving water and minerals. The capacity to maintain or reabsorb water was a critical element in the evolution of terrestrial mammals. The capacity for internal fertilization and the development of the placenta and lactation required a well-developed water regulation system. This shift also provided a protective environment for offspring before and after birth, and the emergence of contemporary versions of the neocortex and cognition.

Genes for the synthesis of OT and AVP are very ancient, estimated to be over 700 million years old (Donaldson and Young, 2008). These genes existed before the split between vertebrates and invertebrates. The original molecular structure, from which the peptides evolved, believed to be vasotocin, differs from OT and AVP by only one amino acid. Vasotocin is found in mammalian fetuses, although its expression is reduced at the time of birth.

The specific coding sequences that define OT and AVP may have emerged more than once, but in their current form probably evolved around the time that mammals first emerged. OT, through its functions in birth and lactation, assists in maternal nurturing of a comparatively immature infant (Numan, 2007; Brunton and Russell, 2008). The capacity of OT to induce uterine contractions, may have allowed the expansion of the human skull and cortex, and eventually cognition. These changes in turn allowed the elaboration of human speech and other forms of social communication that rely on cognitive function.

Neuropeptides influence autonomic functions through effects on the brainstem.

The PVN of the hypothalamus (including cells that synthesize OT and AVP) is an important site of convergence for neural communication coordinating endocrine and cardiovascular responses to
various forms of challenge (Michelini, et al, 2003). At the level of the PVN, OT may influence both the HPA axis and autonomic functions. The presence of oxytocin receptors (OTR) in the brainstem region known as the dorsal vagal complex (DVC containing the DMX) has been verified by autoradiography in rodents (Gimpl and Fahrenholz, 2001). The amygdala with connections to cortex, as well as hypothalamus and lower brainstem, integrates cognitive and emotional responses. The amygdala also contains OT and AVP as well as their receptors, and projections to and from the central nucleus of the amygdala may be critical determinants of emotional reactivity (Viviani and Stoop, 2008). Thus, the central nucleus of the amygdala is one site (among several) where shifts from positive to negative emotions may be managed. According to this model, oxytocin working within the amygdala may down regulate reactivity, while AVP acting in the extended amygdala and lateral septum (and especially in males) might upregulate emotional reactivity, vigilance and defensiveness. These processes explain in part the capacity of OT to down-regulate activity in the amygdala (measured by fMRI), especially under conditions of fear or emotional dysregulation (Meyer-Lindenberg, 2008). AVP plays a complex role in behavior through effects on blood pressure and heart rate, as well as the sympathoadrenal axis and parasympathetic functions. Both the AVP peptide and AVP V1a receptor (V1aR) have been identified in the central nucleus of the amygdala, and implicated in the regulation of brainstem areas including the myelinated vagus, with source nuclei in the brainstem region known as the ventral vagal complex (VVC), where OT-containing processes have been observed and which is necessary for RSA.

Receptors for both OT and AVP are found in pathways regulating the myelinated vagus. However, OTRs are particularly abundant in the dorsal brainstem region (DVC), which regulates the unmyelinated vagus. As described above, the unmyelinated vagus can slow the heart and regulates bradycardia. Under normal conditions the myelinated vagal system (including RSA) restrains the unmyelinated vagus, protecting this system from stopping the heart (Porges, 2007). Under extremely stressful conditions, such as birth, OT may act (on neural targets including the DVC) to protect the autonomic nervous system from reverting to this more primitive vagal system, which could lead to “shutting down,” and reduced emotional, social and cognitive function. Evolutionary changes in functions of neuropeptides, including OT and AVP, allowed the mammalian birth process (Brunton and Russell, 2008), and, in turn, the coordination of mammalian cognition and social behaviors.

Neuropeptides and the management of stressful experiences.

The hypothalamus, and especially the PVN, is important site of convergence for neural communication relating stress, affective disorders, and cardiovascular regulation to social behavior. Thus, it is not surprising that OT influences the HPA axis and autonomic function (Carter, 1998; Viviani and Stoop, 2008). This peptide plays a central role in autonomic tone, as OT-deficient mice show disruptions in sympathovagal balance and an impair ability to manage stress (Michelini, et al., 2003). With regard to endocrine function, OT generally suppresses the activity of the HPA axis (Neumann, 2008).

Oxytocinergic projections from the PVN to key brainstem regions are important in cardiovascular control. The presence of OT binding sites in the DVC has been verified via autoradiography in several species (Gimpl and Fahrenholz, 2001), and OT increases the excitability of vagal neurons. In addition, OT receptors in the brainstem have been shown to modulate baroreflex control of heart rate by facilitating the bradycardic response to pressor challenges. Thus, under optimal conditions systems that rely on OT may modulate and constrain overarousal, which would allow optimal management of challenges, and also be permissive for social engagement and caregiving (Porges, 2007).
Peripheral OT administration is able to reduce heart rate and blood pressure (Michelini, et al., 2003). The protective effects of OT or its absence may be most readily observed in the face of adversity or a stressful environment. For example, in socially monogamous prairie voles (Carter, et al., 1995) exogenous OT ameliorated isolation-induced changes in behavior and heart rate (Grippo, et al., 2009). Prairie voles isolated from their social partner for a period of weeks displayed elevated heart rate before, during and after a social stressor. This effect was blocked by peripheral injections of OT, despite the fact that OT levels are in some cases already heightened during isolation. This suggests that while endogenous increases in OT are not sufficient to ameliorate isolation-induced changes in autonomic function, additional supplementation with exogenous OT may have measurable effects. It is important to note that additional supplementation of OT did not lower heart rate in paired animals. Thus, at least some of the beneficial actions of OT may only become apparent under conditions of adversity.

Centrally released OT can counter the defensive behavioral strategies associated with stressful experiences. OT also may inhibit the central effects of AVP and other adaptive peptides, such as corticotropin-releasing factor (CRF), which plays a major role in the HPA axis (Neumann, 2008). Generally, but not always, the effects of endogenous OT are neuroprotective. We have found, in studies done in prairie voles, that intense stressors (such as restraint and exposure to a social intruder) can release OT and AVP. Milder stressors, such as handling, increase blood levels of AVP, but not usually OT. Experiences such exposure to an infant also may transiently release OT, especially in reproductively naive males. Infant exposure concurrently blocks stress induced increases in adrenal steroids, and has the capacity to facilitate subsequent pair bond formation (Carter, et al., 2008). These and many other examples support the general hypothesis that OT plays a critical role in the management of stressful experiences, while also facilitating social behavior.

Animal research suggests that OT affects the immune system, acting during development to “educate” the thymus. OT can also be a powerful anti-inflammatory agent, with the capacity to reduce inflammatory processes both in vivo and in vitro. For example, OT can restore tissue following exposure to burns, protect against sepsis, and reduce the response to pathogens. At comparatively high levels endogenous OT may promote wound healing, even in humans (Gouin, et al., 2010). These functions of OT could provide another set of mechanisms through which caregiving, under conditions that allow the release of OT, might protect and heal both those who give and receive nurture.

**Putting the Pieces Together: The Social Engagement System.**

As discussed above, pathways from the five cranial nerves that control the muscles of the face and head are critical to human social behavior. Collectively, these motor pathways are labeled as special visceral efferents. The special visceral efferent pathways regulate the muscles of mastication (e.g., ingestion), muscles of the middle ear (e.g., listening to vocalizations), muscles of the face (e.g., emotional expression), muscles of larynx and pharynx (e.g., vocal prosody and intonation), and muscles controlling head tilt and turning (e.g., gesture) (Figure 1). The source nuclei of the circuits regulating the striated muscles of the face and head interact in the brainstem with the source nucleus of the myelinated vagus; together these form an integrated social engagement system. This system, in interaction with neurohormonal mechanisms, provides the neural structures and substrates involved in social and emotional behaviors, and ties these systems to the rest of the body and thus to health.

**Mammalian social communication and the evolution of social cognition.**
Positive forms of communication, usually including speech and other vocalizations, are typically components of successful caregiving. Vocalizations also convey information regarding physiological state. For example, infant cries are indicators of health state and also can elicit caregiving. The coordinated regulation of social communication and visceral systems helps to explain the relationship between positive social experiences and health.

Shared neural pathways underlie social communication and visceral functions, such as the regulation of the cardiovascular, digestive and immune systems. Both heart rate and the acoustic features of vocalizations are parallel outputs of the integrated social engagement system. For example, through the myelinated vagus the brainstem regulates vocal communication (i.e., pathways controlling breath and laryngeal and pharyngeal muscles), as well as heart rate (Porges, 2007).

Thus, features of acoustic vocalizations can reflect vagal regulation of the heart. For example, vocal prosody is a positive feature of vocalizations and may be synchronized with RSA and other rhythmic features of autonomic function. The origins of these coordinated functions are most readily appreciated in the context of the evolution of neuroanatomical mechanisms for social engagement and social communication.

Vocal prosody (acoustic variation perceived as melodic vocal intonations) and heart rate variability (i.e., RSA) are parallel and modulated outputs of the social engagement system (Porges and Lewis, 2009). A depressed social engagement system is characterized by low variability in both heart rate (i.e., low amplitude RSA through the myelinated vagus) and vocal intonations (i.e., lack of prosody). Human voices that lack prosody fail to attract or interest others and are perceived as reflecting an emotionally detached or boring individual. In contrast, an optimally functioning social engagement system will have features of high heart rate variability (i.e., high amplitude RSA) and greater modulation of vocal intonation (i.e., high prosody). Lack of prosody is a risk factor similar to lack of heart rate variability and both may be used as indications of health risk.

Collectively, the muscles of the face and head function as filters that limit social stimuli (e.g., observing facial features and listening to vocalizations) and determinants of engagement with the social environment (Porges, 2003). The neural control of these muscles determines social experiences by changing facial features (especially in humans and other primates), modulating laryngeal and pharyngeal muscles to regulate intonation of vocalizations (prosody), and coordinating both facial and vocal motor tone with respiratory actions. In addition, the frequency of breathing is encoded into the phrasing of vocalizations, which – independent of the content of speech - may express meaning. For example, urgency may be conveyed by short phrases associated with short exhalations (i.e., rapid breathing) while calmness would be conveyed by long phrases associated with long exhalations (i.e., slow breathing) (Porges and Lewis, 2009).

Sex differences in the social engagement system

Sex differences in either the capacity to nurture or be nurtured are frequently observed, and often debated. Women are more likely to give direct nurture, sometimes through their role as a spouse or parent, or in a professional capacity, such as nursing. In men (including in animals) nurturance may be expressed through less direct "caregiving" behaviors, such as defense or protection of the family or resources.

Culture and experience play an important role in the development, expression and maintenance of sex differences. However, it is also likely that male and female differences in the capacity to nurture are based in part on biology, which may in turn influence sexually dimorphic behavioral traits and states (Carter, et al., 2009).
Gonadal steroid hormones and their receptors can affect sex differences, especially in early development. In addition, sex differences in endogenous neuropeptides, such as OT and AVP, or their receptors could influence sexually dimorphic social behaviors. For example, differential exposure to estrogen, across the lifespan, might be expected to enhance the availability of OT. Increased OT in turn might allow individuals to express higher levels of sociality. However, remarkably little research has actually addressed these questions and, at least in blood, often OT does not differ between males and females. In addition, both the effects of estrogen and OT are "context-dependent" (Grippo, et al., 2009). Thus, other systems including the hormones of the HPA and gonadal axes, and autonomic states associated with activation or mobilization may influence the consequences of OT, whether of endogenous or exogenous origins.

AVP levels in blood also do not reliably differ between the sexes. However, a male bias does exist in central AVP, especially in a neural axis that includes the amygdala, bed nucleus of the stria terminalis and lateral septum (De Vries and Panciza, 2006). This system is important for determining reactions to negative and positive stimuli, and may help to explain disorders including autism, which are highly sexually dimorphic and also characterized by differences in social behavior and emotional reactions to stressful experiences. For example, males may be more inclined to show high levels of vigilance or territorial defensiveness, and dysregulation of this system might create vulnerabilities associated with male-biased disorders such as autism (Carter, 2007). As described above, the effects of AVP also can be dynamically influenced by OT and vice versa (Viviani and Stoop, 2008).

Social experiences are likely to be major factors regulating both the synthesis of OT and AVP and their receptors (Carter, et al., 2009). Thus, the social history of an individual may be translated into an ontogenetic recalibration of neuropeptidergic functions, with potential consequences for both physiology and behavior. Developmental exposure to exogenous OT or AVP also can have life long consequences. In many cases males and females show differential responses to exogenous peptides, also with the potential to modify behavioral patterns across the lifespan. It seems likely that epigenetic changes in peptides and their receptors are one of the mechanisms through which social experiences are converted into long-lasting individual differences. Social behaviors, including alloparenting, are especially sensitive to social and hormonal experiences in early life. Thus, the fundamental components of caregiving may have evolved with the capacity to be modified by early experiences, gender, and also by hormones, such as OT and AVP, which are capable of regulating sociality and emotional reactivity in later life.

Based upon our current understanding of the properties of these biological systems, it is likely that differential hormonal states can influence behavioral responses, with effects on behavioral or emotional states associated with a perception of safety or threat. These systems, including hormonal and autonomic pathways, also may be “tuned” by early experiences, such as a history of good parenting or alternatively neglect or abuse (Teicher, et al., 2003). For example, positive early experiences could facilitate access to the social engagement system, a more “cognitive” approach to problems, and concurrently allow some individuals to be particularly resilient in the face of challenge. Alternatively, a history of abuse or neglect might create a vulnerability to either emotional hyper-reactivity or even “shut-down” in the face of threat.

Clinical implications of the social engagement system.

Contemporary medicine, especially over the last century, has focused on mechanisms of disease. Medical advances have been largely technical. The natural mechanisms underlying health and healing remain remarkably poorly understood. Our work advances a new perspective for medicine by suggesting that “person-to-person” interactions that trigger neural circuits promoting calm
physiological states can contribute to health, healing, and growth processes (Harris, 2009). Threatening interactions, on the other hand, trigger defensive strategies associated with physiological states supporting mobilization (e.g., flight-flight behaviors) or immobilization (e.g., behavioral shutdown, syncope, death feigning). As described above, the nervous system is constantly assessing the environment as being safe, dangerous, or life threatening. Through this process of neuroception, neural circuits are triggered that will either support health and healing or support defensive strategies of fight-flight or shutdown. Neuroception involves brain structures, including the amygdala, that can be modulated by neuropeptides including OT and AVP. Under optimal conditions, person-to-person interactions can be innate triggers within the human nervous system for adaptive biobehavioral systems that support health and healing. Both the giving of and receiving of caregiving or love has the capacity to protect, heal and restore. The mechanisms underlying these processes are only now becoming apparent.

In the context of caregiving, the quality of the “person-to-person” interactions between a caregiver and those being cared for is critical. Often this involves contingent and “appropriate” gesture, facial expression, prosody, proximity, and touch. In addition to specific clinical treatments, social support and social engagement behaviors by friends and relatives may also be capable of reversing illness and maintaining health. It is likely that OT is important to the positive consequences of social support, possibly through effects on the autonomic nervous system and immune system. For example, it has been shown in humans that immune responses to an endobacterial challenge (LPS, lipopolysaccharide) can be significantly blocked by concurrent treatment with OT (Clodi, et al., 2008).

Summary

As a species, humans are highly social mammals, dependent on others for survival and reproduction. Under optimal conditions this dependency is both symbiotic and reciprocal. The evolved neural, autonomic and endocrine underpinnings of sociality are shared with other species, permitting a cross-species analysis of the processes responsible for sociality. Awareness of the neurobiology of social engagement offers insights into human concepts, such as social support and caregiving, which in turn can be associated with good health and recovery from illness. These systems are integrated throughout the body, including at the level of the brainstem, where hormones, such as OT and AVP influence behavior, the autonomic nervous system, and the immune system. Projections to and from these ancient systems are experienced by more modern brain structures, including the cortex, as diffuse and sometimes powerful feelings or emotions. The same neuroendocrine and autonomic systems that permit high levels of social behavior and social bonds regulate the management of stressful experiences and the capacity of the mammalian body to heal itself. However, the activities of brainstem and autonomic systems are context-dependent. In a context of safety or comparatively mild or acute stressors, the release of OT and the involvement of the myelinated vagus may down regulate defensive systems and promote reciprocal social interactions with the consequence of enhanced opportunities for symbiotic regulation to support health and restorative processes. In the context of chronic stress or fear, the actions of these same adaptive systems might have consequences that interfere both the establishment of social behavior and the body’s ability to heal and restore. We believe that knowledge of the evolutionary origins and neurobiology of sociality provides a contextual perspective for understanding both the causes and consequences of mammalian caregiving behaviors.
<table>
<thead>
<tr>
<th>Autonomic Nervous System Components</th>
<th>Origin of Motor Neurons</th>
<th>Behavioral Functions</th>
<th>Autonomic Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myelinated vagus</strong> (<em>VVC – ventral vagal complex)</em></td>
<td><strong>Nucleus ambiguus</strong> (NA)</td>
<td><strong>Social engagement and caregiving.</strong> Expressed as a coordinated face-heart connection and observed as enhanced regulation of the striated muscles of the face and head and increased calming of the viscera including an active dampening of sympathetic-adrenal functions and reducing fear. The enhanced regulation of facial muscles result in greater prosody, improved listening, and greater emotional expressivity.</td>
<td><strong>Neuroprotection.</strong> Stabilization of autonomic processes, including producing cardiac respiratory sinus arrhythmia (RSA), which protects the heart and enhances oxygenation of the brain. These functions of the autonomic nervous system, by regulating state and calming the individual, permit sociality and provide resources necessary for symbiotic and reciprocal social interactions.</td>
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<td><strong>Sympathetic-adrenal system</strong> (<em>SNS – sympathetic nervous system)</em></td>
<td><strong>Spinal cord</strong></td>
<td><strong>Mobilization.</strong> Active adaptations including flight/fight responses.</td>
<td><strong>Activation.</strong> Increased heart rate, release of glucocorticoids and catecholamines. Production of energy, including glucose, and conversion of norepinephrine to epinephrine.</td>
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<tr>
<td><strong>Unmyelinated vagus</strong> (<em>DVC – dorsal vagal complex)</em></td>
<td><strong>Dorsal nucleus of the vagus</strong> (DMX)</td>
<td><strong>Immobilization.</strong> Passive adaptations including death feigning and loss of consciousness.</td>
<td><strong>Conservation.</strong> Prevalence of bradycardia (slowing the heart) and apnea (cessation of breathing). Reduced energy production.</td>
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Figure 1. Efferent Pathways of the Mammalian Social Engagement System.
Figure 2. The polyvagal theory: Hierarchical organization of neuroendocrine and autonomic processes implicated in social behavior and the adaptive management of stressful experiences. Neuropeptides, including OT, AVP, CRF and endogenous opioids, as well as neurotransmitters such as 5-HT and NE influence behavior and emotions through direct actions on the brain, as well as indirect effects on different components of the autonomic nervous system and the HPA axis. OT, 5-HT, and endogenous opioids, acting in the brainstem, may be protective during or against shutdown and immobilization.
Selected readings:


Biosketch:  C. Sue Carter, PhD

Sue Carter is currently Professor of Psychiatry and Co-Director of the Brain Body Center at the University of Illinois at Chicago. Her research program, which has focused on socially monogamous mammals, has described new roles for neuropeptide hormones, including oxytocin and vasopressin, in social bonding, aggression and emotional regulation. She also is interested in the developmental effects social experiences and these peptides, which may modulate long-lasting effects of early experience and also social deprivation on the brain and behavior. She is past president of the International Behavioral Neuroscience Society. Dr. Carter has authored over 250 publications, including editorship of 5 books, the most recent of which is *Attachment and Bonding; A New Synthesis* (MIT Press, 2006).

Abstract:

The purpose of this essay is an analysis of major features of the neurobiological and neuroendocrine mechanisms implicated in human caregiving. Anatomical and biochemical systems that first appeared in the evolutionary transition from reptiles to mammals allowed the emergence of mammalian sociality. Human behaviors are characterized by symbiotic and reciprocal interactions which are necessary for positive social interactions. The autonomic nervous system, and especially the parasympathetic system, provides an essential platform for social behaviors and emotional states. Especially critical to coordinating the features of positive sociality are neuropeptides including oxytocin and vasopressin. Social neuropeptides function in part by modulating the mammalian autonomic nervous system, allowing social engagement and social communication, but also when needed defensive behaviors. The same peptides that regulate various aspects of mammalian reproduction including birth, lactation and maternal behavior, also modulate other behaviors associated with mammalian caregiving.
Key words

arginine vasopressin
autonomic nervous system
brainstem
cardiovascular
cortisol or corticosterone
corticotropic releasing factor
demotion
dendocrinology
evolution
dorsal vagal complex.
hypothalamic-pituitary-adrenal axis
heart rate variability
hormones.
maternal behavior
monogamy
myelinated vagus
neuroanatomy
neurobiology
neuroception
nucleus ambiguus
norepinephrine
oxytocin
polyvagal theory
post traumatic stress disorder.
paraventricular nucleus of the hypothalamus
reciprocity
respiratory sinus arrhythmia
sex differences
social attachment
social behavior
social bonding
social cognition
social communication
social engagement system
social monogamy
steroids
stress
symbiosis
unmyelinated vagus
ventral vagal complex