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The Vagus: A Mediator of Behavioral and Physiologic Features Associated with Autism

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The vagus nerve, as a system, provides a rich organizing principle to investigate several of the behavioral, psychological, and physiologic features associated with a diagnosis of autism. The vagus is not only a cranial nerve meandering through the periphery, but also an important bidirectional conduit carrying specialized motor and sensory signals that are part of a larger integrated feedback system that includes brain structures involved in the regulation of visceral state and affect. The premise of this chapter is that several features of autism become more understandable if a more integrated model of the nervous system is applied in which the vagus is a critical component.

The Vagus and Affect Regulation

The relation between affect and vagal afferent activity is not a recent idea. Darwin (1872) noted in *The Expression of Emotions in Man and Animals* the importance of the bidirectional neural communication between the heart and the brain via the "pneumogastric" nerve, now known as the vagus nerve.

For Darwin, emotional state represented a covariation between facial expression and autonomic tone. However, he did not elucidate the specific neurophysiologic mechanisms. Our current knowledge of the neuroanatomy, embryology, and phylogeny of the nervous system was not available to Darwin. In Darwin's time, it was not known that vagal fibers originated in several medullary nuclei, that branches of the vagus exerted control over the periphery through different feedback systems, that sensory information conveyed through the vagus regulated structures in the brain, and that the function of the branches of the vagus followed a phylogenetic principle.

Current research emphasizes the importance of the vagal afferents in the regulation of visceral state, mood, and affect. Studies have demonstrated that stim-

ulation of vagal afferents regulate brain structures involved in epilepsy (Boon et al., 2001), depression (George et al., 2000), and even repetitive self-destructive behaviors often associated with autism (Murphy et al., 2000).

Polyvagal Theory: Three Neural Circuits Regulating Reactivity

Evolutionary forces have molded both human physiology and behavior. Via evolutionary processes, the mammalian nervous system has emerged with specific neural and behavioral features that react to challenge in order to maintain visceral homeostasis. These reactions change physiologic state and, in mammals, limit sensory awareness, motor behaviors, and cognitive activity. To survive, mammals must determine friend from foe, evaluate whether the environment is safe, and communicate with their social unit. These survival-related behaviors are associated with specific neurobehavioral states that limit the extent to which a mammal can be physically approached and whether the mammal can communicate or establish new coalitions. Thus, environmental context can influence neurobehavioral state, and neurobehavioral state can limit a mammal's ability to deal with the environmental challenge.

Through stages of phylogeny, mammals, and especially primates, have evolved a functional neural organization that regulates visceral state to support social behavior. The polyvagal theory (Porges, 1995, 1997, 1998, 2001) emphasizes the phylogenetic origins of brain structures that regulate social and defensive behaviors, domains compromised in individuals with autism. The polyvagal theory proposes that the evolution of the mammalian autonomic nervous system provides the neurophysiologic substrates for the emotional experiences and affective processes that are major components of social behavior. The theory proposes that physiologic state limits the range of behavior and psychological experience. In this context, the evolution of the nervous system determines the range of emotional expression, quality of communication, and the ability to regulate bodily and behavioral state. The polyvagal theory links the evolution of the autonomic nervous system to affective experience, emotional expression, facial gestures, vocal communication, and contingent social behavior. Thus, the theory provides a plausible explanation of several social, emotional, and communication behaviors and disorders associated with autism.

The polyvagal construct was introduced to emphasize and document the neurophysiologic and neuroanatomical distinction between two branches of the vagus and to propose that each vagal branch is associated with a different adaptive behavioral strategy. The theory proposes that the different branches are related to unique, adaptive behavioral strategies and articulates three phylogenetic stages of the development of the mammalian autonomic nervous sys-

tem. These stages reflect the emergence of three distinct subsystems, which are phylogenetically ordered and behaviorally linked to social communication (e.g., facial expression, vocalization, listening), mobilization (e.g., fight-flight behaviors), and immobilization (e.g., feigning death, vasovagal syncope, and behavioral shutdown). The mobilization system is dependent on the functioning of the sympathetic nervous system. The most phylogenetically primitive component, the immobilization system, is dependent on the unmyelinated or "vegetative" vagus, which is shared with most vertebrates. With increased neural complexity due to phylogenetic development, the organism's behavioral and affective repertoire is enriched (see Table 6.1).

The theory emphasizes the functional aspect of neural control of both the striated muscles of the face and the smooth muscles of the viscera, because their functions rely on common brainstem structures. It does not make any assumptions regarding structural damage to either the vagal systems or the brain structures that regulate brainstem structures associated with the vagal systems. Thus, although the compromised brainstem features described by Rodier and colleagues (1996) are consistent with the predictions of the polyvagal theory, the theory emphasizes functional deficits and does not necessarily assume structural damage.

By investigating the phylogeny of the regulation of the vertebrate heart (Morris and Nilsson, 1994), three principles can be extracted. First, there is a phylogenetic shift in the regulation of the heart from endocrine communication, to unmyelinated nerves, and finally to myelinated nerves. Second, there is

TABLE 6.1. The Three Phylogenetic Stages of the Neural Control of the Heart Proposed by the Polyvagal Theory

Phylogenetic Stage	*ANS Component*	*Behavioral Function*	*Lower Motor Neurons*
III	Myelinated vagus	Social communication, self-soothing and calming, inhibit sympathetic-adrenal influences	Nucleus ambiguus
II	Sympathetic-adrenal	Mobilization (active avoidance)	Spinal cord
I	Unmyelinated vagus	Immobilization (death feigning, passive avoidance)	Dorsal motor nucleus of the vagus

a development of opposing neural mechanisms of excitation and inhibition to provide rapid regulation of graded metabolic output. Third, with increased cortical development, the cortex exhibits greater control over the brainstem via direct (e.g., corticobulbar) and indirect (e.g., corticoreticular) neural pathways originating in motor cortex and terminating in the source nuclei of the myelinated motor nerves emerging from the brainstem (e.g., specific neural pathways embedded within cranial nerves V, VII, IX, X, and XI), controlling visceromotor structures (i.e., heart, bronchi, thymus) and somatomotor structures (muscles of the face and head).

These phylogenetic principles provide a basis for speculations regarding the behavioral and physiologic responses associated with autism. With this new vagal system, transitory incursions into the environment or withdrawals from a potential predator can be initiated without the severe biologic cost associated with sympathetic-adrenal activation. Paralleling this change in neural control of the heart is an enhanced neural control of the face, larynx, and pharynx that enables complex facial gestures and vocalizations associated with social communication. This phylogenetic course results in greater central nervous system regulation of physiologic state that supports behaviors needed to engage and disengage with environmental challenges.

The Vagal Brake

Due to the tonic vagal influences to the sinoatrial node (i.e., the heart's pacemaker), resting heart rate is substantially lower than the intrinsic rate of the pacemaker. When the vagal tone to the pacemaker is high, the vagus acts as a brake on the rate at which the heart is beating (Porges et al., 1996). When vagal tone to the pacemaker is low, there is little or no inhibition of the pacemaker. Thus, neurophysiologically, the vagal brake provides a mechanism to rapidly switch between physiologic states that either support social communication or mobilization. Functionally, the vagal brake, by modulating visceral state, enables the individual to rapidly engage and disengage with objects and other individuals and to promote self-soothing behaviors and calm behavioral states. These behaviors are obviously compromised in autism. Is it possible that autism is associated with a deficit in the vagal brake and an inability to switch between neurobiologic states that foster either defensive or social behaviors?

The Social Engagement System

The polyvagal theory provides an explicit neurobiologic model of how difficulties in spontaneous social behavior are linked to both facial expressivity and the

regulation of visceral state. The theory proposes a possible mechanism to explain how these difficulties might form a core domain of several psychiatric profiles. Relevant to autism are the specific deficits in both the somatomotor (e.g., poor gaze, low facial affect, lack of prosody, difficulties in mastication) and visceromotor (e.g., difficulties in autonomic regulation resulting in cardiopulmonary and digestive problems) areas of the social engagement system. Deficits in the social engagement system compromise spontaneous social behavior, social awareness, affect expressivity, prosody, and language development. In contrast, interventions that improve the neural regulation of the social engagement system, hypothetically should enhance spontaneous social behavior and state and affect regulation, reduce stereotypical behaviors, and improve language skills.

During the development of the human embryo, components of several cranial nerves, known as special visceral efferent pathways, develop together to form the neural substrate of a social engagement system (see Porges, 1998). This system, as illustrated in Figure 6.1, provides the neural structures involved in social and emotional behaviors. The social engagement system has a control component in the cortex (i.e., upper motor neurons) that regulates brainstem nuclei (i.e., lower motor neurons) to control eyelid opening (e.g., looking), facial muscles (e.g., emotional expression), middle ear muscles (e.g., extracting the human voice from background noise), muscles of mastication (e.g., ingestion), laryngeal and pharyngeal muscles (e.g., vocalization and language), and head turning muscles (e.g., social gesture, orientation). Collectively, these muscles function as filters that limit social stimuli (e.g., observing facial features, listening to the human voice) and determinants of engagement with the social environment. The neural control of these muscles determines social experiences. In addition, the source nuclei (i.e., lower motor neurons) of these nerves, which are located in the brainstem, communicate directly with an inhibitory neural system that slows heart rate, lowers blood pressure, and actively reduces arousal to promote calm states consistent with the metabolic demands of growth and restoration of human neurophysiologic systems.

Direct corticobulbar pathways reflect the influence of frontal areas of the cortex (i.e., upper motor neurons) on the regulation of this system. Moreover, afferent feedback through the vagus to medullary areas (e.g., the nucleus of the solitary tract, which is the source nucleus of the afferent vagus) influences forebrain areas that are assumed to be involved in several psychiatric disorders. In addition, the anatomical structures involved in the social engagement system have neurophysiologic interactions with the hypothalamic-pituitary-adrenal (HPA) axis, the neuropeptides of oxytocin and vasopressin, and the immune system (Porges, 2001). As a cluster, the difficulties with gaze, extraction of the human voice, facial expression, head gesture, prosody, and state regulation are

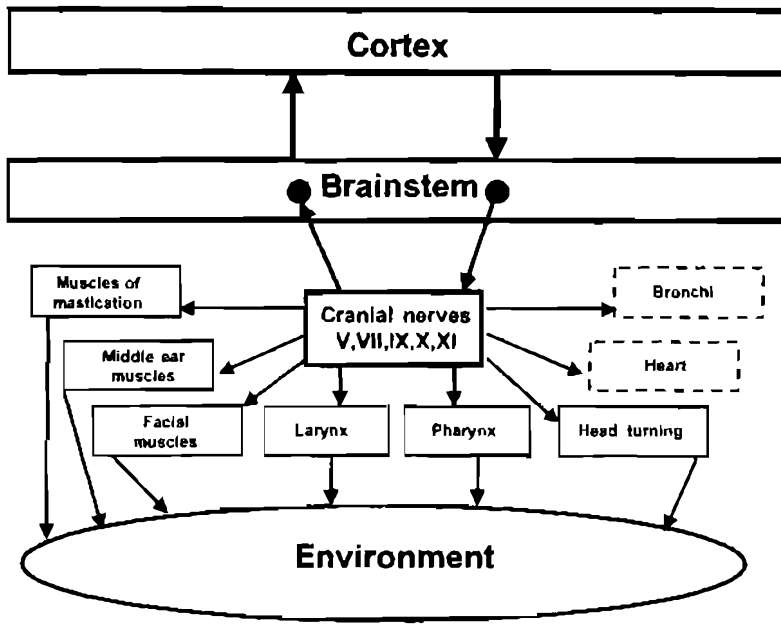

FIGURE 6.1. The social engagement system. Social communication is determined by the cortical regulation of medullary nuclei via corticobulbar pathways. The social engagement system consists of a somatomotor component (special visceral efferent pathways that regulate the muscles of the head and face) and a visceromotor component (the myelinated vagus that regulates the heart and bronchi). Solid blocks indicate the somatomotor component. Dashed blocks indicate the visceromotor component.

common features of individuals with autism. For example, the neural pathway that raises the eyelids also tenses the stapedius muscle in the middle ear, which facilitates hearing the human voice (Borg and Counter, 1989). Thus, the neural mechanisms for making eye contact are shared with those needed to listen to the human voice.

Studies have demonstrated that the neural regulation of middle ear muscles, a necessary mechanism to extract human voice from loud low frequency background noise, is defective in individuals with language delays, learning disabilities, and autistic spectrum disorders (Thomas et al., 1985; Smith et al., 1988). Middle ear infection (i.e., otitis media) may result in a total inability to elicit the "reflexive" contraction of the stapedius muscles (Yagi and Nakatani, 1987). Disorders that influence the neural function of the facial nerve (i.e., Bell's palsy) not only influence the stapedius reflex (Ardic et al., 1997) but also affect the patient's ability to discriminate speech (Wormald et al., 1995). Thus, the observed

difficulties that many autistic individuals have in extracting the human voice from background sounds may be dependent on the same neural system that is involved in facial expression.

Predictions Based on Polyvagal Theory

Observations of the behaviors and physiologic response of autistic individuals suggest that they have great difficulties in recruiting the neural circuit that regulates the social engagement system. It appears that autism is associated with autonomic states that remove the individual from direct social contact by supporting the adaptive defensive strategies of mobilization (i.e., fight-flight behaviors) or immobilization (i.e., shut-down). Behaviorally, the retraction of the neural regulation of the social engagement system is expressed as limited use and regulation of the muscles of the face and head. The functional consequences limit facial expressions and head gestures, compromise the ability to extract the human voice from background sounds, and reduce prosody.

Neurophysiologically, because the vagus is integrated into several feedback systems involving both peripheral and central structures, depression or dysregulation of the vagus might be manifested on several levels. First, it may compromise the regulation of visceral organs, such as the gut, heart, and pancreas. Second, because the vagus is involved in the modulation of pain and the regulation of cytokines and the HPA axis, there may be regulational disorders in those systems. Third, because the brainstem areas regulating the myelinated vagal system provide both output and input to feedback systems involving other brain structures, the vagal system may provide a portal to assess and stimulate higher neural processes. Although there is a limited scientific literature evaluating the role of vagus in autism, the plausibility of these predictions will be reviewed in this chapter and discussed against the current literature, which includes studies with other clinical populations and animal preparations.

Vagal Regulation of Heart Rate and Heart Rate Variability

Because vagal efferent pathways to the heart are cardioinhibitory, changes in vagal tone can influence the metrics used to monitor heart rate and heart rate variability. In general, greater cardiac vagal tone produces slower heart rate and regulates the transitory changes in heart rate in response to stimulation. The myelinated vagal efferents that synapse on the sinoatrial node have a respiratory rhythm. This rhythmic increase and decrease in cardioinhibitory activity through the vagus produces a cardiac rate rhythm known as respiratory sinus arrhythmia. The greater the cardioinhibitory influence through the vagus, the

greater the rhythmic increases and decreases in this heart rate pattern. Thus, the amplitude of respiratory sinus arrhythmia provides a sensitive index of the influence the myelinated vagus has on the heart. The rapid changes in heart rate in response to specific stimuli are primarily under vagal control. The characteristic heart rate pattern to stimulus changes—an immediate deceleration followed by either a continued deceleration or an acceleration—is primarily due to dynamic increases or decreases in cardioinhibitory activity through the myelinated vagus. The literature suggests that autism is associated with reliable differences in the amplitude of respiratory sinus arrhythmia and the transitory heart rate response pattern to various stimuli and task demands.

An early publication by Hutt et al. (1975) reported that normal children suppressed respiratory sinus arrhythmia more than autistic children did. Similarly, Althaus et al. (1999) found that children with a pervasive developmental disorder not otherwise specified (PDD-NOS) did not suppress respiratory sinus arrhythmia. Consistent with these findings, an early study of children diagnosed with schizophrenia (Piggott et al., 1973) identified significant differences in respiration and in the covariation between respiration and heart rate. The schizophrenic children had significantly faster and more shallow breathing patterns, a pattern consistent with reduced vagal efferent activity.

Other studies report that autistic children have dampened transitory heart rate responses to a variety of stimulation. Zahn, Rumsey, and Van Kammen (1987) reported unusually small deceleratory heart rate responses to auditory stimulation. Palkovitz and Wiesenfeld (1980) reported dampened heart rate responses to socially relevant speech, nonsense phrases, and a 500 Hz tone. Corona et al. (1998) reported that the heart rate of children with autism did not change across conditions.

Vagal Nerve Stimulation

Although not currently being used to treat autism, vagal nerve stimulation has been effective in treating epilepsy and depression. Vagal nerve stimulation is based on the assumption that stimulation of vagal afferents has a direct effect on the regulation of higher brain structures. The source nucleus of the vagal afferents is the nucleus of the solitary tract. This medullary nucleus plays an important role in the regulation of behavioral state, respiration, and blood pressure, and in conveying information to higher brain structures. The nucleus of the solitary tract relays the incoming sensory information via three primary pathways: (1) feedback to regulate the periphery, (2) direct projections to the reticular formation in the medulla, and (3) ascending projections to the forebrain, primarily through the parabrachial nucleus and the locus ceruleus. The parabrachial

nucleus and the locus ceruleus send direct connections to all levels of the forebrain (e.g., hypothalamus, amygdala, the thalamic regions that control the insula and orbitofrontal and prefrontal cortices), areas that have been implicated in neuropsychiatric disorders. Thus, vagal afferent stimulation has direct input to both the lower motor neurons in the brainstem and the upper motor neurons in the cortex that regulate the social engagement system. Recent reviews provide a detailed description of the neurophysiologic basis for the intervention (George et al., 2000) and provide an explanation of the neural mechanisms involved in treating depression with vagal nerve stimulation (Marangell et al., 2002). Missing from these explanations is an acknowledgment of the communication between vagal afferents and the source nuclei of the nerves that regulate striated muscles of the face and head (i.e., special visceral efferent pathways), which collectively form the motor part of the social engagement system. It is this interaction that is emphasized in the polyvagal theory (Porges, 2001).

Extrapolating from the vagal nerve stimulation model, one might speculate that other forms of vagal stimulation might have beneficial effects. Behaviorally, one of the most potent strategies for vagal stimulation is to stimulate the peripheral baroreceptors that regulate blood pressure. Rocking and swinging, in which the position of the head is changed relative to the position of the heart, will stimulate the baroreceptors and engage this feedback loop. This suggests that the frequently observed rocking and swinging behaviors in autistic individuals may reflect a naturally occurring biobehavioral strategy to stimulate and regulate a vagal system that is not efficiently functioning.

One publication reported that vagal nerve stimulation reduced autistic-like behaviors (Murphy et al., 2000). In this study, vagal stimulation was administered to six patients with hypothalamic hamartoma, a congenital brain malformation that is associated with medically refractory epilepsy and injurious autistic behavior. Four of the six patients had autistic behaviors that included poor communication, ritualisms, compulsions, no social skills, and injury to self and others. The authors report that during vagal nerve stimulation, all four showed impressive improvements in behavior. In one subject, the behavioral improvements were immediately reversed when the vagal nerve stimulation was temporarily discontinued without worsening of seizure frequency.

Vagal Regulation of the Gut

Due to the high prevalence of gastrointestinal symptoms in individuals with autism (Horvath and Perman, 2002; Wakefield et al., 2002), there has been an interest in a possible link between gut and brain as a determinant of autism. This interest was stimulated by reports from parents who indicated that the adminis-

tration of intravenous secretin reduced autistic symptoms. However, there has been no evidence for the efficacy of secretin when it was administered in a randomized, placebo-controlled, double-blind clinical trial (Owley et al., 2001).

Current research suggests that the prevalence of gastrointestinal symptoms represents an unsolved problem in autism. However, if we conceptualize the problem from a "vagal" perspective, we can identify the vagus as a primary regulator of the gut, with vagal afferents providing important information to brain structures. Support for this argument comes from animal studies in which it has been demonstrated that the vagus is involved in the regulation of secretin (Lu and Owyang, 1995; Li, Chang, and Chey, 1998). Thus, given the compromised behavioral components of the social engagement system, it is not surprising to find that the vagal regulation of gastrointestinal processes is also compromised in autistic individuals.

Additional information regarding the role that vagal afferents from the gut have in modulating sensory experiences comes from research on eating disorders. Research suggests that vagal afferents are involved not only in regulating satiety via vasovagal reflexes but also in regulating nociceptive sensations via solitary-spinal pathways. Faris et al. (2000) and Raymond et al. (1999a) have proposed that vagal afferent activation by binge-eating and vomiting also activates the descending pain inhibitory pathway resulting in an elevated pain threshold. Similarly they have reported elevated pain thresholds in anorexia nervosa subjects (Raymond et al., 1999b). Their research has led to administering ondansetron as an intervention for bulimia nervosa (Faris et al., 2000). Ondansetron is marketed for the prevention of vagally mediated emesis caused by cancer chemotherapeutic agents.

The Vagus and the Immune System

The subdiaphragmatic vagal afferents may be conceptualized as providing a targeted signal to the central structures that regulate immune function. Other researchers have linked the vagal efferent pathways to immune function. Bulloch and Pomerantz (1984) described motor pathways via the vagus to the thymus. The link between the vagal regulation of immune function and the polyvagal theory is not clear. However, it might be plausible to speculate that the neural mediation of the myelinated vagus may, via direct influence on thymus and direct inhibition of the sympathetic nervous system, trigger a physiologic state that would promote immune function. Likewise, mobilization strategies, resulting in a withdrawal of vagal tone to the heart, increased sympathetic tone, and the release of cortisol, have been associated with suppressed immune function. More relevant to the expression of psychiatric disturbances is the find-

ing that the afferent vagus mediates behavioral depression, but not fever, in response to peripheral immune signals following abdominal inflammation (Konsman et al., 2000). Consistent with this model, it has been reported that autism spectrum disorder patients with developmental regression express excessive innate immune responses (Jyonouchi, Sun, and Le, 2001).

Vagal Regulation of the HPA Axis

The vagus is involved in the regulation of the HPA axis. Vagal afferents exhibit an inhibitory influence on HPA axis and reduce cortisol secretion (e.g., Bueno et al., 1989; Miao et al., 1997). Studies (Cacioppo et al., 1995; Gunnar et al., 1995) have demonstrated a covariation between increases in cortisol and decreases in cardiac vagal tone (i.e., the amplitude of respiratory sinus arrhythmia). Thus, there appears to be a coordinated response that functions to promote metabolic activity and mobilization behaviors by withdrawing the vagal tone through the myelinated vagus and increasing both sympathetic activity and activation of the HPA axis.

Several studies have reported that the regulation of the HPA axis is dysfunctional in autistic children. Poorly developing autistic children were more likely to have an abnormal diurnal rhythm and an abnormal response on the dexamethasone suppression test than less severe cases (Hoshino et al., 1987). The results suggest that the negative feedback mechanism of the HPA axis may be disturbed in autistic children, especially in poorly developing individuals. Similarly, Jensen et al. (1985) reported that most of the autistic patients studied failed to suppress cortisol with the dexamethasone test. Consistent with these reports, Jansen et al. (2000) reported the PDD-NOS children had a diminished cortisol response to physical stress.

The Vagal System as an Organizing Principle

In this chapter, I have illustrated how the vagus is involved in the expression of several disparate symptoms associated with autism. Consistent with the polyvagal theory, the symptom clusters are associated with components of the vagal system. First, there are the behavioral characteristics linked to the neural regulation of the striated muscles of the face via special visceral efferent pathways (i.e., the somatomotor component of the social engagement system). Second, autism is associated with dysfunctional regulation of target organs (e.g., heart, gut) regulated by vagal efferent pathways (i.e., the visceromotor component of the social engagement system). Third, the vagal afferents exert a powerful regulatory influence on several systems—including visceral and tactile pain thresholds, the HPA

axis, and the immune system—that are dysfunctional in autism. Fourth, the nucleus of the solitary tract (the source nucleus of the afferent vagus) influences areas of the forebrain that have been speculated to be compromised in autism.

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