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A phylogenetic journey through the vague and ambiguous Xth cranial nerve: A commentary on contemporary heart rate variability research

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Abstract

Contemporary heart rate variability research is discussed within a historical context. Implicit in this history is the discovery that the central nervous system regulates the heart and how information regarding neural regulation of the heart is imbedded in the beat-to-beat heart rate pattern. As methodologies have become more sensitive to neural regulation and as theories have expanded to integrate behavior and psychological processes with neurobiological principles, researchers are becoming better positioned to successfully understand how neurovisceral processes mediate the expression of health and disease. The contributions to this special issue describe research representing different levels of scientific inquiry and focus on different features of the complex neural feedback system that are manifested in the robust relationships between heart rate variability and several behavioral, psychological, physiological, and health processes. This article provides a commentary to these contributions.

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[1]The representation of the phylogenetic trend in vertebrate neural regulation of the heart described in the Polyvagal Theory is distorted. Statements made by Grossman and Taylor are inconsistent with Taylor's previous publications that provide exquisite descriptions of the phylogenetic shifts in neural regulation of the vertebrate heart. The reader is directed to the following sections in the original source of the Polyvagal Theory (Porges, 1995): *Phylogenetic development of the polyvagal system* (p.306-308), *Vagal strategies in mammals and reptiles* (p. 308– 309), *and Phylogenetic origins of vagal response patterns* (p. 309).

[2]Grossman and Taylor state "the polyvagal theory was first proposed in 1995 … as an attempt to a) introduce an evolutionary perspective into relations between parasympathetic activity and behavior (possibly on the basis of a phylogenetic overview of vagal control of the heart in vertebrates reviewed by Taylor, 1994, as suggested by Medique et al., 2001)…" Why the authors would make this statement is baffling, since the authors are knowledgeable of the content differences and the chronology of the Taylor (1994) and Porges (1995) publications. Although Taylor's paper describes the phylogenetic shift in the vagal control of the heart in vertebrates, it is not a theory and does not integrate the well-documented phylogenetic trends with the core features of the Polyvagal Theory, such as a phylogenetically-ordered biobehavioral response hierarchy. The Medique, et al. statement does not suggest that the Polyvagal Theory was based on Taylor's paper, but states that both share a phylogenetic model;" … put forward by Taylor and named the polyvagal theory by Porges (p.654)." Of course, the Polyvagal Theory is based on the extensive literature describing phylogenetic shifts inclusive of several researchers including Taylor (referenced in Porges, 1997) and others (e.g., Nilsson and Holmgren, 1994). Moreover, given that the Taylor article has a publication date of September 1994 in Europe, it is highly unlikely that the journal was easily available to researchers in the United States prior to the presentation of The Polyvagal Theory at the October 8, 1994 meeting of the Society for Psychophysiological Research.

[3]In a paper recently published by Taylor's group (Campbell, Taylor, and Egginton, 2005) an attempt was made to identify RSA in fishes and thus, demonstrate that central control of heart rate was observable and "reject the hypothesis that centrally controlled cardio-respiratory coupling is restricted to mammals, as propounded by the Polyvagal Theory of Porges (1995)." This statement is perplexing, since the specific restriction of cardio-respiratory coupling to mammals was not stated in the Polyvagal Theory. Moreover, as discussed in the commentary, from the Polyvagal perspective, RSA is a uniquely mammalian cardio-respiratory interaction because it is dependent on the outflow the myelinated vagus originating in the nucleus ambiguus. This does not preclude cardio-respiratory interactions involving the unmyelinated vagus originating in the dorsal motor nucleus of the vagus in other vertebrates.

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Keywords

Cardiac vagal control; Cardiac vagal tone; Autonomic nervous system; Heart rate variability; respiratory sinus arrhythmia; Vagus; Polyvagal theory; Parasympathetic; Respiration

The scientific breadth of the articles in this issue, spanning topics from neural mechanisms to clinical applications, highlights the rapid and expansive growth of heart rate variability research. These articles represent research focusing on different levels of inquiry and on different features of the complex neural feedback system that are manifested in the robust relationships between heart rate variability and several behavioral, psychological, physiological, and health processes. Implicit in heart rate variability research is the role of the nervous system in the regulation of the heart and how information regarding neural regulation of the heart is imbedded in the beat-to-beat heart rate pattern.

Historical Context

Central nervous system regulation of visceral organs is the focus of several historic publications that shaped the texture of psychophysiological inquiry. For example, Darwin (1872) acknowledged the dynamic neural relationship between the heart and the brain. "…when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric [vagus] nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body (p. 69)." Although Darwin acknowledged the bidirectional communication between the viscera and the brain, the subsequent formal description of the autonomic nervous system minimized the importance of central regulatory structures and afferents (e.g., Langley, 1921). A focus on the peripheral motor nerves with an emphasis on the paired antagonism between sympathetic and parasympathetic efferent pathways on the target visceral organs resulted in a lack of interest in afferent influences to the brainstem areas regulating specific efferent pathways. The early conceptualization of the vagus focused on an undifferentiated efferent pathway that was assumed to modulate "tone" concurrently to several target organs. Thus, neural circuits regulating the supradiaphragmatic (e.g., myelinated vagal pathways originating in the nucleus ambiguus and terminating primarily above the diaphragm) were not functionally distinguished from the subdiaphragmatic (e.g., unmyelinated vagal pathways originating the dorsal motor nucleus of the vagus and terminating primarily below the diaphragm). Without this distinction, research and theory focused on the paired antagonism between the parasympathetic and sympathetic innervation to target organs. The consequence of an emphasis on paired antagonism in physiology was an acceptance and use of global constructs such as autonomic balance, sympathetic tone, and vagal tone in psychophysiology and psychosomatic medicine. Ironically, the origin of modern psychophysiology is often linked to the classical conditioning of autonomic activity, which, as Pavlov (1927) demonstrated, requires the involvement of higher brain structures in the modulation of visceral responses.

More than 50 years ago, W. Hess (1954) proposed that the "autonomic" nervous system was not solely "vegetative" and automatic, but was an integrated system with both peripheral and central neurons. W. Hess demonstrated the influence of the hypothalamus on the autonomic nervous system. By emphasizing the central mechanisms that mediate the dynamic regulation of peripheral organs, W. Hess anticipated the need for methodologies and technologies to continuously monitor the neural circuits involving both defined brain structures and peripheral nerves in the regulation of visceral function and state. Consistent with these insights, the Polyvagal Theory (Porges, 1995) was proposed and methods suggested (see Porges, this issue) to extract the time course of the influence of two vagal circuits on the beat-to-beat heart rate pattern.

In 1949 W. Hess was awarded the Nobel Prize in Physiology or Medicine. The title of his Nobel lecture was “the Central Control of the Activity of Internal Organs.” The opening paragraph of his lecture provides a framework to evaluate subsequent progress in developing theory, describing neural circuits, providing measurement technologies, and understanding clinical conditions. The lecture provides a succinct statement: 1) to emphasize the importance of feedback circuits linking peripheral organs to brain structures and the bidirectionality of these feedback circuits, and 2) to acknowledge that, although much can be learned about neural structures and functions via traditional experimental paradigms (e.g., neural blockade, surgery, electrical stimulation), the dynamic feedback circuits cannot be adequately studied through these paradigms.

> A recognized fact which goes back to the earliest times is that every living organism is not the sum of a multitude of unitary processes, but is, by virtue of interrelationships and of higher and lower levels of control, an unbroken unity. When research, in the efforts of bringing understanding, as a rule examines isolated processes and studies them, these must of necessity be removed from their context. In general, viewed biologically, this experimental separation involves a sacrifice. In fact, quantitative findings of any material and energy changes preserve their full context only through their being seen and understood as parts of a natural order. This implies that the laws governing organic cohesion, the organization leading from the part to the whole, represent a biological uncertainty, indeed an uncertainty of the first order. It becomes all the more acute, the more rapidly the advances of specialization develop and threaten the ability to grasp, or even to appreciate it. While this state of affairs has just been referred to, our subject is defined by its general content. In particular it deals with the neural mechanisms by which the activity of the internal organs is adapted to constantly changing conditions, and by which they are adjusted to one another, in the sense of interrelated systems of functions. It only remains to be added that broadening of our knowledge in these respects is of benefit not only with regard to the human compulsion to understand, but also to the practical healing art. For man also, in health and sickness, is not just the sum of his organs, but is indeed a human organism.

In the Nobel lecture W. Hess pays respect to Gaskell (1916), Langley (1921), and Meyer and Gottlieb (1926), who contributed to the understanding of the paired antagonistic innervations of the internal organs and the definition of sympathetic and parasympathetic functions. Prior to W. Hess, the prevailing conceptualization of the neural regulation of visceral organs focused on “vegetative” and “autonomic” features. W. Hess notes, however, *“In contrast to the exploration of the vegetative nervous system, which is very far-reaching (even if it is not still without certain inner contradictions) stands a relatively limited understanding of the central organization of the whole mechanism of control.”* W. Hess was aware that, although the components of a feedback circuit might be identified and studied independently, the functioning of independent parts did not explain how the system, as a whole, functioned dynamically during the moment-to-moment challenges of life. This limitation was, in part, dependent on the methodologies of the day that required pharmacological, surgical, or electrical manipulations to block or stimulate “global” branches of the autonomic nervous system that either shared a specific neurotransmitter (e.g., acetylcholine) or an easily identifiable nerve (e.g., vagus) that could be cut, or stimulated.

New Technologies to Address Historical Hypotheses

Contemporary technologies pose the possibility that heart rate variability may provide a portal to the dynamic assessment of vagal function. Paradoxically, these technologies are often validated with surrogate criterion variables operationally defined by limited methodologies such as change in heart rate in response to atropine (see Porges, this issue). Several manuscripts in this issue share an implicit and optimistic assumption that, independent of surgical, electrical,

or pharmacological manipulations, beat-to-beat heart rate variability is a window to the neural regulation of the heart. This implicit assumption was preceded by pioneering research by Hering (1910) that linked respiratory sinus arrhythmia to vagal function and the clinical observations by Eppinger and L. Hess (1915) that associated vagotonia, characterized by high levels of RSA, with clinical disorders.

Observations reported by Hering and others linking the amplitude of the RSA to vagal function led physiologists to quantify the difference in heart rate between the peak and valley (or trough) of RSA (e.g., Eckberg, 1983; Fouad et al., 1984; Hirsch and Bishop, 1981). Following the lead of physiologists, psychophysiologists (e.g., Grossman et al., 1990) applied the peak-valley methodology, often with an added restriction that limits the quantification of RSA to features of the respiratory pattern. While the physiologists conducted studies to evaluate the effects on RSA of traditional manipulations that change vagal efferent activity, psychophysiologists were more interested in measuring stable individual differences or changes in response to definable psychological (e.g., attention) or behavioral (e.g., exercise) manipulations. Thus, the physiologists were concerned with “steady” state manipulations, while the psychophysiologists were more concerned with long-term stable individual differences and very short-term context driven responses. Functionally, the peak-valley methodology attempts to extract the amplitude of rhythmicity from a baseline. In doing this it is making several quantitative and physiological assumptions that do not characterize heart rate variability in the conscious human. When the amplitude of RSA is large relative to the variance in the baseline trend or slower frequencies, the methodology provides a reasonable estimate of dynamic changes in RSA and is highly correlated with other methods (e.g., Grossman et al., 1990). The convergence among methods is based on data that are averaged across several respiratory cycles and the method is not, in its current form, applicable for dynamic RSA cycle-to-cycle measurement. Although the method is distorted by heart rate trend, respiratory frequency, and inspiration/expiration ratio (e.g., Byrne and Porges, 1993), trend and slower periodicities can be removed through various time domain filters such as the moving polynomial (see Porges, 1985; Bohrer and Porges, 1982; Porges and Bohrer, 1990) to provide an excellent tool to measure dynamic changes in RSA. Functionally, this time-domain method, instantiated in the MXedit software[1], via moving polynomial and bandpass filters, extracts a time series representing only the amplitude of RSA (see Porges, this issue) and calculates its variance. Since RSA is not a constant periodic process and may be represented across a band of frequencies, the software accumulates the variances of sine waves associated with the frequencies of spontaneous breathing. Thus, the procedure is a time domain equivalent of spectral analyses with the advantages of being able to calculate RSA amplitude for very short periods of time and to study dynamic regulation of this component of heart rate variability even when RSA is superimposed on a nonstationary baseline (see Denver et al., this issue).

RSA and other Respiration-Heart Rate Interactions

There are several methods to quantify RSA and heart rate variability. Allen, Chambers and Towers (this issue) provide a sampling of these methods. Denver, Reed, and Porges (this issue) demonstrate that RSA frequency is coincident with respiratory frequency. Thus, if respiration frequency is critical to the quantification of RSA, it can be easily obtained from the heart rate data. The question of whether the quantification of RSA needs to be restricted to heart rate data concurrently collected with respiratory parameters is of great interest to psychophysiologists (Denver et al, this issue; Grossman and Taylor, this issue; Porges, this issue). Denver et al., (this issue) review recent studies reporting RSA, both adjusted and unadjusted for respiratory parameters (i.e., respiration rate and tidal volume), published in two psychophysiology

[1]MXedit is a frequently used DOS-based software package that was developed by Delta-Biometrics, Inc. MXedit is no longer being distributed or maintained and Delta-Biometrics no longer exists.

journals. In their limited review, no study reported differences in effects between the unadjusted and adjusted RSA (i.e., using respiration frequency or tidal volume as covariates). This illustrates that the covariation between RSA and respiratory parameters are not robust and consistent across laboratories and conditions. The mechanisms mediating these inconsistencies need to be understood. Research related to respiratory adjustments needs to be empirically conducted to determine under which specific conditions RSA is mediated by respiratory parameters (e.g., slow paced breathing outside of the range of spontaneous breathing or mobilization behaviors).

In the current research milieu, published articles and journal reviews are frequently filled with pejorative statements criticizing studies in which RSA is not statistically adjusted or paced by respiratory parameters. Terms like “corrected,” “confounded,” and “biased” are frequently used. From a scientific perspective, even an atheoretical one, it is difficult to justify these statements as the basis for rejection or criticism. In several instances, it is presumed that RSA is a distorted expression of vagal activity and that this distortion can be effectively corrected by adjusting for easily measured and often manipulated respiratory parameters. In contrast, the literature demonstrates that respiratory adjustments on RSA are not consistent across laboratories and conditions (see Denver et al., this issue); and the criteria used to “validate" successful adjustment are based on surrogate variables that are less sensitive to vagal activity than unadjusted RSA (see Porges, this issue). Certainly, it would be more conducive to the growth of this scientific discipline, if balanced arguments were presented. Ironically, methods are mandated in the literature to remove “confounding” and “biased” influences, although the mechanisms mediating the respiratory-heart interactions are not well understood. Thus, instead of arguing to restrict publication and dialogue by mandating either paced-breathing or statistical corrections (see Allen, Chambers & Towers, this issue, for a critique of the latter), a better understanding of respiratory-heart rate interactions would be gained by systematic research on the influences of peripheral respiratory-related afferents on heart rate.

Does respiration confound or bias RSA as an index of cardiac vagal tone? This point is amply discussed in both the Porges and the Grossman and Taylor papers[2]. The papers provide different perspectives primarily based on two issues: 1) the operational definition of cardiac vagal tone, and 2) the uniqueness of RSA in mammals. Grossman and Taylor assume that there is a construct of “central” cardiac vagal tone and that RSA is an unreliable index of this construct. Porges argues that the construct of “central” cardiac vagal tone is not neurophysiologically meaningful without defining the specific nuclei from which the vagal traffic is originating. In addition, Porges argues that, although physiologists have demonstrated the paired antagonism between branches of the autonomic nervous system on the heart, the construct of “cardiac vagal tone” is antiquated and should be partitioned, based on contemporary neurophysiological and neuroanatomical research, into the functional outflow of the two primary vagal efferent pathways that terminate on the sinoatrial node.

Grossman and Taylor (this issue) assume that RSA in mammals is functionally similar to heart rate-respiratory (or ventilatory) interactions in other vertebrates in which vagal influences are involved. They assume that by demonstrating heart rate-respiration interactions via vagal pathways in vertebrates other than mammals, they have documented a fatal flaw in the Polyvagal Theory. Unfortunately, this is neither a test nor an accurate representation of the Polyvagal Theory. The Polyvagal Theory and subsequent elaborations of the theory (Porges, 1995, 1997, 1998, 2001, 2003) explicitly state that RSA is uniquely mammalian, represents the rhythmic outflow of the myelinated vagus originating in the nucleus ambiguus, and is functionally observed as periodic changes in heart rate restricted to the frequencies associated

[2]Several statements in Grossman and Taylor (this issue) are not accurate representations of the Polyvagal Theory. A few of these points are listed below.

with spontaneous breathing. Consistent with the need anticipated by W. Hess (see above), the quantification of RSA provides a portal to the dynamic regulation of the "nucleus ambiguus-vagal circuit" without disrupting the natural functioning of the system.

If RSA were not specific to the pathways originating in the nucleus ambiguus, then RSA would neurophysiologically be similar to respiratory-heart rate interactions observed in other vertebrates. If this were true, it would not invalidate the Polyvagal Theory, but question the measurement of RSA as an index of the "nucleus ambiguus-vagal circuit." Thus, it would be difficult to test specific hypotheses related to the phylogenetically-ordered hierarchy of autonomic responses. Fortunately, this is not the case, since the literature in clinical medicine, comparative anatomy and electrophysiology supports the interpretation that RSA is a measure of the "nucleus ambiguus-vagal circuit." Research is currently being conducted in several laboratories investigating the mechanisms mediating both the dorsal (i.e., dorsal motor nucleus of the vagus) and ventral (i.e., nucleus ambiguus) vagal circuits. Clinical medicine documents that clinical bradycardia and life-threatening cardiac events are more likely to occur when the background RSA is low. Consistent with the view that RSA is uniquely mammalian, Taylor et al. (1999) describe the phylogenetic shift in central control of cardiorespiratory interactions from vagal neurons located in the dorsal motor nucleus to the nucleus ambiguus. Moreover, Taylor, et al. (2001) emphasize the different mechanisms underlying RSA in mammals and respiratory-heart rate interactions in other vertebrates. They state that the "CVPN [cardiac vagal preganglionic neurones] in the NA [nucleus ambiguus] of mammals receive inhibitory inputs from neighboring inspiratory neurones, causing respiratory sinus arrhythmia (RSA), and the CVPNs in the DVN [dorsal vagal nucleus] of the dogfish may generate cardiorespiratory synchrony (CRS)." However, contradicting earlier propositions, recent papers by Grossman and Taylor (e.g., Campbell et al., 2005; Grossman and Taylor, this issue) propose that mammalian RSA and the cardiorespiratory interactions observed in other vertebrates represent the same phenomenon. Thus, from Grossman and Taylor's perspective, the terms can be used interchangeably when studying vertebrate species other than mammals or when manipulating breathing (e.g., paced breathing, slow breathing) outside the parameters of spontaneous breathing. This is not consistent with features of RSA as defined by the Polyvagal Theory.

An interest in the study of respiratory-heart rate interactions from a neurophysiological perspective leads to an appreciation that respiratory maneuvers influence peripheral afferents involved in the regulation of heart rate. Thus, systematically varying frequency, tidal volume, inhalation/exhalation ratio, and resistance might result in systematic shifts in the amplitude of respiratory-driven heart rate patterns. Theoretically relevant to psychophysiology is the neglected question of which "respiratory-heart rate" interactions reflect the same neurophysiological processes as RSA? Perhaps, restricting the definition of RSA in humans to spontaneous breathing frequencies (i.e., by insuring that it represents the outflow of the myelinated vagus originating in the nucleus ambiguus) would distinguish it from other respiratory-heart rate interactions and foster its use as a more sensitive window to the dynamic function of specific vagal efferent pathways.

Theoretically, respiratory manipulations that require voluntary control must involve cortical processes related to motor movement, intentionality of effort and attentional monitoring. Voluntary respiratory manipulations may impact on both top-down (e.g., corticobulbar and corticospinal pathways) and bottom-up (e.g., afferents from the viscera, skeletal muscle, and striated muscles of the face and head) mechanisms involved in the generation of RSA. Since the cells of origin (i.e. nucleus ambiguus) of the myelinated vagus producing RSA are intrinsically silent (see Porges, this issue), both the top-down and bottom-up processes described above would modulate RSA. Without systematic research on these neural mechanisms, manipulations that attempt to "control" respiration may be influencing RSA in an unpredictable manner.

As Beauchaine et al. (this issue) eloquently state, theories stimulate scientific dialog, generate new research questions, and provide organizing principles to enable new interpretations of existing data. For example, when the Polyvagal Theory was initially presented (Porges, 1995), knowledge of vagal C-fibers was limited. There was no published demonstration that C-fibers could produce a bradycardia of sufficient magnitude to be clinically relevant. Several plausible explanations were presented in an attempt to understand how the massive bradycardia observed during fetal distress could be mediated via unmyelinated vagal pathways (see Reed, et al., 1999). During the intervening years, new findings regarding vagal C-fibers are beginning to explain how few C-fibers can produce clinically relevant bradycardia (see Porges, this issue).

The Vagal Brake

The mammalian vagus functions as an active vagal brake (Porges et al., 1996) in which rapid inhibition and disinhibition of vagal tone to the heart can support behavioral mobilization or self-sooth and calm an individual. When the vagal tone to the pacemaker is high, the vagus acts as a restraint or brake limiting heart rate. When vagal tone to the pacemaker is low, there is little or no inhibition of the pacemaker. Due to vagal influences to the sino-atrial node (i.e., the heart's pacemaker), resting heart rate is substantially lower than the intrinsic rate of the pacemaker. In mammals, the primary vagal inhibitory pathways occur through the myelinated vagus originating in the nucleus ambiguus. Thus, the vagal brake can be monitored by quantifying the dynamically changing amplitude of RSA and may be used as a construct to describe the functional modulation of heart rate by the myelinated vagal efferent pathways. Consistent with assumptions of the Polyvagal Theory, the vagal brake contributes to the modulation of cardiac output by decreasing or increasing the inhibitory vagal control of the heart to influence rate and thereby adjust metabolic resources to support either mobilization or social engagement behaviors.

Several researchers have embraced the concept of the vagal brake to study individual differences in the ability to rapidly change physiological state. Calkins et al. (this issue), conducted research that demonstrated that, although RSA level was not related to early childhood behavior problems at 5 years of age, the pattern of withdrawal of the vagal brake during testing conditions (i.e., dampened depression of RSA) was related to specific behavioral problems. Children with externalizing problems expressed less vagal withdrawal, while children with mixed externalizing/internalizing problems reacted with the greatest suppression of RSA and increase in heart rate preparing the children for efficient fight/flight behaviors. Consistent with an interest in developmental psychopathology, Katz (this issue) evaluated the pattern of RSA reactivity to "peer provocation" as a function of domestic violence in the family. Katz noted that the conduct-problem children, who increased RSA to peer provocation, came from the families with the highest levels of domestic violence.

Contradicting or Paraphrasing the Polyvagal Theory?

Grossman and Taylor (this issue) propose, as an alternative to the Polyvagal Theory, several points stated previously in the Polyvagal Theory (Porges, 1995). They state, "what we measure with any heart rate index of vagal tone are only the final functional vagal effects on cardiac activity." This statement is consistent with summary point four in the Polyvagal Theory (Porges, 1995): "*the functional output of the NA vagus on the heart may be monitored by RSA (p.314).*" They state "variations in RSA magnitude currently provide an unreliable index of central vagal outflow or tone. " This statement is implicit in the first and third summary points of the Polyvagal Theory: "*The vagal system does not represent a unitary dimension*," and "*In mammals the concept that vagal tone represents a single or summed system may have limited physiological or heuristic value* (p.314). They state that RSA serves an active biological function in enhancing "the efficiency of pulmonary gas exchange by matching blood perfusion

to air flow in the lung through each breathing cycle." A similar statement is made in Porges (1995), "*The covariation of the bronchi with heart rate oscillations (e.g., RSA), mediated by NA [nucleus ambiguus], may have a functional influence on the oxygenation of blood (p. 311).* They state that resting RSA reflects a "functional energy reserve capacity from which the organism can draw during more active states." This statement is consistent with the functional impact of the myelinated vagal efferent activity on behavior described in the Polyvagal Theory (1995), "*The high NA vagal tone* [observed as high amplitude RSA] *keeps mammals from, literally, bouncing off the walls. Thus, in contrast to that observed in reptiles, in mammals vagal tone is highest during unchallenged situations such as sleep, and vagal tone is actively withdrawn in response to external demands, including metabolically demanding states such as exercise, stress, attention, and information processing*" (p. 306). These points were subsequently formalized as the vagal brake construct and introduced in Porges et al. (1996), which states that *the theory* [Polyvagal Theory] *proposes that the successful adaptation of mammals is dependent on systematic and reliable withdrawal and reengagement of the vagal brake* [quantified by the amplitude of RSA] *as a mechanism to rapidly regulate metabolic output in response to environmental demands (p. 700).*"

Historical Stages of Scientific Inquiry

Ackerknecht (1974) detailed four historical stages of scientific inquiry into the autonomic nervous system: 1) the discovery of the nerves, 2) the description of paired antagonism, 3) the identification of the influence of the central nervous system, and 4) the diagnosis of neuro-visceral disorders that mediate psychiatric and physiological diseases. The latter point is relevant to several of the papers in this issue. Ackerknecht documents attempts to link visceral function to clinical disorders. In 1823 Lobstein described a cluster of diseases including hypochondria, mania and melancholia, asthma, sudden death, migraine, and insomnia as being related to autonomic dysfunction. In 1863 Eulenburg described a cluster that included angina pectoris, colic, and diabetes. In 1910 [published in English in 1915] Eppinger and L. Hess proposed individual differences in extreme neural regulation and assumed that vagotonic and sympatheticotonic individuals would have different diseases. For example, according to Eppinger and L. Hess, vagotonic diseases would include asthma, spastic constipation, and colitis. Ackerknect concludes, "as extremely helpful as our knowledge of the vegetative system has been in the understanding and treatment of many diseases, it has not been a useful foundation for a pathophysiological system."

Several papers in this issue describe studies dealing with Ackerknecht's fourth stage. These studies focus on associating individual differences in heart rate variability with clinical diagnoses (e.g., psychiatric, behavioral, and physical illnesses and problems). Friedman (this issue) emphasizes the importance of the regulation of vagal influences on the heart in individuals with anxiety disorders. He states that "metaphorically, investigators were searching for a 'sticky accelerator' while overlooking the possibility of 'bad brakes.'" Rottenberg (this issue) investigates the proposed link between heart rate variability and clinical depression. By conducting meta-analyses, Rottenberg demonstrates only a modest association between heart rate variability and depression. The strength of this relation might be mediated by several factors including comorbidity, age, gender, etiology, and variance in clinical expression. Masi et al. (this issue) provide several neural mechanisms explaining the link between RSA and diseases of aging such as obesity, diabetes, and hypertension. Thayer and Lane (this issue) describe a neurovisceral model that emphasizes the role of brain structures in the mediation of vagal regulation of visceral processes. By using several variables that involve vagal mechanisms, such as resting heart rate, heart rate recovery, heart rate variability, and baroreflex sensitivity, Thayer and Lane demonstrate that decreased vagal function is associated with an increased risk for morbidity and mortality, independent of traditional risk factors. DeMeersman and Stein (this issue) describe the age-related reduction in RSA and the covariation of these

changes in vagal activity with depression. Beauchaine et al. (this issue) emphasize the heuristic value of theory. They capitalize on the organizing principles imbedded in the Polyvagal Theory and merge these principles with features derived from Gray's theory of motivation. The resultant model provides new insights into developmental psychopathology and forms the basis for their research program on externalizing disorders in children.

Independent of the issue of variation of diagnosis, the long-term success of strategies relating clinical factors to autonomic variables may be limited due to several factors including: 1) the inability to evaluate or even to conceptualize the specificity of autonomic pathways in their regulation of visceral organs, and 2) the inability to dynamically measure the influence of the neural regulation on the target organs. To optimize strategies studying the bridge between neuro-visceral function and both clinical disorders and health, psychophysiology will need to move beyond hypotheses dependent on the historic paired antagonism model of the autonomic nervous system and to exploit hypotheses dependent on our expanding knowledge of neurophysiology and the central structures involved in both appraisal of context and visceral state and in the neural regulation of visceral organs. In addition, methodologies need to match the research questions and be capable of evaluating dynamic changes in and interaction among various periodic processes and trends in heart rate (as well as other physiological variables including respiration, blood pressure, vasomotor tone, and motor activity). In response to these needs, the Polyvagal Theory was generated. The theory is an attempt to reorganize our conceptualization of the autonomic nervous system with a focus on the specific vagal circuits that regulate visceral organs. Implicit in the theoretical model are four prominent features that impact directly on the development of testable hypotheses: 1) the role specific brain structures and neural circuits have in regulating autonomic state, 2) the justification of developing methods that can distinguish and track the dynamic vagal output to target organs through the myelinated vagus originating in the nucleus ambiguus and the unmyelinated vagus originating in the dorsal motor nucleus, 3) the role visceral afferents and sensory feature detectors have on the switching among the neural circuits regulating autonomic state, and 4) the relation between the regulation of visceral organs and the regulation of the striated muscles of the face and head involved in social engagement behaviors including affect recognition and emotional expression.

Concluding Remarks

As methodologies become more sensitive to neural regulation and as theories integrate behavior and psychological processes with neurobiological principles, researchers will become better positioned to successfully understand how neurovisceral processes may mediate the expression of health and disease. Based on the quality and breadth of manuscripts in this issue, research in heart rate variability has a bright future.

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