Available online at www.sciencedirect.com
ScienceDirect
Biological Psychology 74 (2007) 295–300
BIOLOGICAL PSYCHOLOGY
www.elsevier.com/locate/biopsycho

Whither vagal tone

Gary G. Berntson [a,*], John T. Cacioppo [b], Paul Grossman [c]

[a] The Ohio State University, Department of Psychology, 1835 Neil Avenue, Columbus, OH 43210, United States
[b] The University of Chicago, Department of Psychology, 5848 S. University Avenue, Chicago, IL 60637, United States
[c] Department of Psychosomatic & Internal Medicine, University of Basel Hospital, Hebelstrasse 2, CH-4031 Basel, Switzerland

Accepted 3 August 2006
Available online 12 October 2006

Abstract

Measures of respiratory sinus arrhythmia (RSA) have been widely applied in the physiological and psychophysiological literature as an index of vagal control of the heart. Despite an extensive literature, however, differences in interpretation remain within the field. A guiding conception for several contributions in this issue is the notion of separate brainstem centers involved in parasympathetic control, with distinct evolutionary origins and significance and with divergent influences on cardiac vagal tone as it relates to psychological and behavioral processes. We here consider the biological foundations for this view, discuss some methodological and interpretative caveats for RSA applications and offer suggestions for further development of the field.

Keywords: Cardiac vagal control; Cardiac vagal tone; Re-representation; Nucleus ambiguous; Dorsal motor nucleus; Respiration; Nicotinic; Muscarinic; Parasympathetic; Atropine; Vagal tone; Respiratory sinus arrhythmia; Polyvagal

1. Contributions in the special issue

The contributions in this special issue illustrate a broad range of applications of measures of heart rate variability, especially respiratory sinus arrhythmia (RSA). The papers echo several key concepts or themes.

One is that heart rate variability may serve importantly in health risk stratification. It has been known for some time that heart rate variability is a positive predictor of outcome after myocardial ischemia, and the autonomic and cellular basis for this relationship is beginning to be understood. Sympathetic activation (via beta2 adrenoceptors) can trigger malignant arrhythmias, whereas vagal control has protective effects at the level of the myocardium (Billman, 2006). This may represent, at least in part, the underlying mediator between RSA and positive cardiac outcomes.

In this special issue, Thayer and Lane emphasize the broader health significance of RSA in the context of a model of neurovisceral integration. Whereas the medical literature on myocardial ischemia has generally focused on autonomic effects on the heart, the neurovisceral integration model emphasizes the importance of higher brain systems, such as the medial prefrontal cortex, which have been implicated in cognitive and affective processes and exert descending control of autonomic outflows.

A comprehensive understanding of autonomic/health relations will require a further elucidation of the rostral neurobehavioral substrates that mediate psychophysiological relations and their links to health. Additionally, we need to know more about whether particular cortical brain regions are specifically and solely related to cardiac parasympathetic activation, since the same regions may also be involved in other physiological changes, such as respiratory alteration, which, in fact, themselves may be primary to patterns of cortical activity (Evans et al., 1999; McKay et al., 2003; Smejkal et al., 2000; von Leupoldt and Dahme, 2005). RSA associations with cortical activity may, therefore, be secondary to those other autonomic events.

Friedman considers the neurovisceral integration model in the context of anxiety, which is conceptualized as a systemic inflexibility grounded in poor inhibition. This poor inhibition arises from neurocognitive systems of the *central autonomic network*, which includes the medial prefrontal cortex and serves to integrate central and autonomic functions. A deficiency in this inhibition is considered to lead to a loss of autonomic and behavioral flexibility and to associated low heart rate variability

* Corresponding author. Tel.: +1 614 292 1749; fax: +1 614 688 4733.
E-mail address: berntson@osu.edu (G.G. Berntson).

0301-0511/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2006.08.006

and rigid, perseverative behavior and anxiety. Although these neurobiological models of behavior and autonomic integration are in early stages of development, they represent important efforts to relate psychophysiological relationships to their underlying neural substrates and functional mediators. Although such integration is highly desirable, caution needs to be exercised when applying metaphor or analogy from biology to psychology because the same terms, like inhibition, rigidity and flexibility, may have very different meanings in different disciplines and because underlying mechanisms that mediate effects in behavioral or physiological systems may also vary greatly.

An impediment to conceptual development in this area is the fact that neurobehavioral systems are complex, multilevel and interacting. Vagal control is but one component of a multifarious central autonomic network and not necessarily the most important or central one. Moreover, psychophysiological relations and biomarkers such as RSA are often multiply determined. The mere association of a biomarker or psychosocial variable with a health state or condition does not imply causation nor necessarily inform underlying mediators. Hawkley et al. (2006), for example, observed a significant relation between systolic blood pressure and loneliness, perceived stress and hostility. Further analysis, however, revealed that loneliness was the only of these psychosocial variables to exhibit significant association with blood pressure independent of demographic and other variables. In the present issue, Rottenberg notes diminished cardiac vagal control in depression, although the literature is rather mixed. In part, this appears to arise from the multiple determinants of RSA and/or vagal control (drug regimens, health status, etc.) that may be operating within and between studies. Also in the present issue, Masi et al. outline an analytical approach by which causal links and potential mediators of psychophysiological relationships can be explored. In this study, both RSA and hypertension were found to be significant predictors of cardiovascular disease. Further analyses, however, indicated that hypertension is a likely mediator of the relationship between RSA and cardiovascular disease and RSA is no longer predictive of cardiovascular disease when hypertension is held constant. These studies illustrate that the demonstration of a psychophysiological relationship does not necessarily imply a specific association or a causal link. They also emphasize the importance of multi-measure approaches that permit causal analysis and provide evaluations of potential patterns of response across domains, which may reveal lawful relations that would not be discernable by a single measure.

Another theme or conceptual focus in the special issue has been on emotion and emotion regulation in development. Beauchaine et al. propose a biosocial developmental model of conduct problems, based in part on Gray (1978) and Gray and McNaughton (1996) activation (BAS) and inhibition (BIS) systems, as well as Porges polyvagal theory and its proposed distinction between components of the vagal system. In the Beauchaine et al. model, ‘‘emotion regulation and social affiliation are considered emergent properties of the regulatory functions served by the smart vagus’’ and disturbances in this system are believed to predispose toward emotional liability. Based in part on PEP measures, children with aggressive ODD/CD are reported to exhibit sympathetic underarousal at baseline and sympathetic insensitivity to reward, reflecting a general disinhibitory tendency. In addition, based in part on RSA measures, these children are said to have parasympathetic nervous system deficiencies that contribute to increased emotional liability. In this regard, Calkins et al., examined the patterns of heart rate and RSA response to behavioral challenges. Subjects at risk for externalizing problems or for mixed externalizing/internalizing problems displayed greater RSA reduction and greater heart rate acceleration than those at low risk. Indeed, a common finding in many of the papers of the special issue is that anomalous RSA levels or RSA reactivity may accompany many psychopathological or maladaptive states or conditions, or even normal aging. In addition to the emotion regulation literature and anxiety states and depression as considered above, the paper by De Meersman and Stein documents an aging-related decrease in RSA, that may be exaggerated in disease states, including cardiovascular disease, obesity and depression. Whether the changes in RSA are predictive of these disease states is an important open issue. Moreover, the results of Katz indicate that changes in RSA in unhealthy states or contexts are not always decreases. Children with behavior disorders from families with domestic violence may show an atypical augmentation of, rather than a decrease in, this index of vagal control when anticipating negative peer interactions. Moreover, relations between RSA and emotion are frequently inconsistent (e.g., Rottenberg, this volume) with key aspects of current theoretical models described in this volume and this will require further clarification.

The wide-ranging conditions under which alterations in RSA are noted and the varying direction of RSA change raise important questions as to the sensitivity and specificity of these changes for particular behavioral states. Additionally, a major assumption running through many of the above-mentioned contributions, that inter-individual or intra-individual variations in RSA reflects cardiac vagal tone, may be context-specific and has been challenged based on a critical evaluation of the literature (see Grossman and Taylor, this volume). We will return to these issues below, but first we will review the current status of the polyvagal theory and the literature, it has stimulated.

2. Status of the polyvagal theory

One important contribution of theories, in general, is their generative effects in stimulating and directing research. The contributions in this special issue document a clear impact of the polyvagal theory in this regard. Another important role for theory is in organizing meaningful patterns in data that might otherwise go unnoticed and providing explanatory concepts for those patterns. The notion of an evolutionary development of neurobehavioral systems and the existence of multilevel organizations with evolutionary layering of the neuraxis is not particularly provocative. This is the essence of what John

Hughlings Jackson referred to in his 19th-century essay "*Evolution and dissolution of the nervous system*" as re-representation of functions through evolution (Jackson, 1884). It is a central concept in the neurobehavioral literature (Berntson and Cacioppo, 2000; Grossman, 1992).

An interesting feature of the polyvagal theory is its postulate of the phylogenetic emergence of distinct systems underlying adaptive behavior. These include the most primitive immobilization system (said to relate to the unmyelinated or vegetative vagus), the intermediate mobilization system (said to be related to the sympathetic system) and the most recently developed social engagement system (said to be associated with the myelinated or 'smart' vagus). In addition to immobilization and mobilization systems, even primitive organisms have need for and are endowed with, systems for social engagement. So in the Jacksonian sense of re-representation, of course, each of these three behavioral systems or domains would have its proper representation at all evolutionary levels of the brain. What would differ in the Jacksonian scheme would be the degree of development and refinement of these systems across distinct levels. This consideration aside for the moment, the polyvagal theory entails a psychological model of these behavioral systems and seeks to link these systems to general domains of behavioral function.

Beauchaine et al., (this volume) further develop and incorporate these behavioral systems into a conceptual model of emotional dysregulation. An important component of this model is said to be the sympathetic and the two (polyvagal) parasympathetic branches of the autonomic nervous system. It is important to note, however, that a neurobiological component would not be necessary. Theories restricted to the psychological or behavioral domain are perfectly legitimate. Their utility would be judged by their ability to generate testable hypotheses, to organize facts and knowledge and to provide meaningful explanations. Reference to vagal systems could be extracted completely from the polyvagal theory, without necessarily having impact upon its status as a behavioral or psychological theory. In this regard, the vagal component could be considered as something of a sacrament. If more than this, then the real issues revolve around the formal status of the biological components of the theory and the contributions that they make to the theory.

As discussed above, a central feature of the polyvagal theory is the existence of separate brainstem centers involved in parasympathetic control, with distinct evolutionary origins and significance and with divergent influences on cardiac vagal tone related to psychological and behavioral processes. The nucleus ambiguus (NA) is considered the origin of the more recently developed "smart" vagus and the dorsal motor nucleus (DMN) is part of the more primitive "vegetative" vagus. It is argued that RSA specifically reflects the NA vagal effects upon the heart, whereas the DMN only exerts more tonic effects on heart rate. As discussed by Grossman and Taylor (this volume), comparative evolutionary considerations seriously challenge the proposed differentiation between these two source nuclei. As these issues were well covered in that chapter, we will not reiterate that discussion here, except to highlight a few salient issues.

First, as documented by Grossman and Taylor, cardio-respiratory interactions are not a unique mammalian endowment, but are apparent across vertebrate species. With emergence of terrestrial air-breathers, there has clearly been some evolutionary development of extended vagal source nuclei from the DMN, through the intermediate zone and to the NA. Although qualitative differences are observed in myelination and other characteristics between NA and DMN cardiac neurons, respiratory rhythms can be seen in both B and C fibers and both project to the primary relay neurons (Principal Neurons) in cardiac ganglia (see Cheng et al., 1999; O'Leary and Jones, 2003). This does not imply that there are no functional differences between these nuclear groups, as the NA is the predominant regulator of cardiac chronotropy in mammals. These findings do, however, question the distinction between NA projections acting via a nicotinic ganglionic pathway and the DMN via a slower muscarinic ganglionic pathway. In fact, blockade of muscarinic receptors by atropine blocks virtually all autonomic-mediated RSA and is generally accepted as one of the gold standards for judging vagal control of the heart, especially when potential confounds are considered (Berntson et al., 1994a,b; Cacioppo et al., 1994; Grossman et al., 1990; Grossman and Kollai, 1993; O'Leary and Jones, 2003; see also De Meersman, this issue). There is little basis at this point for positing separate pathways for vagal cardiac control. Moreover, because NA and DMN contributions to cardiac vagal control cannot currently be assessed invasively or non-invasively in humans, attributions of differential influence upon psychophysiological functioning and human behavioral must remain speculative.

Secondly, RSA reflects a multiply determined phasic fluctuation in vagal control of the heart. Although the level of tonic vagal activity is one important contributor to RSA, the degree of phasic modulation of this tonic activity is widely recognized by physiologists to be a function of respiratory frequency and depth (Eckberg, 2003; Grossman et al., 1991; Grossman and Taylor, this volume). The fact that RSA may not be highly correlated with respiratory rate or depth in a particular sample or context (Denver and Porges, this issue), does not preclude the need to assess potential respiratory confounds in RSA (e.g., Ritz and Dahme, 2006). Respiratory parameters can have large effects on RSA within individuals (see Grossman and Taylor, this issue) or between individuals (de Geus et al., 1995; Grossman and Wientjes, 1986; Kollai and Kollai, 1992; Kollai and Mizsei, 1990; Snieder et al., 1997). In addition, moderate-to-large changes in sympathetic outflow may confound the relation between RSA and vagal tone, due to sympathetic-parasympathetic interactions. This is not to suggest that RSA has no utility as a metric of vagal control of the heart, but rather that it is a multiply determined index and those determinants need to be considered in experimental applications. Monitoring respiration is prudent and is recommended by the Society for Psychophysiology Research committee report (Berntson et al., 1997). Quite apart from changes in the RSA transfer function across the respiratory frequency band (i.e., RSA decreases as respiration rate increases), monitoring of respiration is important to ensure

that the respiratory power falls wholly within the specified band. This can pose a serious confound if there are individual differences in respiration or differences across experimental conditions that push part of the respiratory power either outside the analytical bandwidth, or into end-regions of the bandwidth where RSA underestimation can occur due to an attenuated frequency-response characteristic.

Finally, it is important to recognize that RSA is not a regulated end point, or even an end point, in a psychophysiologically meaningful sense. When carefully measured and considered, it may represent an important metric of autonomic control, which in turn may be associated with neurobiological processes. Nevertheless, the NA or vagal outflow cannot properly be said to ''mediate'' behavioral processes or even serve as a marker or indicator of a process. Typically, psychophysiologists experimentally control, or merely observe, a behavior state or process (Ψ) and record ongoing physiological (Φ) parameters. This yields a relationship of the general form: if Ψ then Φ, where Φ constitutes an *outcome* (see Cacioppo and Tassinary, 1990; Cacioppo et al., 2000a,b). What is often desired, however, is to use the physiological parameter to infer the psychological state. Porges (this volume), for example, points out that ''Psychophysiology as a discipline has been interested in using physiological variables to infer information about specific psychological processes.'' This is an inference of the form: if Φ then Ψ. The latter inference based on the former empirical demonstration represents a logical error. Because of the multiple determinants and probable context dependency of RSA, a singular measure of RSA cannot be used to infer psychological states or processes. In order for the latter type of inference to be drawn, Φ would have to be elevated to the level of an *invariant* (having a context-independent, one-to-one relation to Ψ) or at least a *marker* (context-dependent, one-to-one relation to Ψ). It is for this reason that the issue of specificity is so important.

3. Directions for the future

The polyvagal theory is an attempt, within a systems perspective, to integrate physiology, behavior and psychosocial processes in a unified framework that emphasizes one branch of the autonomic nervous system in relation to evolution and neuroanatomy. As such, it has several ingredients that make it attractive to researchers searching for a conceptual model for their work. For future development, the theory could benefit by further formalizations or modifications that enhance its empirical physiological grounding and its ability to generate testable neurobiologically relevant hypotheses.

Differential NA and DMN contributions to human vagal heart rate control are central to the polyvagal theory, but the physiological basis of these differential roles remain to be clearly established. In mammals, the NA is the predominant source of chronotropic control of the heart and the more modest contribution of the DMN follows the same final common pathway to the sinoartic node via Principal Neurons (Cheng and Powley, 2000). Consequently, curare would not selectively isolate the functional contributions of the two source nuclei. It would block both, at the ganglionic level, not to mention the complication from neuromuscular blockade. Although hexamethonium might be a more ganglion selective approach, it too would block the final common ganglionic projection to the SA node. The generally accepted method of determining vagal cardiac control is the use of atropine, which virtually eliminates all RSA and vagal influences on the heart, not by ganglionic blockade, but the blockade of the postganglionic muscarinic receptors common to the DMN and NA pathways. Consequently, there is not presently a viable pharmacological approach to teasing apart the purported functional contributions of these two source nuclei. In fact, it is not even clear at this point how to experimentally approach the role of the DMN in the normal or abnormal range of human cardiac regulation! This is a sparsely studied terrain with no human studies. Methodologically, it is a very difficult topic to investigate in animals, let alone humans and there are likely to be species differences even among mammals (Loewy and Spyer, 1990). The NA, on the other hand, appears to be primarily responsible for vagal control of heart rate under a wide range of conditions (Cheng et al., 2002, 2004). Documenting potential functional differences among these source nuclei, at both a psychophysiological and a behavioral level, is an issue that needs to be addressed.

Perhaps an even more fundamental issue is how vagal tone should be precisely defined and operationalized in a manner consistent with existing physiological research. Because of its multiple determinants, the use of RSA alone as a criterion variable obscures the physiological underpinnings of the concept of vagal tone. Grossman and Taylor propose the heart rate changes associated with atropine blockade of the heart as a criterion measure, an approach that has been widely applied and accepted in the physiological as well as the psychophysiological literature (Berntson et al., 1994a,b; Cacioppo et al., 1994; Grossman et al., 1990; Grossman and Kollai, 1993; O'Leary and Jones, 2003; see also De Meersman, this issue).

For any alternative to be accepted, its physiological foundations would have to be clearly established. Short of that, perhaps a more neutral designation would be something like *phasic vagal cardiac control*, rather than vagal tone. The former more descriptively characterizes what is actually being measured (RSA) without the conceptual baggage of the phrase vagal tone. The employment of RSA as a reflection of phasic vagal impact upon the heart would seem to be more in keeping with the literature, as it could be seen as related to cardiac vagal tone, as well as a product of several additional determinants including central and peripheral parasympathetic levels, respiratory parameters, age, bodyweight and possibly cardiac sympathetic tone. RSA could continue to remain a primary outcome variable in many studies, but this conception would allow us to both consider and attempt to tease apart more empirically established determining causes of RSA, as opposed to merely invoking brainstem vagal nuclei as an explanatory mechanism.

Additionally important for the further development and maturation of the field and for applications of RSA to the elucidation of behavioral processes is the advancement beyond

the correlative approach among a restricted set of variables. In his lead article, Porges points out that "The Polyvagal Theory provides an important bridge from the historical correlative approach to a more integrative model ... ." Many of the contributions to this literature, however, focus on limited psychophysiological and behavioral dimensions and contexts. This is fine, as far as it goes, but further integration across constructs and findings in the literature needs to be achieved. As illustrated by the Masi et al. contribution, a more comprehensive approach may be called for. For multiply determined psychophysiological relations, it is increasingly important to assess the generality of findings across contexts and populations and to explore the mediating links in observed relations. If we begin to think about RSA and vagal activity in terms of multivariate, correlated antecedents and consequences, in light of contextual specificity and generality, then we are more likely to be able to see where the connections/associations are real and where they are absent or spurious.

Returning to the discussion above of psychophysiological inference, the multivariate approach may facilitate the identification and development of psychological markers or invariants. There is nothing wrong with a causal hypothesis, but the limitations of the correlative findings need to be appreciated, along with alternative interpretations to the favored hypothesis. Just because the results are consistent with one's hypothesis does not mean that one's hypothesis is the most plausible or parsimonious. As discussed above, the proposition if Ψ then Φ does not permit the inference if Φ then Ψ (see Cacioppo and Tassinary, 1990; Cacioppo et al., 2000a,b). If RSA is multiply determined, then Ψ (e.g., stress and emotional dysregulation) may be only one variable that can yield changes in RSA, so the appearance of changes in RSA is ambiguous with regard to its origin in the multiple determinants. That is, there is a many-to-one mapping to RSA. Moreover, the relation between Ψ and Φ may not even be directly causal but may be attributable to a correlated variable, which serves as the mediator in the causal chain. A multivariate approach allows analysis of these causal pathways and can assist in identifying the most relevant variable or variables. To the extent to which the many-to-one relations can be identified and the other determinants controlled or held constant, the many-to-one relation could be reduced to a few-to-one, or even a one-to-one, at least within that controlled context. This elevates Ψ (or a set of Ψs, e.g., Ψ_1, Ψ_2, Ψ_3, ...) from an *outcome* to the status of a *marker* of a psychological state or process.

The establishment of a psychophysiological marker does allow inferences from Φ to Ψ, but it still does not necessarily constitute or identify the pathways or mediating variables that underlie the relation. For this, not only multivariate, but also multilevel research, which cuts across behavioral and physiological domains will be necessary (e.g., see Cacioppo et al., 2000a,b). Understanding the multiple determinants and causal pathways will be especially important in the development of intervention strategies (e.g., see De Meersman and Stein, this issue), as interventions on a non-causal dimension may not yield behavioral or health benefits. It is this mapping across domains that the polyvagal theory or other biobehavioral theories of RSA (e.g., Grossman and Taylor, this volume) seek. Hopefully, the considerations outlined above will contribute to the development of the field.

References

Berntson, G.G., Bigger, J.T., Eckberg, D.L., Grossman, P., Kaufmann, P.G., Malik, M., Nagaraja, H.N., Porges, S.W., Saul, J.P., Stone, P.H., van der Molen, M.W., 1997. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 34, 623–648.

Berntson, G.G., Cacioppo, J.T., 2000. Psychobiology and social psychology: past, present and future. Personality and Social Psychology Review 4, 3–15.

Berntson, G.G., Cacioppo, J.T., Quigley, K.S., 1994a. Autonomic cardiac control. I. Estimation and validation from pharmacological blockades. Psychophysiology 31, 572–585.

Berntson, G.G., Cacioppo, J.T., Binkley, P.F., Uchino, B.N., Quigley, K.S., Fieldstone, A., 1994b. Autonomic cardiac control: III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. Psychophysiology 31, 599–608.

Billman, G.E., 2006. A comprehensive review and analysis of 25 years of data from an in vivo canine model of sudden cardiac death: implications for future anti-arrhythmic drug development. Pharmacology and Therapeutics 111, 808–835.

Cacioppo, J.T., Berntson, G.G., Binkley, P.F., Quigley, K.S., Uchino, B.N., Fieldstone, A., 1994. Autonomic cardiac control. II. Basal response, noninvasive indices, and autonomic space as revealed by autonomic blockades. Psychophysiology 31, 586–598.

Cacioppo, J.T., Berntson, G.G., Sheridan, J.F., McClintock, M.K., 2000a. Multi-level integrative analyses of human behavior: the complementing nature of social and biological approaches. Psychological Bulletin 126, 829–843.

Cacioppo, J.T., Tassinary, L.G., 1990. Inferring psychological significance from physiological signals. American Psychologist 45, 16–28.

Cacioppo, J.T., Tassinary, L.G., Berntson, G.G., 2000b. Psychophysiological science. In: Cacioppo, J.T., Tassinary, L.G., Berntson, G.G. (Eds.), Handbook of Psychophysiology. Cambridge University Press, Cambridge, UK, Cambridge, pp. 3–23.

Cheng, Z., Guo, S.Z., Lipton, A.J., Gozal, D., 2002. Domoic acid lesions in nucleus of the solitary tract: time-dependent recovery of hypoxic ventilatory response and peripheral afferent axonal plasticity. Journal of Neuroscience 15, 3215–3226.

Cheng, Z., Powley, T.L., 2000. Nucleus ambiguus projections to cardiac ganglia of rat atria: an anterograde tracing study. Journal of Comparative Neurology 424, 588–606.

Cheng, Z., Powley, T.L., Schwaber, J.S., Doyle, F.J., 1999. Projections of the dorsal motor nucleus of the vagus to cardiac ganglia of rat atria: an anterograde tracing study. Journal of Comparative Neurology 410, 320–341.

Cheng, Z., Zhang, H., Yu, J., Wurster, R.D., Gozal, D., 2004. Attenuation of baroreflex sensitivity after domoic acid lesion of the nucleus ambiguus of rats. Journal of Applied Physiology 96, 1137–1145.

de Geus, E.J., Willemsen, G.H., Klaver, C.H., van Doornen, L.J., 1995. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. Biological Psychology 41, 205–227.

Eckberg, D.L., 2003. The human respiratory gate. Journal of Physiology 548, 339–352.

Evans, K.C., Shea, S.A., Saykin, A.J., 1999. Functional MRI localisation of central nervous system regions associated with volitional inspiration in humans. Journal of Physiology 520, 383–392.

Gray, J.A., 1978. The neuropsychology of anxiety. British Journal of Psychology 69, 417–434.

Gray, J.A., McNaughton, N., 1996. The neuropsychology of anxiety: reprise. Nebraska Symposium on Motivation 43, 61–134.

Grossman, P., 1992. Respiratory and cardiac rhythms as windows to central and autonomic biobehavioral regulation: selection of window frames, keeping the panes clean and viewing the neural topography. Biological Psychology 34, 131–161.

Grossman, P., Karemaker, J., Wieling, W., 1991. Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: the need for respiratory control. Psychophysiology 28, 201–216.

Grossman, P., Kollai, M., 1993. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. Psychophysiology 30, 486–495.

Grossman, P., Stemmler, G., Meinhardt, E., 1990. Paced respiratory sinus arrhythmia as an index of cardiac parasympathetic tone during varying behavioral tasks. Psychophysiology 27, 404–416.

Grossman, P., Wientjes, C., 1986. Respiratory sinus arrhythmia as cardiac parasympathetic index: empirical data bearing upon conceptual issues and quantification techniques. In: Grossman, P., Janssen, K., Vaitl, D. (Eds.), Cardiorespiratory and Cardiosomatic Psychophysiology. Plenum, New York, pp. 117–138.

Hawkley, L.C., Masi, C.M., Berry, J.D., Cacioppo, J.T., 2006. Loneliness is a unique predictor of age-related differences in systolic blood pressure. Psychology of Aging 21, 152–164.

Jackson, J.H. 1884. Evolution and dissolution of the nervous system (Croonian Lectures). Reprinted in: Taylor, J. (Ed.), 1958, Selected writings of John Hughlings Jackson. Basic Books, New York.

Kollai, M., Kollai, B., 1992. Cardiac vagal tone in generalised anxiety disorder. British Journal of Psychiatry 161, 831–835.

Kollai, M., Mizsei, G., 1990. Respiratory sinus arrhythmia is a limited measure of cardiac vagal tone. Journal of Physiology (London) 424, 329–342.

Loewy, A.D., Spyer, K.M., 1990. Vagal preganglionic neurons. In: Loewy, A.D., Spyer, K.M. (Eds.), Central Regulation of Autonomic Functions. Oxford University, London, pp. 68–87.

McKay, L.C., Evans, K.C., Frackowiak, R.S., Corfield, D.R., 2003. Neural correlates of voluntary breathing in humans. Journal of Applied Physiology 95, 1170–1178.

O'Leary, D.M., Jones, J.F., 2003. Discharge patterns of preganglionic neurones with axons in a cardiac vagal branch in the rat. Experimental Physiology 88, 711–723.

Ritz, T., Dahme, B., 2006. Implementation and interpretation of respiratory sinus arrhythmia measures in psychosomatic medicine. Psychosomatic Medicine 68, 617–627.

Smejkal, V., Druga, R., Tintera, J., 2000. Brain activation during volitional control of breathing. Physiological Research 49, 659–663.

Snieder, H., Boomsma, D.I., Van Doornen, L.J., De Geus, E.J., 1997. Heritability of respiratory sinus arrhythmia: dependency on task and respiration rate. Psychophysiology 34, 317–328.

von Leupoldt, A., Dahme, B., 2005. Cortical substrates for the perception of dyspnea. Chest 128, 345–354.