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Cardiac Psychophysiology and Autonomic Space in Humans: Empirical Perspectives and Conceptual Implications

Gary G. Berntson, John T. Cacioppo, and Karen S. Quigley

Contemporary findings reveal that autonomic control of dually innervated visceral organs does not lie along a single continuum extending from parasympathetic to sympathetic dominance. Rather, a bivariate autonomic space bounded by sympathetic and parasympathetic axes is the minimal representation necessary to capture the modes of autonomic control. We here empirically instantiate a quantitative bivariate model for the chronotropic control of the heart in humans. This model provides a more comprehensive characterization of psychophysiological response than simple measures of end-organ state and permits a differentiation of behavioral states and processes that would otherwise remain obscure. The model also illuminates and subsumes general principles such as the law of initial values and reveals a fundamental physiological rationale for the selection of heart period over heart rate as a metric for cardiac chronotropy. The present article also considers strategies for psychophysiological investigations within the autonomic space model, the limitations of these methods, and analytical tools for assessing their validity.

The psychophysiological approach capitalizes on both inherent and acquired links between the behavioral and physiological domains. This approach seeks to develop integrated theoretical perspectives on behavioral–physiological relationships and often uses physiological measures to illuminate behavioral states and processes. What has emerged clearly from the literature is that psychological variables can significantly impact on physiological function and that physiological processes are important determinants of behavior (Cacioppo & Berntson, 1992). These relationships assume special significance for the study of psychosomatic functions and dysfunctions and offer important tools for studies of emotion, motivation, learning, memory, and other cognitive processes. One complication in the psychophysiological approach is that behavioral and physiological concepts and measures are rarely isomorphic but rather evidence many-to-one mappings between these domains (Cacioppo & Tassinary, 1990). An understanding of these mappings is important in deriving psychophysiological inferences and can greatly enhance the potential utility of psychophysiological approaches.

Relationships between behavioral processes and visceral reactions comprise a complex stream of transformations, from contextual variables to central behavioral states to patterns of autonomic outflow to functional effects on target organs. Although physiologists and neuroscientists have tended to focus on a limited set of these transformational stages, the problems and issues addressed by psychophysiologists and behavioral scientists frequently entail this entire transformational cascade. The differences in experimental questions and levels of analysis across disciplines has undoubtedly hindered their integration (Cacioppo & Berntson, 1992). Fortunately, that integration is currently underway, as physiologists recognize the importance of behavioral variables on autonomic function and as psychophysiological models evidence increasing physiological sophistication (Berntson, Cacioppo, & Quigley, 1991; Berntson, Cacioppo, Quigley, & Fabro, in press; J. R. Jennings, 1992; Porges, 1986; Somsen, Molenaar, van der Molen, & Jennings, 1991; Stemmler, Grossman, Schmid, & Foerster, 1991). The interdisciplinary perspective is especially important in efforts to clarify the mappings between psychological and physiological processes.

The traditional *doctrine of autonomic reciprocity* held that the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) are subject to reciprocal central control, with increasing activity of one branch associated with decreasing activity of the other. Contemporary findings, however, reveal that autonomic control of dually innervated target organs cannot adequately be viewed as a continuum extending from parasympathetic to sympathetic dominance. It is now clear that the two autonomic branches can vary reciprocally, independently or coactively (Berntson et al., 1991; Berntson et al., in press; Fukuda, Sato, Suzuki, & Trzebski, 1989; Iwata & LeDoux, 1988; Koizumi, Kollai, & Terui, 1986; Koizumi, Terui, & Kollai, 1983; Obrist, Wood, & Perez-Reyes, 1965; Quigley & Berntson, 1990). Consequently, a bivariate autonomic space with orthogonal sympathetic and parasympathetic axes is the minimal representation necessary to capture the multiple modes of autonomic control. This is important in mapping behavioral–physiological relationships, as simple measures of end-organ state may not provide an accurate reflection of the underlying autonomic response. Because the two autonomic divisions exert opposing control over the heart, a concurrent activation of sympathetic and parasympathetic controls, for example, may not yield an alteration in heart period. Similarly, a given tachycardic response may arise from distinct autonomic origins, such as sympathetic activation, parasympathetic with-

Gary G. Berntson, John T. Cacioppo, and Karen S. Quigley, Department of Psychology, Ohio State University.

Correspondence concerning this article should be addressed to Gary G. Berntson, 48 Townshend Hall, Ohio State University, Columbus, Ohio 43212. Electronic mail may be sent to gberntso@magnus.acs.ohio-state.edu (INTERNET).

drawal, or both. Failure to recognize these alternative origins can obscure psychophysiological relationships. This is illustrated by the conditioning study of Iwata and LeDoux (1988), which reported equivalent tachycardic responses to a conditioned stimulus (CS) in conditioned and pseudoconditioned rats. When viewed from the restricted perspective of the doctrine of reciprocity, these findings suggest that cardiac measures may not be sensitive to the learning history of the subjects. The similar tachycardic responses of the two groups of animals, however, were found to arise from distinct patterns of autonomic reaction. The tachycardia of pseudoconditioned animals arose from selective sympathetic activation, but that of conditioned animals was due to a notable coactivation of both autonomic divisions. When viewed from this broader autonomic perspective, the psychophysiological responses clearly differentiated among the groups—a differentiation that would not be apparent from simple measures of end-organ state.

In a recent theoretical article, we developed a quantitative model of autonomic control and consequence, grounded in contemporary understandings of autonomic physiology and applied to psychophysiological issues and approaches (Berntson et al., 1991). In the present article, we empirically instantiate this conceptual model for autonomic control of cardiac chronotropy in humans. This quantitative model subsumes the doctrine of autonomic reciprocity within a broader conception of the modes of autonomic control (Berntson et al., 1991). As illustrated in Figure 1, this model entails a bivariate autonomic plane bounded by sympathetic and parasympathetic axes. Any basal locus on this plane is specified by its cartesian coordinates along the autonomic axes, and phasic autonomic responses are characterized by time-related movements within this plane. This autonomic plane represents all possible combinations of activities of the two autonomic divisions. Given a two-dimensional representation of autonomic control, the functional state of a target organ can be represented along a third (*z*-axis) dimension (Lévy & Zieske, 1969). The functional state of the target organ for any location in autonomic space can be expressed by the following general equation (Berntson et al., 1991):

$$\text{Equation 1: } f_{ij} = \beta + c_s \cdot s_i + c_p \cdot p_j + I_{ij} + \epsilon,$$

where f_{ij} is the functional state of the target organ for any i (sympathetic) and j (parasympathetic) locus on the autonomic plane, β is the basal state in the absence of autonomic input, s_i and p_j are the independent activities of the sympathetic and parasympathetic innervations at point ij, and c_s and c_p are coupling coefficients that reflect the relative functional impact of sympathetic and parasympathetic activities on the target organ. For illustrative purposes, potential interactions among the ANS divisions are expressed in the general term I_{ij}, which can be expanded into polynomial components ($s_i \cdot p_j$, $s_i^2 \cdot p_j$, $s_i \cdot p_j^2$, $s_i^2 \cdot p_j^2$, . . .). Finally, ϵ is an error term.

Equation 1 represents a general form of the quantitative model of Levy and Zieske (1969) for the autonomic control of the heart.[1] The terms of this equation reflect the three principles of autonomic control outlined by Berntson et al. (1991). The *principle of innervation* states that target organs can be either singly or dually innervated by the autonomic branches. For dually innervated organs, both coupling coefficients are nonzero, whereas for singly innervated organs, one coefficient assumes the value of zero. The *principle of conjoint action* maintains that the two autonomic divisions may have either opposing or synergistic actions on dually innervated organs. This principle is manifest in the signs of the coefficients, c_s and c_p, which are equivalent for concordant actions and opposite for antagonistic actions. Finally, the *principle of multiple modes* stipulates that the two autonomic branches may vary reciprocally, independently or coactively. This principle is captured by the separate i and j indices on the activation functions s_i and p_j.

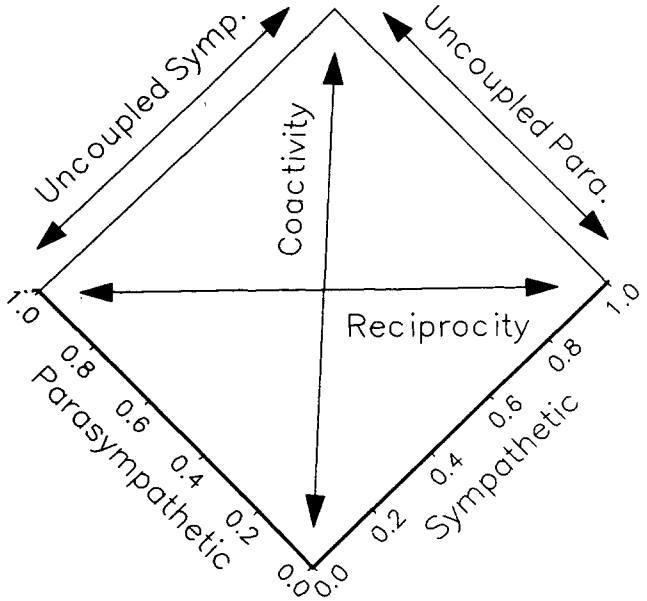

Figure 1. Two-dimensional representation of autonomic space. (Axes are expressed in proportional units of activation of the sympathetic and parasympathetic branches. The arrow extending from the left to the right axes intersections depicts the diagonal of reciprocity. The arrow extending from the back to the front axes intersections represents the diagonal of coactivity. The arrows along the axes depict uncoupled changes in the single autonomic nervous system divisions. These arrows, and vectors parallel to them, illustrate the major modes of autonomic control.)

Equation 1 characterizes the functional state of a target organ for any locus in autonomic space and thus describes an effector surface overlying the bivariate autonomic plane. In a recent article, we further developed and empirically instantiated this general model of autonomic space for cardiac chronotropic control in the rat (Berntson et al., in press). Based on studies

[1] Levy and Zieske (1969) proposed a more expanded form of this equation, which included higher order polynomial components. As documented in the present article, and by Levy and Zieske, however, these higher order nonlinear components capture only a small proportion of the variance. Levy and Zieske used direct neural stimulation to drive the cardiac nerves of the dog. Their primary interest was in interactions among the autonomic branches, and they did not address the issue of autonomic modes of control. A major departure of the present article is that natural behavioral stimuli can evoke a wide range of control modes, and hence a bivariate equation is necessary to represent psychophysiological responses.

from our own laboratory and from the literature, we defined the parameters of Equation 1 and described the chronotropic effector surface for this species (Berntson et al., in press). In the present article, we extend this development to the autonomic control of cardiac chronotropy in humans. First, we formally document the need for a bivariate model of autonomic control and consider the derivation of the parameter estimates necessary to define this effector surface. We then consider the available information on autonomic chronotropic space in humans and address the limitations in parameter estimates and caveats in psychophysiological applications. Finally, we show that the autonomic space model (a) provides a more comprehensive characterization of cardiac response than simple measures of end-organ state; (b) permits a parsing of the multiple transformations underlying psychophysiological responses; (c) extends, illuminates, and subsumes psychophysiological principles such as the law of initial values; (d) reveals the interpretive advantages of heart period as a metric for cardiac chronotropy; and (e) has fundamental implications for the direction and interpretation of a broad range of psychophysiological studies.

Autonomic Chronotropic Space in Humans and Rats

The instantiation of a quantitative model of autonomic space requires specification of four sets of parameters that define the terms of Equation 1. These include (a) the intrinsic heart period (β) that represents the null point of autonomic control; (b) the minima and maxima (dynamic ranges) of the sympathetic and parasympathetic axes, which define the relative impact of the autonomic branches and the values of the coefficients c_s and c_p; and (c) the potential interactions among the branches, which allow specification of the interaction term (I_{ij}). These parameters permit the construction of an effector surface for chronotropic control of the heart. The intrinsic heart period in the absence of autonomic influences (β) represents the basal starting point for autonomic control (0, 0 axes intersection of Figure 1). The dynamic ranges of the autonomic branches specify the coefficients c_s and c_p of Equation 1, which represent the range of chronotropic control (in milliseconds) for the sympathetic and parasympathetic branches. These coefficients thus represent scaling factors that capture the relative functional effects of the autonomic branches on the heart. With the autonomic axes expressed in proportional units of activation (0 to 1), the intrinsic heart period (β) together with the values of the coefficients (c_s and c_p) define the longest heart period under maximal vagal and minimal sympathetic control (0, 1 axis intersection) and the shortest heart period under maximal sympathetic and minimal vagal control (1, 0 axis intersection). The final axis intersection (1, 1) is defined by the additive effects of maximal sympathetic and maximal vagal control, adjusted by the interaction term (I_{ij}).

We have empirically instantiated this general model of autonomic space by defining these parameters for chronotropic control in the rat (Berntson et al., in press). A considerable literature also provides estimates of the terms of Equation 1 for human subjects. This literature highlights additional complexities in the human, including individual differences related to age, aerobic condition, and other factors. In the present section, we develop a preliminary model of autonomic chronotropic space and its effector surface in humans, and we demonstrate the general similarity of its surface features to those of the rat. We also consider limitations and caveats in the application of this model and detail the necessary information and strategies for the further development and refinement of this model. Finally, we consider the utility and implications of this model for psychophysiology.

Effector Transform Functions: Autonomic Outflows and Effector State

Considerable evidence documents an essentially linear relationship between vagal activity and cardiac chronotropy (as indexed by heart period). One of the more definitive lines of evidence comes from direct stimulation of vagal cardiac nerves, which reveals an approximately linear relationship between stimulation frequency and heart period in a wide range of species, including humans, dogs, cats, and rabbits (Berger, Saul, & Cohen, 1989; Berntson, Quigley, Fabro, & Cacioppo, 1992; Carlson et al., 1992; Dexter, Levy, & Rudy, 1989; Ford & McWilliam, 1986; Furukawa, Wallick, Carlson, & Martin, 1990; Parker, Celler, Potter, & McCloskey, 1984; Stramba-Badiale et al., 1991; Versprille & Wise, 1971). Further support comes from neurophysiological recording studies of endogenous vagal activity, which again reveal a linear relationship between heart period and vagal outflow (Jewett, 1964; Katona, Poitras, Barnett, & Terry, 1970; Koizumi, Terui, & Kollai, 1985). Because linear relationships in biological systems are rare, the linearity between vagal outflow and cardiac chronotropy may be somewhat surprising. Evidence from physiology, neuropharmacology, and neurobiology reveals that this linearity represents a contingent consequence of multiple nonlinear processes. According to the quantitative neurobiological model of Dexter et al. (1989), the linearity of vagal control of cardiac chronotropy arises as a result of two principal nonlinear processes. These are (a) a negatively accelerating exponential function between vagal activity and the accumulation of acetylcholine at cardiac synapses and (b) a positively accelerating exponential function relating acetylcholine concentration and pacemaker activity. The net effect of these two nonlinear processes is an essentially linear relationship between vagal activity and cardiac chronotropy. Indeed, this linearity appears to be a generalized feature of autonomic chronotropic control in mammals.

Of particular relevance to the present consideration are the autonomic–effector relationships in the human in comparison to the rat. In a recent vagal stimulation study, we confirmed the linearity between vagal frequency and heart period in rats (Berntson et al., 1992). Regression of heart period on stimulation frequency revealed that between 93% and 99% of the variance in heart period could be accounted for by a linear function. Although there is a limited literature on the shape of the functions relating autonomic outflow to chronotropic control in humans, the existing data confirm the generality of this linear relationship. Direct electrical stimulation of cardiac nerves in humans was accomplished early in this century on revived hearts (Kountz, Pearson, & Koenig, 1934). Two more recent studies have systematically examined the relationship between stimulation frequency and cardiac chronotropy (Carlson et al., 1992; Carlsten, Folkow, & Hamberger, 1957). Both studies reveal a linear relationship between stimulation frequency and

heart period up to maximal levels.[2] Thus, a linear relationship between vagal activity and cardiac chronotropy appears to characterize virtually every mammalian species examined, including humans.

Stimulation of sympathetic cardiac nerves also reveals an approximately linear relationship between sympathetic activity and cardiac chronotropic control, up to asymptotic levels. As with vagal stimulation, the linearity between stimulation frequency and heart period appears to be species general (Berger et al., 1989; Levy & Zieske, 1969; Rosenbleuth, 1932). Similarly, a linear function has been reported between endogenous sympathetic activity and heart period over a wide dynamic range (Koizumi et al., 1985). Together, these studies uniformly indicate that the transforms between autonomic outflows and heart period are essentially linear up to asymptotic levels.

Intrinsic Heart Period: β

The intrinsic heart period reflects the zero point of autonomic control (β). This can be estimated by dual pharmacological blockade of the autonomic branches.[3] For the Sprague-Dawley rat, reported basal heart period under relatively complete dual blockade has been quite consistent, ranging from 158 ms (Head & McCarty, 1987) to 161 ms (Corre, Cho, & Barnard, 1976) to 166 ms from our laboratory. The average of these values (162 ms, corresponding to a heart rate of 370 beats per minute, bpm) provides an estimate of β, or the basal chronotropic state of the rat heart at the (0, 0) intersection of Figure 1 (Berntson et al., in press).

Similarly, estimates of intrinsic heart period in humans as derived from dual autonomic blockade are highly reliable, with a mean test–retest discrepancy over a 1-week interval of 10 ms (Jose, Stitt, & Collison, 1970). There are, however, notable individual differences in this intrinsic heart period level. As derived from the data of Sutton, Cole, Gunning, Hickie, and Seldon (1967), the distribution of intrinsic heart period approximated the normal for a large group of students (n = 70, 18–26 years old) with a mean of 561 ms and a rather wide standard deviation (60 ms). These individual differences in intrinsic heart period are partly attributable to a significant relationship between β and aerobic capacity. In the Sutton et al. (1967) study, the 14 subjects with the highest aerobic capacities (>50 ml O_2/kg/min) evidenced a mean intrinsic heart period of 667 ms, compared with an overall mean of 561 ms. Moreover, the relationship between aerobic capacity and β appears to be causal, because an explicit endurance regimen can yield significant within-subject increases in intrinsic heart period (Kingwell, Dart, Jennings, & Korner, 1992; Sutton et al., 1967). Table 1 depicts the intrinsic heart period obtained across a number of studies selected for the relatively effective levels of autonomic blockade used.[4] As is apparent in Table 1, postural variables can lead to rather dramatic changes in autonomic control of resting heart period, although β remains relatively stable across these postural manipulations. The means listed in Table 1 also confirm the general relationship between intrinsic heart period and aerobic capacity, with trained subjects displaying a mean β of 742 ms, compared with 617 ms under similar conditions for untrained subjects.

Additional factors also appear to systematically influence β. For example, Jose et al. (1970) reported a significant increase in intrinsic heart period with age (4 ms/year). Although considerable individual differences clearly exist in the value of β, to an appreciable extent these differences appear to be systematic rather than random. This fact, together with the high test–retest reliability of β, suggests that dual blockade offers a viable approach to the determination of intrinsic heart period (Jose et al., 1970). Moreover, empirical refinement of the quantitative relationships between β and age, aerobic condition, and other potential determinants may offer the basis for a viable estimate of β even in the absence of explicit autonomic blockade.

Axes End Points and Dynamic Ranges

Parasympathetic control. Potent parasympathetic reflexes and direct stimulation of vagal nerves can provide converging estimates of the dynamic range of parasympathetic control. An estimate of maximal parasympathetic control for the rat (0, 1 axis intersection of Figure 1) can be derived from the dive reflex. This reflex is a potentially life-preserving response to submersion, triggered by trigeminal afferents and amplified by chemoreceptor reflexes (Blix & Folkow, 1983; Daly, 1984; Elsner & Gooden, 1983). The dive reflex entails a redistribution of blood from the periphery to the central core, coupled with a massive vagal outflow. Although this reflex is most fully developed in diving species, it is also striking in rats, and it yields a dramatic vagal bradycardia and a virtually complete withdrawal of sympathetic cardiac tone (Lin, 1974). Two controlled studies of the dive reflex in unanesthetized rats revealed a rapid increase in heart period to a mean of 411 ms (403 ms, Huang & Peng, 1976; 419 ms, Lin, 1974). This heart period value provides one estimate of maximal parasympathetic effect on the heart. Convergence on this estimate comes from the results of direct stimulation of the vagus nerve (Berntson et al., 1992). The longest heart period attainable with vagal stimula-

[2] This was a particularly relevant study methodologically because stimulation was delivered directly to the pericardial fat pad containing selective vagal fibers to the sinus node. This minimizes potential indirect effects of activation of the greater vagal trunk.

[3] Surgical denervation associated with cardiac transplantation can also provide additional estimates. Transplant data are severely limited, however, by (a) potential trauma, biochemical changes secondary to transplantation, or both; (b) potential neural reinnervation of the heart over time; (c) the frequent polypharmacy administered to transplant recipients, and (d) the fact that the denervated heart remains responsive and may become hypersensitive to circulating catecholamines (Vatner et al., 1985). Moreover, a recent well-controlled animal study raises the possibility that cardiac denervation may yield a biased estimate of β, due to the disruption of potential trophic influences of the intact innervation (Randall, Randall, Brown, Yingling, & Raisch, 1992). Nevertheless, it is interesting to note that the range of resting heart periods reported in transplant patients (e.g., McLaughlin et al., 1978; Pope, Stinson, Daughters, Ingels, & Alderman, 1980; Sloan, Shapiro, & Gorman, 1990) corresponds closely to the distribution of intrinsic periods derived from dual autonomic blockade.

[4] Because receptor blockade is competitive (for the blockers used), antagonism of autonomic effects is relative. In the present article, we consider only results obtained with doses of the beta-adrenergic antagonist propranolol of at least 0.2 mg/kg (or 15 mg), and doses of atropine of at least 0.03 mg/kg (or 2 mg). These doses have been shown to achieve relatively complete autonomic blockade in humans (Epstein, Robinson, Kahler, & Braunwald, 1965; Jose & Taylor, 1969).

Table 1
Intrinsic Heart Period (β)

Study	Population	Age	Posture	Rest heart rate	Blockade (β)
Jose et al. (1970)	6 healthy males	*M* = 23	Supine	822	594
Katona et al. (1982)	10 healthy males	20–26	Supine	963	589
Lewis, Nylander, et al. (1980)	8 sedentary males	*M* = 26	Supine	857	582
Lewis, Thompson, et al. (1980)	10 sedentary males	*M* = 21	Supine	1,000	632
Nordenfelt (1971)	11 healthy males	20–34	Supine	909	625
Nyberg (1981)	6 healthy males	22–29	Supine	1,017	625
Ribeiro et al. (1991)	11 healthy males	*M* = 26	Supine	984	612
Robinson et al. (1966)	4 healthy males	19–28	Supine	1,132	652
Smith et al. (1989)	10 sedentary males	20–26	Supine	855	693
Sutton et al. (1967)	70 students	18–26	Supine	706	561
M				925	617
SD				120	38
Kelbaek et al. (1987)	6 males and 2 females	18–28	Sitting	822	619
Nyberg (1981)	Same 6 subjects as above		Sitting	915	645
Robinson et al. (1966)	Same 4 subjects as above		45° tilt	896	632
M				878	632
SD				49	13
Nyberg (1981)	Same 6 subjects as above		Standing	789	588
Robinson et al. (1966)	Same 4 subjects as above		80° tilt	732	619
Sato et al. (1980)	9 healthy males	23–31	Standing	682	631
M				734	613
SD				54	22
Grand mean				880	619
SD				122	32
	Endurance-trained subjects				
Katona et al. (1982)	8 male oarsmen	20–25	Supine	1,090	741
Lewis, Nylander, et al. (1980)	8 male cyclists	*M* = 21	Supine	1,132	714
Savin et al. (1982)[a]	6 athletic males	19–41	Supine	1,017	759
Smith et al. (1989)	10 male runners	*M* = 25	Supine	1,097	755
M				1,084	742
SD				48	20

Note. All estimates of intrinsic rate (β) are derived from resting heart period under dual autonomic blockade. Vagal blockade was achieved in all studies by a minimal atropine dose of 0.03 mg/kg (or 2 mg). Sympathetic blockade was achieved in all studies by a minimal propranolol dose of 0.2 mg/kg or a minimal dose of metoprolol, a cardioselective $beta_1$ blocker, of 0.17 mg/kg.
[a] Four of the 6 subjects were runners (15–50 mi, or 24–80 km, per week); the other 2 were moderately athletic.

tion in the rat, prior to the emergence of arrhythmias or sinus block, averaged 401 ms, which closely approximates that identified from the dive reflex (411 ms). The average of the longest heart period values derived from the dive reflex and from vagal stimulation yield an estimated maximal parasympathetic control of 406 ms (in the absence of sympathetic influences). In fact, however, both vagal stimulation and the dive reflex can yield even longer heart period values. These extremes are generally associated with cardiac arrhythmias or even sinus block and probably represent levels of vagal control that are not normally encountered. Given an operational limit of 406 ms for vagal control of heart period, and an intrinsic heart period of 162 ms, the dynamic range of vagal chronotropic control is 244 ms (Berntson et al., in press).

Similar lines of evidence are available for humans. Human data are available on the effects of potent vagal reflexes, including the dive reflex, the chemoreceptor reflex, and the oculocardiac reflex. Consistent with the results from rats, these studies reveal a wide dynamic range of vagal control of cardiac chronotropy in humans. As in animals, the dive reflex exerts potent control over vagal outflow in humans. As illustrated in Table 2, the dive reflex can yield a profound bradycardia in human subjects. This bradycardia is blocked by atropine, revealing its fundamental vagal origin (Elsner & Gooden, 1983; Heistad, Abboud, & Eckstein, 1968).

Considerable variation emerges across studies and subjects in the magnitude of diving bradycardia, however, and multiple factors affect its magnitude, including the degree of hypoxia, depth of the dive, and experience of the diver (Elsner & Gooden, 1983; Gooden, 1982). Moreover, stressors such as mental arithmetic can attenuate the dive reflex presumably by triggering a counteracting vagal withdrawal or sympathetic activation (Gooden, 1982; Ross & Steptoe, 1980). Although most studies report more moderate responses, under optimal reflex conditions (cold water, depth, and experienced divers) extreme levels of vagal cardiac control can be demonstrated in humans. Heart periods greater than 3,000 ms (20 bpm) have been reported with breath-hold dives (R. W. Arnold, 1985; Elsner &

Table 2
Maximal Parasympathetic Effect on Heart Period

Study	Method	Population	Age	HP_{max}[a]
Arnold (1985)	Breath-hold face immersion	18 males and 9 females	16–54	>4,000[b]
Carlson et al. (1992)	Vagal nerve stimulation	13 cardiac patients	57 ± 5	2,993[c]
Ferrigno et al. (1991)	Depth diving (100 s)	3 divers	27–56	3,000
Heidorn & McNamara (1956)	Carotid sinus massage	40 healthy males	25–58	2,000–5,700[d]
Landsberg (1974)	Breath-hold dive (135 s)	8 adult divers	24–60	2,500
Schamroth (1958)	Oculocardiac reflex	28 healthy nurses	?	4,000[c]

[a] Estimate of maximal vagally driven heart period (in milliseconds). [b] Five (4 male and 1 female) of 27 subjects showed peak diving bradycardia lower than 15 beats per minute (bpm), the lowest being 5.6 bpm. [c] All subjects showed bradycardia, 5 of the 28 had sinus arrest up to 4 s in duration. [d] Nine of 40 subjects showed ventricular asystole for 2–5.7 s (5 from sinoatrial arrest and 4 from atrioventricular block). [e] Most patients had coronary artery disease, 4 had Wolff-Parkinson-White syndrome, 1 had aortic stenosis, and 1 had dilated cardiomyopathy. Two subjects evidenced transient cardiac arrest on stimulation. The value given is the mean maximal cycle length (SE = 661).

Gooden, 1983; Ferrigno et al., 1991; Folgering, Wijnheymer, & Geeraedts, 1983). Extreme vagal control is further indicated by the frequent occurrence of cardiac arrhythmias during the dive reflex, and it has been suggested that associated sinus block or cardiac arrest may contribute to untoward sudden underwater deaths (Elsner & Gooden, 1983).

The hypoxia associated with apneic dives triggers powerful chemoreceptor reflexes that amplify the vagal bradycardia of the dive reflex. Hypoxia also exerts direct biphasic nonautonomic effects on heart period that can confound estimates of the vagal contribution (Jose & Stitt, 1969). Other vagal maneuvers, however, can evoke similar levels of extreme bradycardia in the absence of significant hypoxia. As illustrated in Table 2, both carotid sinus massage and the oculocardiac reflex (to ocular pressure) can also yield vagally driven heart periods of greater than 3,000 ms in humans. Again, these extremes are generally associated with a variety of cardiac arrhythmias, including sinus block.

Further documentation of the potency of parasympathetic chronotropic control comes from direct electrical stimulation of the vagal innervation of the heart in humans. Carlson et al. (1992) report that vagal stimulation yielded an average maximum heart period of 2,993 ms in a group of 13 patients and resulted in complete cardiac arrest in 2 subjects. (Sinus rhythm returned on stimulation offset.) Although interpretation of these results may be complicated by the presence of clinical pathology (see Table 2), most of the subjects underwent surgery for coronary artery disease rather than for rhythm disturbances. Moreover, these results are highly consistent with studies in normal animals that demonstrate that vagal stimulation can yield extremes of bradycardia, including sinus arrest (Berntson et al., 1992).

The findings outlined above are consistent in revealing that vagal activation can yield a powerful inhibitory influence on cardiac chronotropy, which can in fact exceed that observed under typical physiological conditions. Indeed, there may be no fundamental limit to vagal chronotropic control in humans, prior to the point of sinus arrest or conduction block. Hence, the selection of a specific value for maximal parasympathetic control is somewhat arbitrary. The extreme levels of vagal control documented above are beyond the normal physiological regulation of the heart and are not typically encountered naturally. For initial development of autonomic space for humans, a conservative estimate of maximal parasympathetic control can be derived as the lower confidence limit of the mean heart period obtained with vagal stimulation (2,332 ms, or 26 bpm; Carlson et al., 1992). Although the extremes of reflex bradycardia detailed in Table 2 can exceed this value, these extreme levels are generally seen in only a modest percentage of subjects. The 2,332-ms boundary derived from stimulation, however, was achieved or exceeded by the mean dive reflex across all 8 subjects of the Ferrigno et al. (1991) study, and by each of the 3 divers of the Landsberg (1974) study. Because extremes of vagal control may exceed this 2,332-ms value, however, it should be viewed as an operating boundary rather than an absolute physiological limit.

In summary, the above findings reveal that vagal control of the heart can be sufficiently potent to yield complete sinus arrest. At the same time, extreme levels of reflexive vagal control may not be representative of all subjects and are not typically encountered in normal function. The value of 2,332 ms as derived above represents a realistic starting point for the development of a model of autonomic space in the human. For a mean intrinsic heart period (β) of 619 ms (see Table 1), this would represent a dynamic range of 1,713 ms for vagal control of the heart.

Sympathetic control. Estimates of maximal sympathetic control can be derived from potent sympathoexcitatory conditions such as exercise, baroreflex activation, or the effects of beta-adrenergic agonists. We have used data from each of these sources to derive an estimate of maximal sympathetic control in the rat (Berntson et al., in press). Strenuous exercise in the rat yields complete parasympathetic withdrawal, maximum sympathetic activation, and the shortest heart periods attainable (Bolter & Atkinson, 1988b; Corre et al., 1976; Ekblom, Kilbom, & Soltysiak, 1973). Reported heart periods under maximal exercise in rats generally range from 100 ms to 110 ms (Bolter & Atkinson, 1988b; Corre et al., 1976; Sonne & Galbo, 1980), yielding a mean estimate of the maximal-exercise heart period of 105 ms (571 bpm). After nonautonomic (thermal) contributions to the effect of exercise are extracted (Bolter & Atkinson, 1988b), an estimate of peak sympathetically driven heart period for the rat is 120 ms (500 bpm). Converging evidence on this value comes from data on the baroreflex and from direct administration of adrenergic agonists.

Variations in blood pressure are monitored by arterial baroreceptors, which exert potent reflexive control over autonomic outflows. Decreases in blood pressure, for example, lead to

sympathetic activation and parasympathetic withdrawal. Head and McCarty (1987) demonstrated that extreme hypotension yields maximal baroreflex activation of sympathetic outflow and virtually complete inhibition of vagal control of the heart (see also Berntson et al., in press). At asymptotic levels, the baroreflex yielded a peak sympathetically driven heart period of 119 ms. This index of maximal sympathetic control, which is largely unconfounded by thermal effects, is highly comparable to the estimated 120 ms derived from exercise data. Further converging data come from the finding of Bolter and Atkinson (1988b) that the shortest heart period obtainable with the beta-adrenergic agonist isoproterenol was 122 ms in vivo and 120 in vitro, which converges closely on the former estimates. Based on these converging lines of evidence, peak sympathetic drive yields a minimal heart period of 120 ms for the rat. Given an intrinsic heart period (β) of 162 ms, this yields a dynamic range of sympathetic chronotropic control of 42 ms.

Parallel data on the dynamic range of sympathetic chronotropic control are also available for humans, although species differences must be considered in deriving accurate parameter estimates. The baroreflex yields maximal or near-maximal activation of sympathetic chronotropic control in the rat and yields an estimate of sympathetic control that closely converges on that derived from beta-adrenergic agonists and from exercise (Head & McCarty, 1987; see also Berntson et al., in press). In a comprehensive study, Robinson, Epstein, Beiser, and Braunwald (1966) examined the baroreflex in humans under single and dual autonomic blockades during both rest and moderate exercise. An estimate of the dynamic range of sympathetic chronotropic control can be derived from these data by the baroreflex-induced heart period responses under parasympathetic blockade. The minimum asymptotic heart period achieved at the lowest arterial pressures averaged 461 ms. From the intrinsic heart period (β) of 663 ms for these subjects, this yields an estimated dynamic range of sympathetic control of 202 ms.

Infusions of epinephrine or other beta-adrenergic agonists lead to decreases in heart period by direct activation of cardiac beta-receptors and can provide another index of maximal potential sympathetic effects. Unfortunately, direct and indirect effects of these agents on vascular or other organ systems can lead to reflexive changes in vagal outflow or result in other alterations that confound estimates of direct adrenergic chronotropic actions (J. M. O. Arnold & McDevitt, 1984). A number of studies, however, have controlled for potential reflexive confounds by additional pharmacological blockades. Among the more thorough are the reports of G. Jennings, Bobik, Oddie, Hargreaves, and Korner (1983) and Martinson, Lindvall, Melcher, and Hjemdahl (1989) that examined the chronotropic effects in healthy subjects of the cardioselective $beta_1$ agonist prenalterol, the nonspecific beta-adrenergic agonist isoproterenol, or both. Both included Dose × Response studies of these agonists during blockade with atropine (to preclude reflexive vagal contributions) and alpha-adrenergic blockade with clonidine (to minimize vascular effects). Over four separate studies, the mean heart period increase at maximal doses of the agonists was 230 ms.[5] For three of the four studies, responses were clearly approaching asymptotic levels at the highest doses. Although in vivo agonist studies can be problematic given potentially widespread actions of the agents, these well-controlled Dose × Response studies yielded an estimate of maximal sympathetic control that is only slightly larger than that derived from the baroreflex (230 ms vs. 202 ms).

Considerable data are also available on autonomic control of heart period during exercise in humans. In contrast to the rat, however, maximal exercise does not appear to offer a viable index of the dynamic range of sympathetic chronotropic control in humans. This is because nonautonomic factors in the human appear to decrease heart periods sufficiently to approach physiological limits of the pacemaker, which may mask the potential impact of autonomic sympathetic control.

As is the case for the rat, maximal exercise (maximal oxygen consumption, Vo_{2max}) in humans yields powerful sympathetic activation and virtually complete withdrawal of parasympathetic chronotropic control (Atterhög & Loogna, 1977; Davies, Brotherhood, Few, & ZeidiFard, 1976; Ekblom, Goldbarg, Kilbom, & Astrand, 1972; Ribeiro, Ibanez, & Stein, 1991; Rowell, 1986). The minimum heart period observable in normal human adults is consistently achieved during maximal exercise, which for young healthy adults generally ranges from about 300 ms to 324 ms (185–200 bpm; Rowell, 1986). This heart period decrease, however, is to a significant extent attributable to nonautonomic contributions from thermal, metabolic, and mechanical variables (Jose et al., 1970; Rowell, 1986). These nonautonomic contributions to maximal-exercise heart period can be estimated by the effects of exercise during dual autonomic blockade, because the influences of both autonomic branches would be precluded. Table 3 summarizes the results of studies of autonomic blockade at maximal or near-maximal exercise heart periods (see Footnote 4). This table illustrates the intrinsic heart period ($M = 630$ ms), the maximal-exercise heart period (324 ms), and the maximal-exercise heart period under sympathetic or dual blockade (448 ms). These data reveal an overall mean exercise heart period response of −306 ms, a nonautonomic component of −182 ms, and an autonomic sympathetic component of only −124 ms. This is considerably less than the estimate derived above from the baroreflex and from the direct effects of beta agonists.

This discrepancy may arise from notable species differences in the determinants of exercise tachycardia. For the rat, the predominant nonautonomic contribution to exercise heart period is temperature (Bolter & Atkinson, 1988a, 1988b), and parsing the thermal effect on heart period yields a residual sympathetic component that closely approximates other indices of maximal sympathetic control. In contrast, thermal effects on heart period during exercise are small in humans (Jose et al., 1970), although other nonautonomic contributions (e.g., metabolic) are considerable (Jose & Stitt, 1969; Rowell, 1986). These potent nonautonomic factors appear to decrease heart period toward its physiological limit (300 ms, Rowell, 1986) and thereby constrain the impact of sympathetic actions under maximal exercise in humans. This is supported by the fact that plasma catecholamine levels continue to rise up to maximal

[5] This 230-ms estimate also approximates the largest response (243 ms) obtained in revived, denervated, and externally perfused human hearts, when adrenalin was added to the perfusate (Kountz, Pearson, & Koenig, 1934).

Table 3
Autonomic Contributions to Heart Period During Maximal or Near-Maximal Exercise

Study	Method	Population	Mean age	Exercise minimum HP	Blockade HP			ANS Control[a]			
					Vagal	Sympathetic	Dual	Vagal	Sympathetic	β^b	HP_{max}[c]
Atterhög & Loogna (1977)	Cycle ergometer	6 healthy males	26	333	337	—	—	−4	—	—	—
Davies et al. (1976)	Treadmill	5 healthy males	36	324	325	—	—	−1	—	—	—
Ekblom et al. (1972)	Cycle ergometer	4 healthy males	?	313	316	—	—	−3	—	—	—
Jose et al. (1970)	Cycle ergometer	6 healthy males	23	330	—	—	454	—	−124	571	447
	(near maximal)	6 older males	50	375	—	—	504	—	−129	667	538
Lewis, Nylander, et al. (1980)[d]	Cycle ergometer	8 trained cyclists	21	326	—	—	444	—	−118	714	596
		8 untrained males	26	308	—	—	405	—	−97	583	486
Lewis, Thompson, et al. (1980)	Cycle ergometer	10 healthy males	21	331	—	—	464	—	−133	632	499
Ribeiro et al. (1991)	Cycle ergometer	11 healthy males	25	311	306	408	403	+5	−97	612	515
Wilmore et al. (1985)[e]	Treadmill	15 healthy males	24	303	—	401	—	—	−98	—	—
M				324	321	405	446	−1	−114	630	514

Note. All autonomic values are expressed in milliseconds of heart period (HP). In all cases, the minimum atropine dose was 0.025 mg/kg, and the minimum propranolol dose was 0.2 mg/kg. ANS = autonomic nervous system.
[a] Relative contributions of the two autonomic branches (in milliseconds) to heart period during peak exercise. Values were derived by subtracting the heart period after vagal or sympathetic blockade from the minimal heart period in the unblocked condition. If only dual blockades were given, the sympathetic contribution was estimated by the difference between heart periods under dual blockade and the unblocked condition. This is justified by the fact that the vagal division has no significant impact at maximum exercise. [b] Intrinsic heart period, estimated by the resting heart period under dual autonomic blockade. [c] Estimate of the heart period under maximal sympathetic chronotropic control, in the absence of other influences. [d] Essentially identical results were obtained with metoprolol (0.5 mg/kg), a cardioselective beta blocker. To check the completeness of blockade, additional doses of blockers were administered to a subset of subjects to ensure that no further change in heart period would ensue. [e] Subjects were given nondrug control tests, took propranolol (160 mg/day, orally) for 1 week and then were retested on exercise 2–3 hr after the last drug dose. A placebo control group revealed no difference in heart periods over the repeated tests under saline conditions.

exercise, suggesting a progressive sympathetic activation (Davies et al., 1976; Rowell, 1986). Moreover, although heart period also shows a progressive decrease up to maximal exercise levels (Ekblom et al., 1972; Ribeiro et al., 1991; Rowell, 1986), estimates of autonomic contributions to heart period plateau or begin to decline well before maximal exercise is achieved (Ribeiro et al., 1991; also apparent in Ekblom et al., 1972; Lewis, Nylander, Gad, & Areskog, 1980). This is consistent with a physiological constraint on sympathetic effects at maximal exercise levels, which leads to an underestimate of the dynamic range of sympathetic control of the human heart.[6] At the same time, however, these extreme effects of exercise emphasize the importance of nonautonomic determinants of heart period, which must be considered in any general model of chronotropic control. We return to this issue below.

The available data on exercise thus do not appear to offer a viable estimate of the dynamic range of sympathetic control in humans. Consequently, we rely on the estimate of the dynamic range of sympathetic control derived from the effects of adrenergic agonists. As noted above, this value (230 ms) is only slightly larger than that derived from the baroreflex (202 ms) and may offer the most viable index because the baroreflex does not appear to quite achieve maximal sympathetic activation (Berntson et al., in press; Head & McCarty, 1987). Consequently, the 230-ms value derived from the adrenergic agonist studies may afford a more realistic estimate of the dynamic range of sympathetic control of cardiac chronotropy in humans.[7] From a mean β of 619 ms (Table 1), peak sympathetic activation in the absence of vagal control could thus yield a minimal heart period of 389 ms (154 bpm), although the heart period could be further decreased by nonautonomic factors.

Quantitative Models of Chronotropic Control

The findings reviewed above permit specification of the parameters of Equation 1, which define the chronotropic effector

[6] Rather than simply limiting sympathetic effects, exercise could in fact reduce the gain of sympathetic effects and therefore alter the value of the sympathetic coefficient. This, however, does not appear to be the case. Although exercise may reduce the sensitivity of the baroreflex, the data of Robinson, Epstein, Beiser, and Braunwald (1966) indicate an equivalent overall dynamic range of sympathetic baroreflex control during rest and moderate exercise (see also DiCarlo & Bishop, 1992; Walgenbach-Telford, 1991). Indeed, the sympathetic component of the baroreflex was sufficiently potent to drive the heart period in 2 subjects very close to the maximal-exercise limit (331 ms and 337 ms), when intrinsic heart period was increased by moderate exercise. This finding is consistent with the general linearity between sympathetic activity and chronotropic control and suggests a constant sympathetic coefficient. It appears, however, that physiological constraints on minimal heart period (i.e., floor effects) may limit sympathetic manifestations at the extremes of exercise.

[7] It is possible that rapid, phasic sympathetic responses may have an increased impact on cardiac chronotropy. This would require expansion of the estimate of the dynamic range of sympathetic control, and hence the value of the sympathetic coefficient. In this case, autonomic control would still be represented on a single effector surface having a single maximal boundary. If maximal tonic control was found to be less than the phasic value, it would simply mean that tonic levels would not reach the absolute boundary.

surfaces for the autonomic control of the heart in humans and in rats. As is apparent below, the general features of these surfaces show notable similarities.

The chronotropic effector surface in the rat. Given the estimate of β (162 ms) and the dynamic ranges of the autonomic branches as defined above for the rat, Equation 1 becomes

$$\text{Equation 2: } f_{ij} = 162 - 42 \cdot s_i + 244 \cdot p_j + I_{ij} + \epsilon,$$

where the coefficients c_s and c_p are replaced by the signed dynamic ranges of the sympathetic and parasympathetic divisions and β is replaced by the intrinsic heart period.

In the absence of interactions, Equation 2 yields a cardiac effector surface that describes the heart period associated with any point on the autonomic plane (i.e., for all possible combinations of sympathetic and parasympathetic activity). The autonomic plane and effector surface as illustrated in Figure 2 (left panel) exhaustively represent all loci within autonomic space, and the chronotropic state of the heart for each locus within this space. Each of the autonomic axes ranges from 0 to 1, reflecting the proportional activation in the corresponding autonomic division. For illustration, the lengths of the axes are scaled relative to the overall dynamic range of sympathetic and parasympathetic chronotropic control (i.e., by the magnitude of the coefficients c_s and c_p). This normalizes directional displacements of a given distance on the effector surface to equivalent heart period changes.

The chronotropic effector surface in humans. The values derived above for human chronotropic control similarly permit the specification of the parameters for Equation 1 and define the cardiac effector surface for the human. Based on these parameters, Equation 1 becomes

$$\text{Equation 3: } f_{ij} = \beta - 230 \cdot s_i + 1{,}713 \cdot p_j + I_{ij} + \epsilon,$$

where the coefficients c_s and c_p are replaced by the signed dynamic ranges of the sympathetic and parasympathetic divisions. Unlike the rat, however, the tonic nonautonomic contributions continue to be represented by β, because considerable individual differences exist in this term.

Although the specific parameters of autonomic space for the human differ from those of the rat, the general features of its effector surface (Figure 2, right panel) are highly similar. In both species, chronotropic control is linearly related to autonomic neural activity, with the vagal branch having a considerably wider dynamic range than the sympathetic division. The extensive human research on individual differences in intrinsic heart period and its determinants, however, mandates the specification of the *z*-axis (heart period) units as a change from tonic nonautonomic basal values (β) rather than in absolute heart period values. Thus, β represents a tonic offset that anchors the *z*-axis scale.

As outlined above, the effects of exercise also document the influence of transient or phasic nonautonomic contributions to heart period, including nonautonomic factors such as temperature, hypoxia, hypercapnia, or other metabolic variables. These factors could be included in the β term, but there are reasons to parse these phasic determinants from the tonic contributions to intrinsic heart period. First, tonic nonautonomic contributions represent relatively enduring individual characteristics (Jose et al., 1970). Although β can be altered through aerobic conditioning, this is a relatively slow adjustment extending over weeks or months. Hence, within the temporal confines of most experiments, β represents a stable individual characteristic. In contrast, the phasic nonautonomic effects of temperature or exercise reflect factors that are common across subjects and are dependent on specific and defined contextual variables. We represent these phasic nonautonomic contributions to heart period by the term gamma (γ). Hence, Equation 3 becomes

$$\text{Equation 4: } f_{ij} = \beta + \gamma - 230 \cdot s_i + 1{,}713 \cdot p_j + I_{ij} + \epsilon,$$

where β represents the tonic nonautonomic contributions to intrinsic heart period and γ represents the phasic nonautonomic variations in heart period. Under typical resting conditions, gamma (γ) approaches zero (see below).

The autonomic plane and its effector surface as defined by Equation 4 represent a comprehensive model of autonomic control and its chronotropic consequence. As we consider below, this model has substantial implications for the design, quantification, and interpretation of psychophysiological studies.

Isoeffector contours. An important feature of the surfaces depicted in Figure 2 is that a given chronotropic state of the heart is ambiguous with regard to its autonomic origins. This is evident in the *isoeffector* contour lines on the autonomic planes of this figure. These contours illustrate the multiple loci on the autonomic plane that yield an equivalent physiological state of the target organ. These contour lines were derived by holding the right side (heart period) of Equations 2 and 4 constant, varying the value of s, and mapping its effect on p (or vice versa). The many-to-one mapping from the autonomic plane to the effector surface underscores the indeterminism when inferring changes in autonomic activities or behavioral processes based solely on changes in the functional state of dually innervated organs (Cacioppo & Tassinary, 1990). Because identical physiological outcomes may arise from different autonomic loci, information beyond a simple measure of end-organ state may be necessary to disambiguate autonomic origins of organ responses.

Phasic reactivity as movements within autonomic space. The cardiac effector surfaces of Figure 2 represent the chronotropic state of the heart associated with all possible loci in autonomic space. The baseline chronotropic state can thus be specified by the resting location in this autonomic space. Moreover, phasic responses can be characterized by the pattern of movement within autonomic space, which translates into a response trajectory across the autonomic plane and effector surface. Indeed, any change in the location on the autonomic plane would necessarily result in a corresponding movement on the effector surface. Given the existence of isoeffector contours, however, this may or may not manifest in an alteration of the physiological state of the organ. Consequently, time-varying locations in autonomic space provide an unambiguous account of autonomic response, whereas alterations in chronotropic state of the heart may not. Reciprocal modes of control are manifested by translations on the autonomic plane and effector surface along, or parallel to, the reciprocal diagonal of autonomic space (left-to-right axes intersections). In contrast, autonomic coactivation or

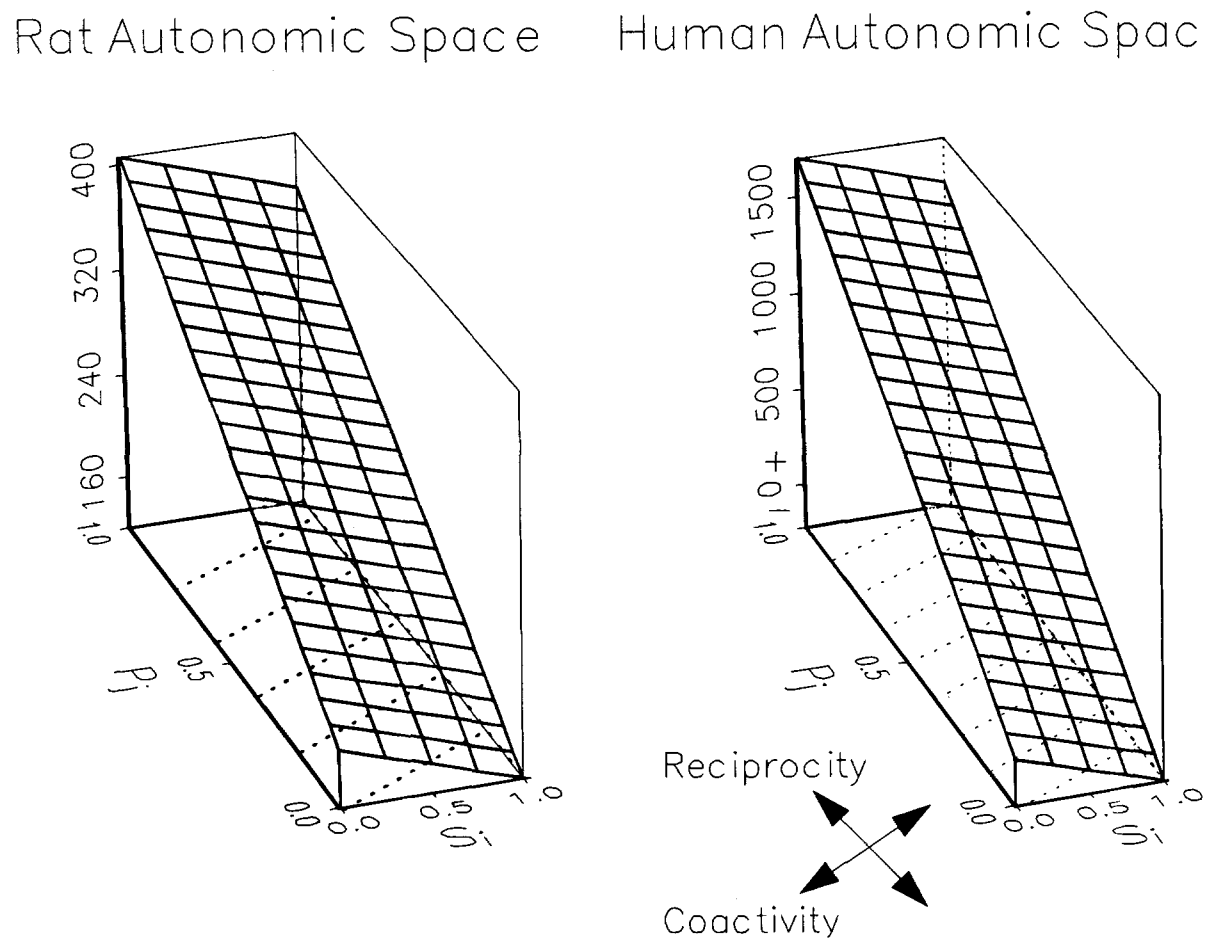

Figure 2. Bivariate autonomic plane and its associated effector surface for the rat (left panel) and human (right panel). (The effector surfaces overlying the autonomic plane represent the chronotropic state of the target organ for all loci within autonomic space, as derived from Equations 2, for the rat, and 4, for the human. The axes are expressed in proportional units of activation. For illustrative purposes, the lengths of the axes are scaled in proportion to relative dynamic ranges of control of the autonomic branches. For the human autonomic space depiction, the *z*-axis is expressed in relative units, because considerable individual differences are apparent in intrinsic heart period. HP_a thus represents the autonomic contribution to heart period as a change from the intrinsic period, β. Absolute heart period can be obtained by adding the autonomic component to the nonautonomic component, β. Dotted lines represent isoeffector contours projected from the effector surface onto the autonomic plane. These contour lines illustrate loci on the autonomic plane that yield equivalent chronotropic effects. The arrows indicate the directional vectors associated with reciprocal and coactive modes of autonomic control. s_i and p_j are the independent activities of the sympathetic and parasympathetic innervations at point *ij.)*

coinhibition is reflected by translations along, or parallel to, the diagonal of coactivity (front-to-back axes intersections). Finally, uncoupled changes in the autonomic divisions manifest by translations parallel to the autonomic axes, where the activity of one branch varies while the other remains constant.

Interactions among the autonomic divisions. The effector surfaces of Figure 2 are based on a simple additive model of the independent activities of the autonomic branches. Interactions among the branches at the level of the heart could alter the shapes of these surfaces. Inhibitory interactions between the autonomic branches are known to exist in both directions, the most widely recognized being a vagal inhibition of sympathetic chronotropic effects (Hall & Potter, 1990; Levy, 1984; Levy & Zieske, 1969; Manabe et al., 1991; Stramba-Badiale et al., 1991; Warner & Levy, 1989; Yang & Levy, 1984). Although interactions between the autonomic branches do not alter representations of responses on the autonomic plane, they can distort the cardiac effector surface.

Potential autonomic interactions, however, do not appear to seriously confound analysis of psychophysiological responses in the rat (Berntson et al., in press). Interactions would be expected to be greatest at maximal levels of vagal and sympathetic coactivation (rear-axis intersections of Figure 2) and would decline as a function of distance from this point. Indeed, no interactions would be possible at the three remaining corners of autonomic space, where activity of one or both of the autonomic

divisions is null. The absence of apparent confounding by interactions in the rat is likely due to two factors. First, there is a relatively low level of activity in the autonomic branches under basal conditions. Second, psychophysiological responses in this species entail moderate changes in autonomic activities, relative to the overall dynamic ranges of the autonomic branches. Both of these factors likely minimize the impact of autonomic interactions in psychophysiological response in this species. A similar situation appears to obtain for humans. We return to this consideration below.

Basal State and Psychophysiological Response in Autonomic Space

The human autonomic plane and effector surface of Figure 2 characterize both basal autonomic state and psychophysiological response. The cardiac effector surface of Figure 2 represents the chronotropic state of the heart associated with all possible loci in autonomic space. Hence, knowledge of the location in autonomic space can uniquely define basal states of autonomic control of chronotropic state. Psychophysiological responses are represented by phasic movements on the autonomic plane that translate into a response trajectory across the effector surface. These time-varying locations in autonomic space provide an unambiguous account of autonomic response, including movements along isoeffector contours that do not manifest in heart period changes.

Basal Autonomic Locus

Figure 3 (left panel) illustrates the basal resting location for all studies and conditions listed in Table 4. The coordinates of these data points on the autonomic axes were based on estimates of resting vagal and sympathetic control as derived from autonomic blockades. These estimates (right-hand columns of Table 4) were scaled by the dynamic ranges of the autonomic branches to transform these data into the proportional (0 to 1) units of the autonomic axes. Although considerable differences exist in basal autonomic tone, the distribution of basal loci appears to be systematic. In general, basal loci lie within the lower one third of the vagal dynamic range, and within the middle two thirds of the sympathetic range. Moreover, all data points tend to line up along the reciprocal diagonal. If basal vagal tone is relatively high, sympathetic tone is reduced and vice versa. This suggests that basal heart period is primarily modulated by reciprocal autonomic controls. One likely possibility is the baroreflex, which is highly sensitive to posture and is among the more potent reflexes operative under resting basal conditions.

Orthostatic factors pose homeostatic challenges for the maintenance of circulation, and orthostatic reflexes constitute potent determinants of basal autonomic tone. This is apparent in Figure 3 (right panel), which depicts the mean basal loci under the varied postural conditions of Table 4. As is apparent, a supine position is associated with the highest level of vagal control and the lowest level of sympathetic control, and the opposite is true for an upright posture. These differences are not artifacts of comparisons across studies, because the same relationship is apparent for within-subject variations in postural tilt (Figure 3, open symbols). Thus, much of the variation in basal autonomic locus can be accounted for by postural variables, and this relationship appears to be relatively consistent across studies. Moreover, previous studies reveal that aerobic conditioning does not consistently alter basal autonomic control. This is apparent in Table 3, where the resting sympathetic and vagal control for endurance-trained subjects and untrained subjects are not appreciably different. Because aerobic conditioning can substantially alter β, however, we return below to the issue of individual differences and the effects of aerobic conditioning.

Psychophysiological Response and the Modes of Autonomic Control

The bivariate model of the autonomic plane and its overlying three-dimensional effector surface are necessary for the comprehensive characterization of psychophysiological response. A recent conditioning study in animals illustrates the utility of the representation of cardiac responses in autonomic space, and the ambiguity that can result from simple end-organ measures of chronotropic state (Iwata & LeDoux, 1988). An auditory CS and a shock unconditioned stimulus (US) were presented to two groups of rats, a forward conditioning group and a pseudoconditioning group. In spite of the different stimulus contingencies in these two groups, both showed a comparable cardioacceleratory response to the CS. Control rats given random presentations of the CS and US uniformly displayed tachycardia in response to the CS, presumably reflecting a nonspecific sensitization. The forward-paired experimental group showed a statistically similar acceleratory response to the CS.

Analysis of the independent activities of the autonomic branches in the context of autonomic space, however, revealed that the heart period responses of the two groups arose from distinct modes of autonomic control. For the conditioning group, vagal blockade dramatically increased the cardioacceleratory response, suggesting that the CS evoked a concurrent vagal activation that normally dampened the sympathetically driven acceleratory response. Consistent with this interpretation, sympathetic blockade unmasked a notable bradycardia to the CS (see Figure 4, top left). This represents the prototypic pattern of coactivation (Berntson et al., 1991). In contrast, the cardioacceleratory response of the pseudoconditioning group was virtually eliminated by sympathetic blockade and was largely unaltered by parasympathetic blockade (Figure 4, lower left). These results in control animals are consistent with a CS-induced increase in sympathetic drive to the heart (uncoupled sympathetic mode), which may be attributable to the nonspecific conditioned fear or anxiety reactions to the general contextual cues.

The differences in autonomic modes of response in the conditioned and pseudoconditioned groups are illustrated by the autonomic space representations presented in the right panels of Figure 4. These plots were derived from Equation 2, based on the independent activities of the autonomic branches as revealed by autonomic blockades. The relevant segments of the

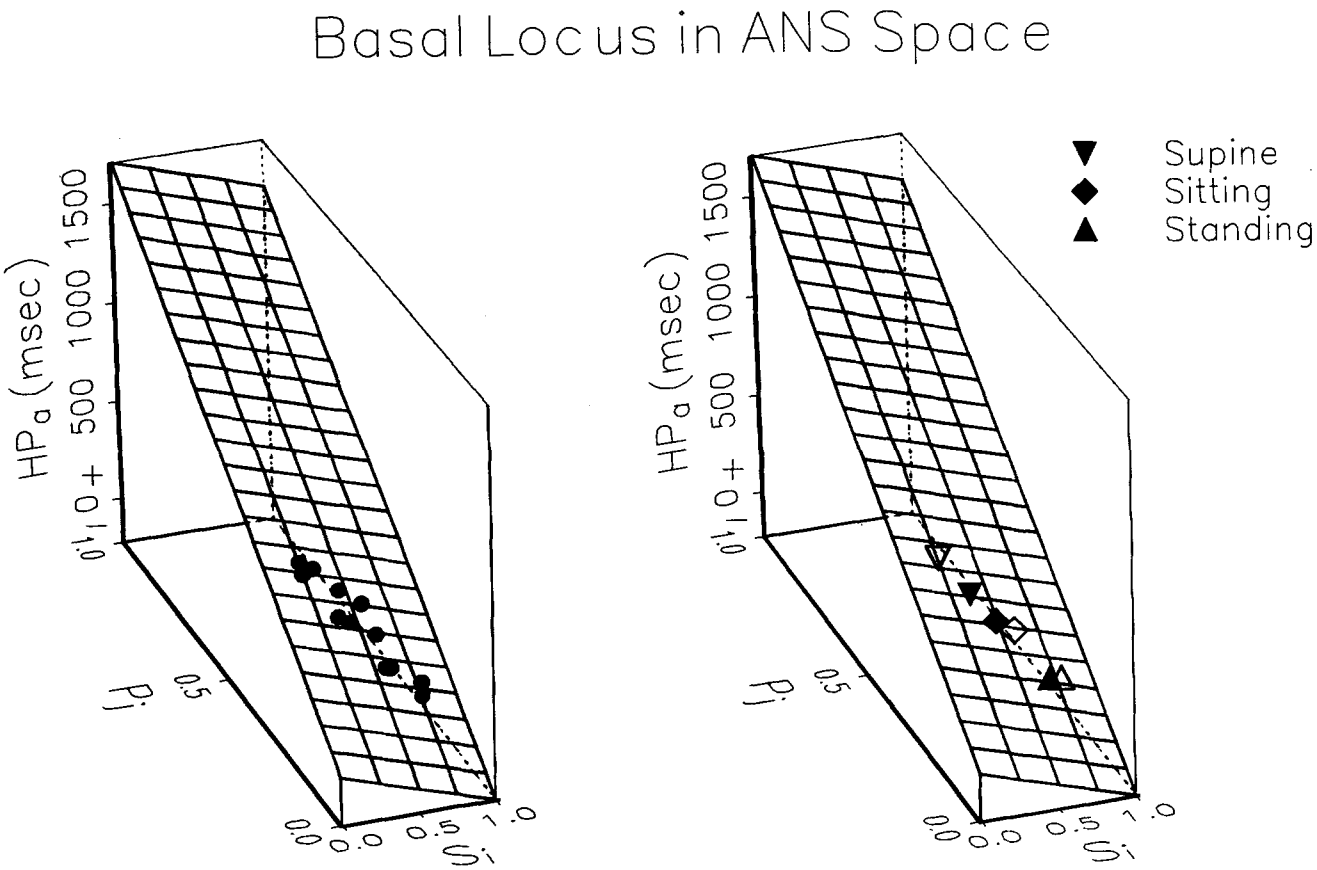

Figure 3. Basal (resting) loci of chronotropic control for human subjects, as represented on the autonomic effector surface. Left: Mean values from the studies in Table 4 under all postural conditions. (Each data point—solid circle—represents a row in Table 4.) Right: Average basal loci (solid symbols) under the different postural conditions represented in Table 4, and the corresponding within-subject data (open symbols) of Robinson, Epstein, Beiser, and Braunwald, 1966. (ANS = autonomic nervous system; HP_a = autonomic contribution to heart period as a change from the intrinsic period, β. s_i and p_j are the independent activities of the sympathetic and parasympathetic innervations at point ij.)

effector surfaces are expanded in the inserts of Figure 4, which depict the temporally unfolding cardiac responses as movements along the two autonomic axes. The data points in the inserts represent the momentary autonomic locus over successive (2-s) time periods, beginning at the baseline locus (at the 0, 0 intersection). The upper insert of Figure 4 reveals a predominant autonomic coactivation in the conditioning group, characterized by a sustained sympathetic activation, and a later increase in parasympathetic control. In contrast, the lower insert reveals a predominant uncoupled sympathetic mode of response in the pseudoconditioning group. If these results were considered solely from the perspective of the cardiac responses in unblocked animals, no evidence of conditioning would have been apparent. Substantive differences between the groups were revealed, however, by selective autonomic blockade that permitted an evaluation of the independent activities of the autonomic divisions.

Although directly equivalent data do not exist for human subjects, the study of Obrist et al. (1965) suggests a similar pattern of coactivation in an aversive classical conditioning paradigm in humans. In this study, colored lights served as the CSs and an aversive shock as the US. As illustrated in Figure 5 (left panel), the overall heart period response to the conditioned stimulus was an initial tachycardia followed by a more sustained bradycardia. The short-latency tachycardia was largely eliminated by atropine, indicating its vagal origin. Under atropine, however, the longer latency bradycardia reverted to a notable tachycardia. This tachycardia appeared to arise from a concurrent sympathetic activation that was masked in the unblocked condition by the more potent vagal response. Indeed, the reversal of response direction with autonomic blockade is a hallmark of autonomic coactivation (Berntson et al., 1991).

These results suggest that the conditioned autonomic response to an aversive stimulus shows highly consistent features across species. This consistency, however, cannot be found in the overall cardiac response, which was characterized by bradycardia in humans and tachycardia in rats. Rather, the organizing feature of the chronotropic response is the mode of auto-

Table 4
Basal (Resting) Autonomic Control

Study	Population	Age	Posture	HP rest	Autonomic blockade			Resting ANS Control[a]	
					Sympathetic	Vagal	Dual	Sympathetic	Vagal
Katona et al. (1982)	10 healthy males	20–26	Supine	963	1,176	513	589	−76	587
Nyberg (1981)	6 healthy males	22–29	Supine	1,017	1,071	522	625	−103	446
Ribeiro et al. (1991)	11 healthy males	*M* = 26	Supine	984	1,176	556	612	−56	564
Robinson et al. (1966)	4 healthy males	19–28	Supine	1,132	1,250	594	652	−58	598
Smith et al. (1989)	10 sedentary males	20–26	Supine	855	1,027	552	693	−141	334
M				990	1,140	547	634	−87	506
Nyberg (1981)	Same 6 subjects as above		Sitting	915	1,045	500	588	−88	457
Robinson et al. (1966)	Same 4 subjects as above		45° tilt	896	1,053	496	632	−136	421
M				905	1,049	498	610	−112	439
Nyberg (1981)	Same 6 subjects as above		Standing	789	920	455	588	−133	332
Robinson et al. (1966)	Same 4 subjects as above		80° tilt	732	923	438	619	−181	304
Sato et al. (1980)	9 healthy males	23–31	Standing	682	897	457	631	−174	266
M				734	913	450	613	−163	300
			Endurance trained						
Katona et al. (1982)	8 male oarsmen	20–25	Supine	1,090	1,276	637	741	−104	535
Smith et al. (1989)	10 male runners	*M* = 25	Supine	1,097	1,260	598	755	−157	505
M				1,094	1,268	618	748	−131	520

Note. Vagal blockade was achieved in all studies by a minimal atropine dose of 0.03 mg/kg (or 2 mg). Sympathetic blockade was achieved in all studies by a minimal propranolol dose of 0.2 mg/kg or a minimal dose of metoprolol, a cardioselective $beta_1$ blocker, of 0.17 mg/kg. ANS = autonomic nervous system.

[a] Resting autonomic control was derived as the difference between the intrinsic heart period (dual blockade) and the heart period with one of the two branches unblocked. (Vagal control = heart period under sympathetic blockade − heart period under dual blockade; sympathetic control = heart period under vagal blockade − heart period under dual blockade.)

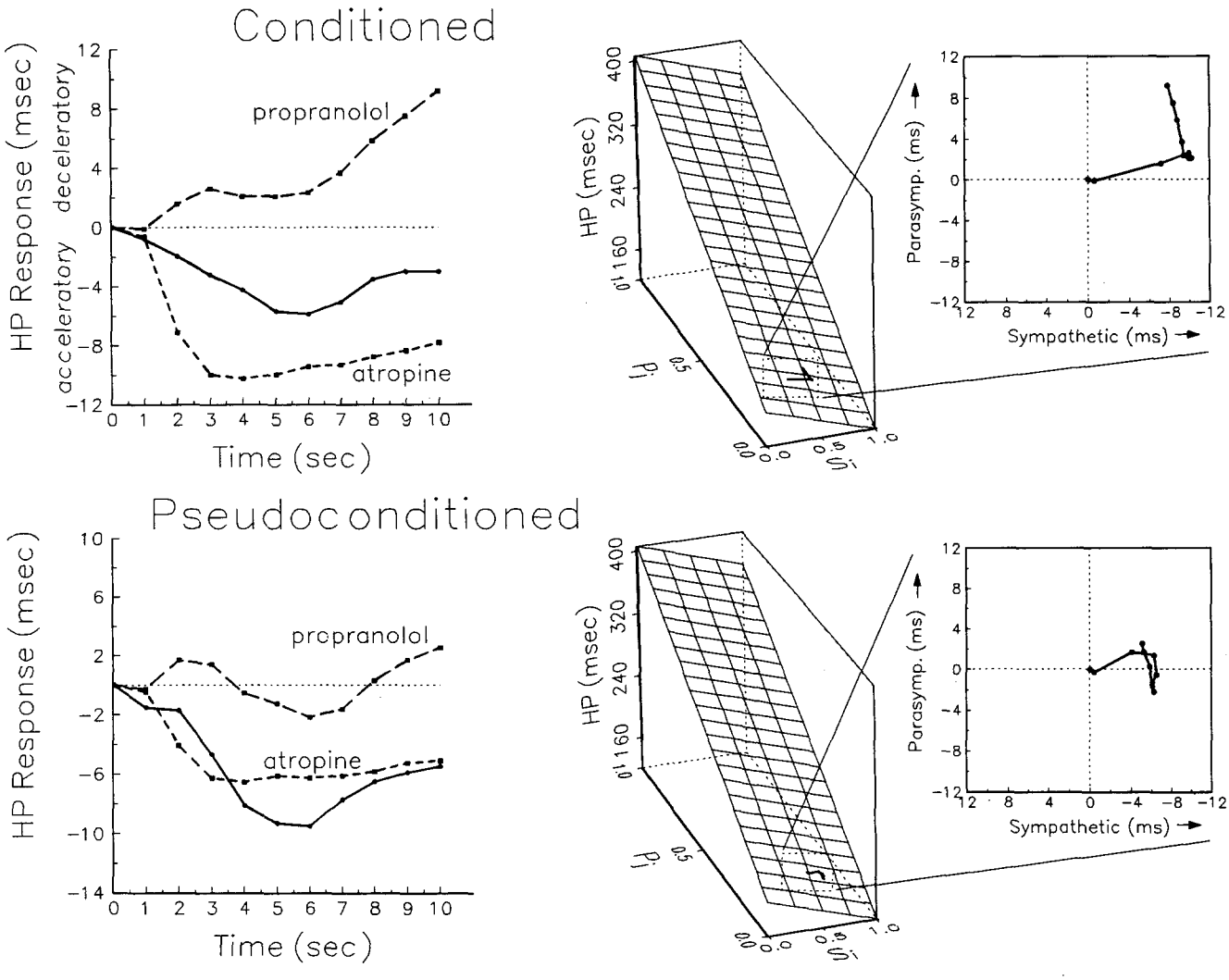

Figure 4. Cardiac responses to an auditory conditioned stimulus (CS) for shock in conditioned and pseudoconditioned rats. Left panels: Heart period (HP) responses in the unblocked condition (solid lines), and after sympathetic (propranolol, 1 mg/kg) or parasympathetic (atropine, 2 mg/kg) blockade. Right panels: Heart period responses to an auditory CS in conditioned and pseudoconditioned animals as depicted on autonomic space and the effector surface. (The functions depicted on the effector surface are derived from Equation 2 and represent the time-varying loci associated with the poststimulus responses depicted in the left panel. The relevant segments of the effector surface are expanded in the inserts. These inserts depict the cardiac response as movements along the two autonomic axes. For illustration, the axes units of the inserts are expressed in millisecond changes in heart period from baseline, that is, $c_i s_i$ and $c_j p_j$, of Equation 2. The large dot at the center—0, 0—of the insert is the basal starting point, and the lines extending from, and returning toward, this basal point depict the temporally unfolding cardiac response. Data points—small dots—depict the cardiac response over 2-s intervals. For clarity, several data points are omitted at the end of the poststimulus time functions. The overall pattern of autonomic response in the conditioned animals is distributed predominantly along the diagonal of coactivity, from lower left to upper right, with an initial sustained sympathetic activation followed by parasympathetic activation. The response of pseudoconditioned animals lies predominantly along a line parallel to the sympathetic axis, an uncoupled sympathetic mode. s_i and p_j are the independent activities of the sympathetic and parasympathetic innervations at point ij. Data are derived from Iwata & LeDoux, 1988.)

nomic control. For both rats and humans, the conditioned response to an aversive stimulus entailed a coactivation of autonomic controls of the heart. In fact, this mode accords with the inconsistent *direction* of the cardiac response across species, because coactive modes of autonomic control are characterized by a generally low *directional stability* of the unblocked cardiac response (Berntson et al., 1991).

Unfortunately, the Obrist et al. (1965) study lacked important blockade conditions (sympathetic blockade and dual blockade), which are important to confirm the validity of inferences de-

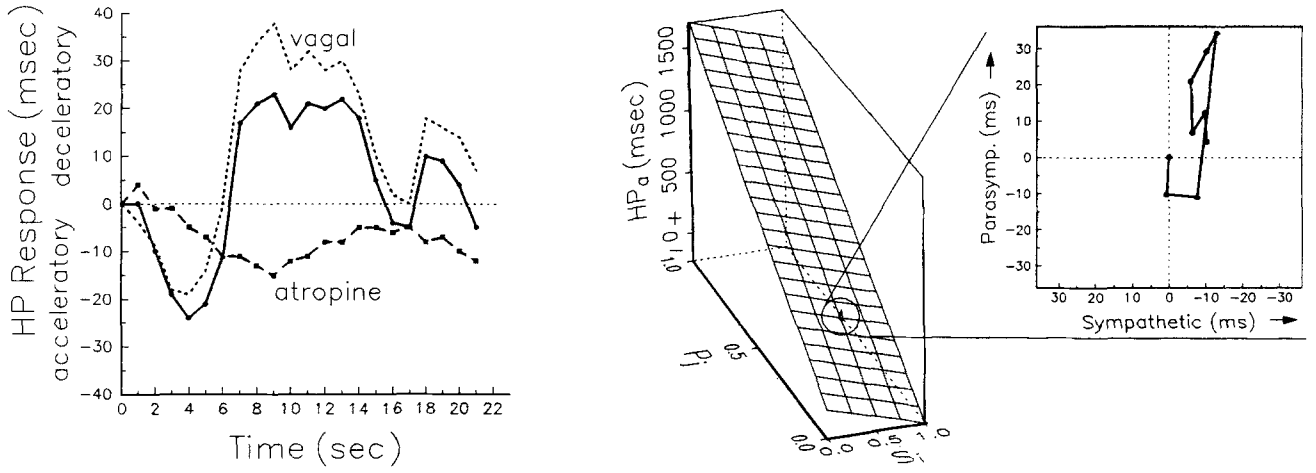

Figure 5. Cardiac responses to a visual conditioned stimulus (CS) for shock in human subjects. Left panel: Cardiac responses in the unblocked condition (solid lines) and after parasympathetic blockade with atropine (dashed line). (Although sympathetic blockade was not used, an estimate of the vagal response—dotted line—was derived from the difference between the unblocked response and that after vagal blockade.) Right panel: Heart period (HP) responses to the CS as depicted on autonomic space and the effector surface. (Because sympathetic blockade was not used, the basal locus in autonomic space—circle—was estimated from the atropine and vagal functions in the left panel. The relevant segments of the underlying autonomic space are expanded in the inserts. For illustration, the axes units of the inserts are expressed in millisecond changes in heart period, that is, $c_s \cdot s_i$ and $c_p \cdot p_j$ from Equation 4. The expanded inserts depict the cardiac response as movements along the two autonomic axes. The large dot at the center—0, 0—of the insert is the basal starting point, and the lines extending from this basal point depict the temporally unfolding cardiac response. Data points—small dots—depict the cardiac response over 2-s intervals. Several points are omitted at the end of the time function for clarity. With the exception of the initial parasympathetic withdrawal, the pattern of the response to the CS is generally similar to that observed in animals—see Figure 4—and is distributed predominantly in the upper right quadrant of coactivity—lower left to upper right. HP_a = autonomic contribution to heart period as a change from the intrinsic period, β. s_i and p_j are the independent activities of the sympathetic and parasympathetic innervations at point *ij*. Data are those presented by Obrist, Wood, & Perez-Reyes, 1965.)

rived from blockade studies[8] (Berntson et al., 1991; Stemmler et al., 1991). Consequently, the representation of the results of this study in autonomic space remains tentative. For purposes of illustration, however, an expected vagal response function is derived as the difference between the unblocked response and the response under vagal blockade. This function is depicted by the dotted line in Figure 5 (left panel). As illustrated in the right panel of Figure 5, the general mode of the autonomic conditioned response in humans was similar to that of rats, both functions being represented largely in the upper right quadrant of the autonomic space inserts (right panels of Figures 4 and 5). We return below to the explicit confirmation of inferences derived from blockade studies.

Taken together, the findings with aversive conditioning as represented within the autonomic space model reveal an important autonomic distinction between conditioned and pseudoconditioned responses and suggest a fundamental parallel in the conditioned aversive responses of humans and rats. Importantly, neither of these features would have been apparent from measures of end-organ response alone.

Autonomic Interactions in Human Psychophysiological Response

As discussed above, interactions between the autonomic divisions would not confound representations of psychophysiological responses on the autonomic plane but could alter end-organ manifestations and hence the cardiac effector surface.

We have previously demonstrated that autonomic interactions do not seriously confound analysis of psychophysiological responses in the rat (Berntson et al., in press). Thus, the independent activities of the autonomic branches ($c_s \cdot s_i + c_p \cdot p_j$ in Equation 2) accurately predicted the unblocked cardiac responses of the rat, in the absence of an interaction term (Berntson et al., in

[8] Discussion of the interpretation of the results of autonomic blockade can be found in Berntson, Cacioppo, and Quigley (1991) and Stemmler, Grossman, Schmid, and Foerster (1991). One potential complication arises from the possibility that blockade of one autonomic division may result in reflexive changes in the other, so that the results under selective blockade do not accurately represent responses of the two branches in the unblocked condition. As we have discussed elsewhere (Berntson, Cacioppo, & Quigley, 1991), this is generally less of a problem for chronotropic measures than for dimensions such as blood pressure, which are physiologically monitored and explicitly regulated. Consequently, an accurate interpretation of the effects of blockade requires that the independent estimates of activities of the two autonomic branches yield a predicted response that converges on the observed response in the unblocked condition. Stemmler, Grossman, Schmid, and Foerster offer a critical discussion of interactions in blockade studies and provide quantitative strategies for decomposing these interactions.

press). This is likely due to the fact that psychophysiological responses generally entail relatively small displacements in autonomic space and are largely confined to the lower end of the vagal dynamic range, where interactions would be minimal. The same considerations appear to hold for humans, as indicated by the basal loci in Figures 3 and 5, and the modest responses observed in Figure 4, relative to the overall dimensions of autonomic space (see also the handgrip and reaction time tasks of Figure 9).

A more direct test of the impact of interactions comes from analysis of the baroreflex, which is able to drive autonomic branches over a considerable dynamic range. As revealed by Equation 4, a significant interaction term (I_{ij}) would impact on the observed heart period response, which would therefore not be accurately predicted by the independent activities of the autonomic branches alone ($c_s s_i + c_p p_j$). Indeed, the sine qua non of interactions is a deviation of the unblocked cardiac response from the function predicted by the simple summation of the sympathetic and parasympathetic components of Equation 4. Figure 6 illustrates the sigmoidal best fit curves of the baroreflex function in humans under unblocked conditions and after selective autonomic blockades (Robinson et al., 1966). Also illustrated is the predicted heart period response function, derived from Equation 4 on the basis of the independent activities of the autonomic branches under selective blockades (with the interaction term set to zero). As is apparent, the observed arterial pressure–heart period function in the unblocked condition corresponds closely with that predicted by the independent activities of the autonomic branches in the absence of an interaction term.

As was the case for the rat, potential interactions may not seriously distort autonomic space analyses in humans. The baroreflex, however, is associated with a reciprocal mode of autonomic control that precludes high levels of concurrent activity in both autonomic divisions. This would be expected to minimize interactions. It is the coactivation mode that would be expected to yield the most salient interactions, as manifested by a discrepancy between the predicted and observed response functions. In fact, the comparison of the predicted and observed response functions constitutes a formal test for the presence of a confounding autonomic interaction and offers a powerful tool for the noninvasive study of these interactions in human subjects. In the face of such a discrepancy, potential interactions should be considered, especially for responses associated with autonomic coactivation. In most cases, however, autonomic interactions would not appear to seriously confound the analysis of cardiac responses in behavioral contexts.

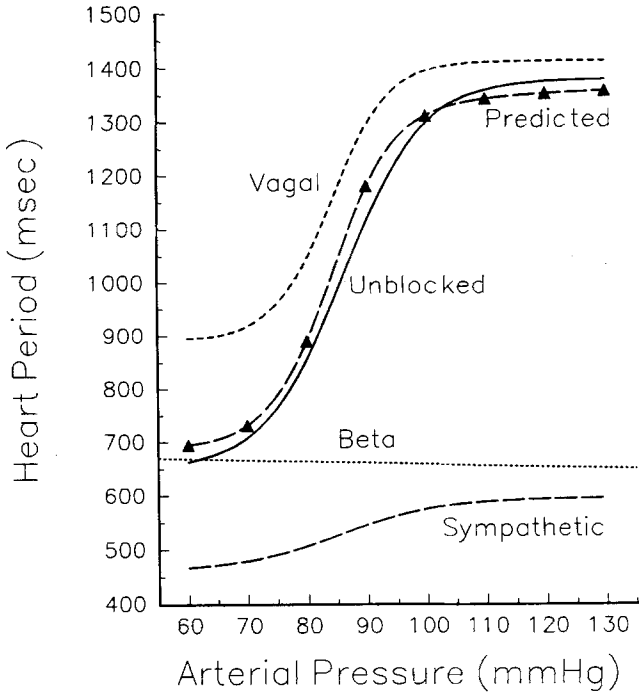

Figure 6. Baroreflex–heart period function in humans. (The solid line is the best fit sigmoidal function depicting the covariation of heart period with mean arterial pressure in the unblocked control condition. Responses obtained after sympathetic—propranolol—or parasympathetic—atropine—blockade are illustrated by the dashed lines. The dotted line depicts the predicted baroreflex function as derived from Equation 4, based on the independent responses of the autonomic branches under selective blockades. Data are derived from Robinson Epstein, Beiser, & Braunwald, 1966).

Nonautonomic Contributions to Heart Period: Individual Differences

The human autonomic plane and effector surface of Figure 3 can provide an accurate representation of autonomic contributions to basal chronotropic state and psychophysiological response. Given the difference scaling of the *z*-axis in Figure 3, however, the specification of absolute heart period requires consideration of the nonautonomic contributions (β and γ). In Equation 4, β captures the tonic and γ, the phasic nonautonomic determinants of heart period. These factors represent the aggregate effects of local metabolic, mechanical, thermal, hormonal, and other influences that are not directly or indirectly mediated by cardiac nerves or sympathoadrenal catecholamines.[9] Although the specific mechanisms contributing to these nonautonomic influences are still being clarified, it is possible to derive an aggregate estimate of these influences by the residual heart period after dual autonomic blockade. Fortunately, individual differences in these nonautonomic determinants of heart period appear to be lawful, and noninvasive estimates should ultimately be possible through normative parametric studies.

β. As discussed above, considerable individual differences in basal or intrinsic heart period have been observed across

[9] Studies in both humans and dogs following total cardiac denervation demonstrate that cardiac transplantation largely eliminates dramatic, short-latency cardiac responses in behavioral contexts (Randall, Kaye, Randall, Brady, & Martin, 1976; Sloan, Shapiro, & Gorman, 1990). Adrenomedullary catecholamines, however, can mediate delayed, attenuated responses. Neural and adrenal components of sympathetic control could be parsed in future refinements of the present model by adrenalectomy, the use of selective catecholamine receptor antagonists and blockers of catecholamine release from sympathetic nerve terminals, or both. In the present model, however, sympathoadrenal catecholamines are simply considered one form of sympathetic control.

studies. Importantly, these individual differences appear to be stable and reliable (Jose et al., 1970). Two important determinants of these differences have been defined: age and aerobic capacity. As illustrated in Table 1, intrinsic heart period is considerably longer for aerobically conditioned subjects than for unconditioned subjects (M = 742 ms vs. 617 ms), and Jose et al. identified a significant increase in resting heart period with age (588 ms at mean age = 23 and 667 ms at mean age = 50). These factors account for much of the between-subjects variance in β. Clearly, further parametric studies are necessary to quantitatively refine these relationships, identify additional potential determinants, and permit normative or noninvasive estimates of β.

γ. In addition to the tonic nonautonomic contributions to heart period, nonautonomic phasic or state variables also influence absolute heart period values. Again, many of the phasic determinants of γ, including core temperature and aerobic output, have been defined. Even with maximal exercise, however, changes in core temperature are generally less than 1 °C (Jose et al., 1970; Nordenfelt, 1971). This fact, together with the relatively low slope of the temperature–heart period function (7 ms/°C; Jose et al., 1970), renders thermal effects minimal except perhaps under extreme conditions. The more potent phasic contribution to heart period is metabolic activity as indexed by oxygen utilization (Vo_2). This variable can yield large nonautonomic alterations in heart period. As illustrated in Figure 7, nonautonomic metabolic contributions to heart period are lawfully related to the percent maximal O_2 utilization and to aerobic capacity. The lawfulness of these relationships should again permit relatively accurate estimates of γ for a given subject group in a specific performance context.

The parametric studies proposed above hold considerable promise for the ultimate estimation of nonautonomic contributions to absolute heart period, and their covariance with factors such as age, sex, and aerobic capacity. Additional work is necessary to more fully define nonautonomic contributions to heart period and to allow normative estimates and noninvasive indices of these contributions to heart period.

Functional Surfaces and Psychophysiological Nonlinearities

Psychophysiological relationships between behavioral processes and visceral states entail two major classes of transforms: (a) from psychophysiological antecedents to autonomic outflows and (b) from autonomic outflows to functional effects on target organs. An inherent confound therefore exists as to the form and locus of psychophysiological relationships, because transformations at one stage can obscure or confound other transformational stages. The linearity outlined above between autonomic outflows and chronotropic effects has significant implications for psychophysiological theory and research. By defining the relationship between autonomic outflows and cardiac chronotropy, the autonomic space model permits a parsing of nonlinearities in psychophysiological relationships. As long as autonomic boundaries are not approached, heart period is essentially linearly related to autonomic outflows. This implies that nonlinearities in psychophysiological relationships between antecedent conditions and cardiac effects are attributable to earlier transform stages (i.e., from antecedents to autonomic outflows).

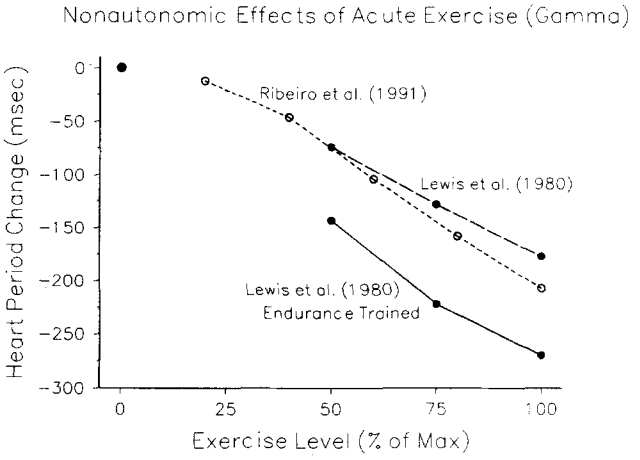

Figure 7. Phasic, nonautonomic contributions (γ) to heart period during exercise. (The ordinate is in units of heart period change from β under dual autonomic blockade, as a function of level of exercise. In all cases, γ shows a relatively linear increase in magnitude with increasing exercise, although the function is somewhat steeper for endurance-trained subjects. Lewis et al. = Lewis, Nylander, Gad, & Areskog.)

An example of such nonlinearities in antecedent–effector relationships derives from the baroreceptor–heart period reflex. As is the case for animals, a unit change in blood pressure does not translate into a fixed increment in autonomic outflow in humans. This is due to the nonlinearities in baroreceptor response to changes in blood pressure together with nonlinearities inherent in central baroreflex networks (Chapleau, Hajduczok, & Abboud, 1991; Kunze & Andresen, 1991). These nonlinearities can be illustrated by an alternate representation of *functional autonomic space,* in which only the relevant subcomponent of autonomic space is depicted, and where axes are specified in functional units of the antecedent stimulus or condition (blood pressure in the case of the baroreflex). The data set for baroreflex mapping was derived from the study of Robinson et al. (1966) as described above (Figure 6). Blood pressure was experimentally manipulated by nitroprusside and phenylephrine, and reflexive changes in chronotropic state were measured in the unblocked condition and during single and dual autonomic blockades.

The general results of this study are presented in Figure 6, which displays heart period as a function of blood pressure in the unblocked state and under autonomic blockade. The data obtained under selective autonomic blockades provide the marginal functions needed to map the reflex onto the autonomic plane and its effector surface, as illustrated in Figure 8 (left panel). The nonlinearities between blood pressure and heart period are readily apparent in the asymptotic portions of the baroreflex function, because further blood pressure variations no longer have appreciable impact on heart period. The nonlinearities are illustrated in the insert of Figure 8, which shows the relationship between equal increments (10 mmHg) in blood pressure and units of autonomic activation. As is appar-

ent, the spacing of these blood pressure units is not equivalent over the autonomic axes and becomes especially compressed in the asymptotic regions of the baroreflex. The nonlinear mapping of blood pressure onto the autonomic axes may be partly attributable to the proximity of the lower asymptote of the baroreflex to the sympathetic maxima of autonomic space. The parallel nonlinearity at the upper asymptote, however, cannot be accounted for by limits of autonomic space because the function does not approach autonomic boundaries at that point, especially for the vagal division. Rather, this nonlinearity appears to arise in large part from the demonstrated nonlinearities in baroreceptors and reflex circuits (Head & McCarty, 1987; Spyer, 1990).

Limitations in the range of autonomic control achieved by the baroreflex and the nonlinearities in the mapping of blood pressure onto the autonomic axes suggest an alternate representation of the baroreflex, as well as other psychophysiological relationships. This alternate, functional representation would entail a restricted mapping onto a subcomponent of autonomic space and a rescaling of the axes into functional (e.g., physiological, stimulus, or behavioral) units. For this representation, axes units could be specified in terms of physiological parameters such as blood pressure, physical dimensions such as tone intensity, perceptual variables such as pain ratings, or other antecedent variables relevant to the experimental question. The natural boundaries of this restricted functional space would be the dynamic limits of the effects of the antecedent variable on autonomic outflows, and psychophysiological responses could be represented as relative movements within this potential dynamic range. The axes of this functional subspace would thus be expressed in units of the experimentally relevant independent variable, and the chronotropic impact of this variable would be reflected in the features of the functional surface. As illustrated in Figure 8 for the baroreflex, however, these functional units may not map linearly onto the autonomic axes.

In the full autonomic space maps considered thus far, the nonlinearities related to the transforms from the antecedent stimulus to autonomic outflows are excluded, because these maps express only the relationship between autonomic outflows and chronotropic state. If the axes were expressed in functional units, however, the resulting surface would also incorporate the transformation between antecedent conditions and autonomic outflows. That is, the functional surface would capture all transformations between the antecedent conditions and the functional target-organ state. In a previous theoretical review, we modeled functional surfaces for a wide variety of antecedent activation functions (Berntson et al., 1991). This modeling revealed common features of functional surfaces that transcend specific shapes or slopes of the activation functions. The alternate perspective offered by these functional surfaces may render some psychophysiological principles and relationships more readily apparent than the full effector surface.

The functional space representation of the baroreflex is illustrated in Figure 8 (right panel). The sigmoidal relationships between blood pressure and the relative activities of the sympathetic and vagal branches are apparent in Figure 6, and manifest in the curvilinear baroreflex function on the full effector surface of Figure 8 (left panel). For the alternate functional space and surface of Figure 8 (right panel), however, the units of the autonomic axes are expressed in blood pressure, and the nonlinear mapping of blood pressure onto autonomic outflows now manifests in sigmoidal rather than linear functions between the axes and heart period. These sigmoids are apparent at the sympathetic and parasympathetic marginals of the functional surface, and these nonlinearities manifest in a nonlinear functional surface topography. These surface nonlinearities reflect the fact that the functional surface captures both the transform between autonomic outflows and chronotropic state, which is linear, and the transform between antecedent conditions and autonomic outflows, which is nonlinear.

The functional surface of Figure 8 offers a graphical depiction of the nonlinearities inherent in the transform from the antecedent condition of the baroreflex (blood pressure) and the chronotropic state of the heart. In the baroreflex example of Figure 8, the functional surface represents merely a conceptual model for illustration, because it could not be fully populated or realized empirically. This is because the units of the functional axes (mmHg) are equivalent, so that translation along one axis is necessarily associated with an equivalent translation along the other. Given the monotonic autonomic activation sigmoids of the baroreflex, the resulting empirical function (see Figure 8) would lie along a single line on the autonomic plane and along a corresponding vector on the functional surface. With orthogonal axes units related to distinct antecedents, however, the full functional surface could be manifest empirically. Given the essential linearity between autonomic outflows and heart period, the functional surface would represent a topological model of the nonlinearities inherent in the transformation from antecedent conditions to autonomic outflows. These nonlinearities themselves probably reflect several components, including nonlinearities in receptor transduction as well as nonlinearities inherent in central processing substrates. Both classes of nonlinear transforms are likely to be operative in behavioral contexts and to figure prominently in many psychophysiological relationships. Importantly, the autonomic space model offers an initial step toward the parsing of the origins of these nonlinearities.

Psychophysiological Implications

Modes of Autonomic Control

Psychophysiological implications of the autonomic space model are considerable. As a heuristic, this model explicitly recognizes the multiple modes of autonomic control. Although there is little debate over the existence of these multiple autonomic modes (reciprocal, uncoupled, and coactive), they often receive little attention in the physiological and psychophysiological literatures. Although the multiple modes of autonomic control may add an additional level of complexity to psychophysiological analyses, the organizing power of the autonomic space model overshadows the added cost in analytical complexity. Limited measures of end-organ response can blur the order in psychophysiological data and impede the development of organizing concepts.

A comprehensive characterization of psychophysiological response for dually innervated organs mandates a bivariate model of autonomic control. This is documented by the conditioning

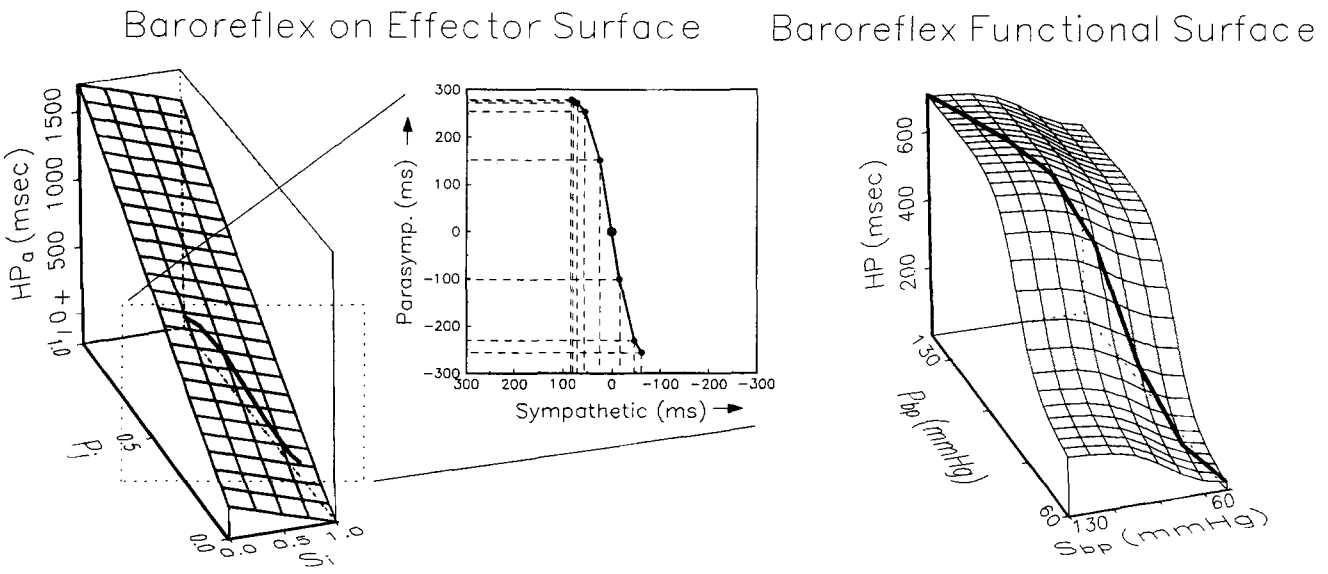

Figure 8. Baroreflex–heart period (HP) functions. Left panel: Baroreflex function of Figure 6, as depicted on autonomic space and the effector surface. (The relevant segment of the effector surface is expanded in the insert for illustration. The axes units of the inserts are expressed as millisecond changes in heart period. The expanded insert depicts the chronotropic state associated with varied blood pressure, as displacements along the two autonomic axes. The large dot at the center—0, 0—of the insert is the basal starting point, and the remaining data points—small dots—depict the chronotropic state for each 10-mmHg change in blood pressure. The solid line represents the baroreflex function extending from 60 mmHg—lower right data point in the insert—to 130 mmHg—upper left data point. The dotted lines extending from the data points to the sympathetic and parasympathetic axes illustrate the nonlinear mapping of the equivalent 10-mmHg steps onto the autonomic axes. The general autonomic mode of the baroreflex is reciprocal.) Right panel: Baroreflex functional space and surface. (The parasympathetic and sympathetic axes are expressed in functional units of blood pressure over the dynamic range of the baroreflex, 60–130 mmHg. The sigmoidal functions apparent along the autonomic marginals represent the independent activities of the autonomic branches, as obtained under selective autonomic blockades. See Figure 6. The overlying surface depicts the relative chronotropic state of the heart, as derived from Equation 4, associated with all loci in functional space. The solid line extending from the lower right to the upper left corner of the functional surface illustrates the baroreflex–heart period function of Figure 6. Because in this case the axes are correlated (both expressed in mmHg), the remainder of the functional surface is not populated. HP_a = autonomic contribution to heart period as a change from the intrinsic period, β; P_{bp} = parasympathetic effect of blood pressure; S_{bp} = sympathetic effect of blood pressure. s_i and p_j are the independent activities of the sympathetic and parasympathetic innervations at point ij. Data are derived from Robinson, Epstein, Beiser, & Braunwald, 1966.)

studies of Iwata and LeDoux (1988) and Obrist et al. (1965) as discussed above. Analysis of the cardiac responses alone may fail to differentiate between conditioned and pseudoconditioned responses and further suggests a fundamental species difference in the conditioned response to aversive stimuli. When viewed from the perspective of autonomic space, however, substantive differences emerge between conditioned and pseudoconditioned cardiac responses, and common features of the cardiac response become apparent across species.

Heart Period Versus Heart Rate

The present analysis clarifies issues of the propriety of heart period versus heart rate measures. Although heart period has been suggested to be superior to heart rate under certain conditions (Graham, 1978; Linnemeyer & Porges, 1986), a general consensus has not emerged in the literature on these alternate chronotropic metrics.

Regardless of the form reported or displayed by a particular monitoring device, measures of cardiac chronotropy are based on the time interval between beats. The expression of this basic data in heart rate requires a nonlinear transformation of the basic heart period data. Although this transformation may be appropriate in some instances, the imposition of a nonlinear transform can be problematic and would need to be explicitly justified. The linearity between autonomic outflows and heart period confers both pragmatic and theoretical advantage to the metric of heart period for both tonic state and phasic response. First, units of time, rather than transformed units of rate, have a more natural relationship to the temporally dependent ionic processes of sinoatrial pacemaker cells (Dexter et al., 1989). In fact, time units are necessary for analysis of cardiac cycle effects or other within-beat processes. Second, because heart period is linearly related to autonomic activities, a given millisecond change in heart period represents an equivalent change in autonomic outflow independent of baseline state.

The study of Pollak and Obrist (1988) illustrates the interpretive difficulties that can arise from analyses of nonlinear functions such as heart rate. This study examined the autonomic origins of heart rate responses during handgrip and reaction time tasks. Separate groups of subjects were tested on both tasks under (a) unblocked conditions, (b) vagal blockade with atropine, or (c) sympathetic blockade with propranolol. The task-related heart rate change during vagal blockade served as an independent index of sympathetic response, and that during sympathetic blockade served as an index of vagal response. Based on the results, Pollak and Obrist concluded that heart rate changes during the handgrip task entailed an increase in sympathetic and a reciprocal decrease in vagal control. In contrast, they argued that the reaction time task was characterized by an uncoupled sympathetic activation. The essence of the latter argument was that atropine did not significantly reduce the heart rate response to the reaction time task and thus provided no evidence of a vagal contribution.

The Pollak and Obrist (1988) analysis, however, is seriously confounded by the basal increase in heart rate after atropine, which is attributable to the blockade of resting vagal tone. Their analysis assumes that a given heart rate change is equivalent regardless of the basal heart rate level. Because heart rate is a nonlinear scale, this assumption is unwarranted. In view of the linearity between autonomic outflow and heart period, and the nonlinear transform between heart period and heart rate, a given increase in *heart rate* represents a diminishing increment in sympathetic control at higher basal heart rates. This is illustrated by the data of Pollak and Obrist. Under saline conditions, the reaction time task was associated with an increase in heart rate from a basal level of 62 bpm to a final value of 76 bpm. This yields a heart rate increase of 14 bpm during the reaction time task. Under vagal blockade, the basal rate increased to 102 bpm, and the maximal heart rate during the reaction time task was 112 bpm. The heart rate increase under vagal blockade was thus 10 bpm, which represents only a 29% reduction from the 14-bpm response in the unblocked condition. The authors concluded that parasympathetic withdrawal did not appreciably contribute to heart rate change in the reaction time task.

When these data are transformed into a linear heart period scale, however, a rather different picture emerges. Under saline conditions, the basal heart period was 968 ms (62 bpm), and this heart period shortened to 789 ms (76 bpm) during the task. This yields a heart period response of 179 ms. With vagal blockade, the basal heart period decreased to 588 ms (102 bpm), and the reaction time task led to a further decrease in heart period to 536 ms (112 bpm). This yields a task-related heart period response of 52 ms under vagal blockade, which represents a 71% reduction from the 179-ms response in the unlocked condition. Further consistent with a vagal contribution was the fact that sympathetic blockade attenuated but did not eliminate the heart rate response to the task.

In view of the considerations discussed above, we reanalyzed the data presented by Pollak and Obrist (1988) within the context of autonomic space. The left-hand panels of Figure 9 depict the heart period changes from baseline as a function of time for the reaction time tasks (top) and handgrip tasks (bottom). The solid lines illustrate the heart period change for the unblocked (saline) group, and the dashed lines depict the responses for the vagal and sympathetic blockade groups. The responses under autonomic blockades provide the marginal functions for the sympathetic and parasympathetic axes, which permits plotting of the functions on the autonomic surface (right panels). The inserts illustrate the relative changes from baseline in sympathetic and parasympathetic control over the four (15-s) time points of the tasks. This analysis reveals that both tasks were associated with sympathetic activation and reciprocal vagal withdrawal. Indeed, the most notable difference was merely in the greater magnitude of the response in the handgrip condition. This illustrates the erroneous inferences that can be drawn from analyses based on nonlinear heart rate measures, especially when variations in basal levels are expected, whether due to situational variables or individual differences.

Validity of Blockade Measures of Psychophysiological Response

The validity of psychophysiological inferences derived from autonomic blockades is dependent on two assumptions: (a) that the pharmacological blockades are relatively complete and (b) that blockade of one division does not indirectly alter the activity of the unblocked division. Fortunately, violations of these assumptions can be explicitly tested.

Incomplete blockades can underestimate the independent activities of the autonomic branches, because residual influences of the partially blocked division continue to contaminate heart period responses. Ideally, studies using pharmacological antagonists should include a dual blockade condition to confirm the effectiveness of the autonomic blockade. Under these conditions, autonomic responses should be eliminated and the heart period should remain relatively stable, as long as nonautonomic factors are not altered. Because nonautonomic factors (e.g., from different levels of somatic demand) may yield heart period changes across conditions, dual blockade can provide an appropriate baseline from which autonomic influences can be derived. Although Pollak and Obrist (1988) did not include a double blockade condition in their study, the effectiveness of their blockades can be evaluated, as we discuss below.

A second source of confound can arise from potential indirect effects of autonomic blockade on the unblocked division. One source of such effects is reflexive adjustments secondary to the autonomic blockade. This is generally less of a problem for heart period, because cardiac chronotropy is not directly monitored physiologically. However, nonselective beta blockers such as propranolol can result in a pressor response that could reflexively alter vagal control. Such interactions could yield independent estimates of autonomic control that deviate from the actual responses in the unblocked condition. Fortunately, it is also possible to explicitly test for such interactions. Equation 4 permits the derivation of an expected heart period response template, based on the independent estimates of the activities of the autonomic branches. Any bias in the estimates of these autonomic activities, as derived from blockade conditions, would thus yield an expected response template that deviates from the response observed in the unblocked condition.[10] The

[10] Deviations between predicted and observed response functions can arise from three major sources, including incomplete blockade, indirect reflexive changes in the unblocked division, and direct inter-

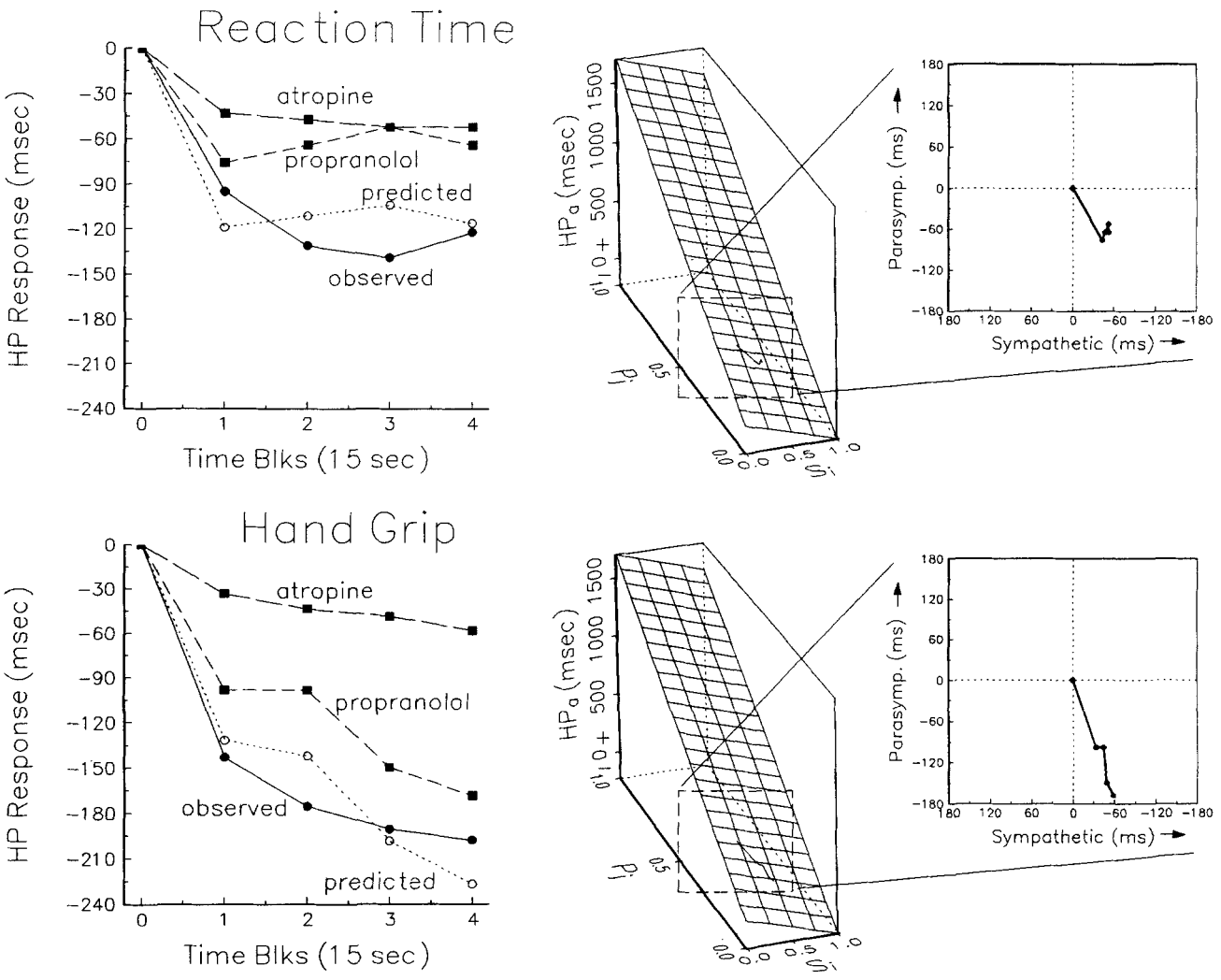

Figure 9. Cardiac responses during reaction time and handgrip tasks under unblocked conditions and during autonomic blockades. Left panels: Heart period (HP) responses in the unblocked condition (solid lines), and after sympathetic (propranolol) or parasympathetic (atropine) blockade. (The dotted line and open circles illustrate the predicted cardiac response function, derived from Equation 4, based on the independent activities of the autonomic branches estimated from autonomic blockades.) Right panels: Corresponding heart period responses as depicted on autonomic space and the effector surface. (The relevant segments of the underlying autonomic space are expanded in the inserts. For illustration, the axes units of the inserts are expressed in millisecond changes in heart period. The expanded inserts depict the cardiac response as movements along the two autonomic axes. The large dot at the center—0, 0—of the insert is the basal starting point, and the lines extending from this basal point depict the temporally unfolding cardiac response. Data points—small dots—depict the cardiac responses over 15-s time blocks. The general pattern of autonomic response for both tasks is distributed predominantly along the reciprocal diagonal and reflect a reciprocal sympathetic activation mode. HP_a = autonomic contribution to heart period as a change from the intrinsic period (β). s_i and p_j are the independent activities of the sympathetic and parasympathetic innnervations at point ij. Data are derived from Pollak & Obrist, 1988.)

predicted response templates for the Pollak and Obrist (1988) study are illustrated by the dotted lines in the left panels of Figure 9. As is apparent, there is reasonable agreement between the predicted heart period response and that observed in the unblocked condition. The general similarity in the predicted and observed functions is particularly striking in view of the fact that the blockade and the unblocked data were derived from separate subject groups.

The correspondence between the predicted and observed response functions also allays concerns over the possibility of incomplete blockades. Ineffective or partial blockades would

actions between the autonomic divisions at the level of the heart. Although a deviation between the predicted and observed responses does not identify the source of variance, this deviation does afford an evaluation of the validity of blockade data.

systematically bias estimates of the independent activities of the autonomic branches and yield an expected response template that again would deviate from the observed response. Although the doses of pharmacological blockers were rather low in the Pollak and Obrist (1988) study, the general agreement between the predicted and observed responses suggests that incomplete blockade did not seriously confound the present autonomic space analysis.

The Law of Initial Values as a Special Case of the Laws of Autonomic Constraint

The law of initial values was formulated by Wilder (1967, 1931/1976) to account for the baseline dependency frequently observed for physiological responses. In general, Wilder asserts that an elevation of the baseline or initial functional level results in smaller subsequent incremental responses and larger decremental responses to evocative stimuli. This is often expressed in a negative correlation between baseline level and the magnitude of an evoked response. The autonomic space model illuminates several issues related to the limits or constraints on autonomic response. We previously enumerated three *laws of autonomic constraint* that characterize the fundamental limits imposed on autonomic reactivity (Berntson et al., 1991). The first of these, the *law of dynamic range,* is most relevant for the present considerations. This law stipulates that the magnitude of a physiological response is constrained by the boundaries of autonomic space.

The law of dynamic range derives in part from physiological limits on the extremes of autonomic activity. Because autonomic space is bounded by the dynamic range of the ANS divisions, the extent to which each division can vary is constrained by proximity to its physiological boundaries. The law of dynamic range imposes constraints on both the modes of autonomic control and the related target-organ manifestations. The effect of baseline state on psychophysiological reactivity has long been recognized (Lacey & Lacey, 1962; Wilder, 1967, 1931/1976). Results consistent with the law of initial values are frequently apparent in psychophysiological studies, although they are not universally observed (Furedy & Scher, 1989; Scher, Furedy, & Heslegrave, 1985; Stern, Ray, & Davis, 1980). Indeed, although the law of initial values is one of the few general laws to emerge in psychophysiology, it has had a rather inconsistent and checkered history. The autonomic space model and the laws of autonomic constraint subsume the law of initial values as a special case instantiation and clarify the basis for this inconsistent history.

The law of initial values is empirically based, being inferred from changes in the functional state of the end organ. Decreases in heart period, for example, may constrain further decreases as heart period approaches some functional limit. This is exemplified by a translation of basal autonomic state along the solid arrow of Figure 10. As illustrated by this arrow, a change in basal autonomic state toward the maximal sympathetic boundary would be associated with a decrease in heart period. At the point of the solid arrow, basal state would now lie proximate to the maximal sympathetic boundary, and further sympathetic activation and associated decreases in heart period would be severely limited. This is the essence of the law of initial values and is also captured by the law of dynamic range. The law of dynamic range is more general than the law of initial values, however, as illustrated by the dashed arrow of Figure 10. Translation of basal state along the trajectory of the dashed arrow also leads to a similar constraint on sympathetic activation, and this constraint is captured by the law of dynamic range because the point of this arrow is also proximate to the sympathetic boundary. The triggering condition for the invocation of the law of initial values, however, is a change or variation in basal chronotropic state. Variations in autonomic constraints that are not associated with a change in basal state are thus not captured by the law of initial values. Because the basal translation depicted by the dashed arrow occurs along an isoeffector contour, it is not reflected in an alteration in heart period. Consequently, the associated variations in autonomic constraint escape the law of initial values. The law of dynamic range is more inclusive and can subsume the law of initial values as a special case instantiation, where the variation in basal state is explicitly associated with an alteration in chronotropic state.

Even for basal changes that are associated with alterations in functional state, predictions of the law of initial values are dependent on the mode of autonomic control and will be straightforward only for reactive changes that lie along a given vector in autonomic space. Although heart period decreases related to sympathetic activation may be precluded at the solid arrowhead in Figure 10, similar decreases can still arise from parasympathetic withdrawal. Although the multiple modes of autonomic control can confound applications of the law of initial values, these modes and their associated constraints are inherent in the law of dynamic range. The law of initial values may thus predict spurious constraints with changes in basal heart period level. This is also illustrated by the open arrow of Figure 10. Translation of the basal autonomic locus along this arrow would yield a comparable decrease in heart period to that of the solid arrow discussed above and would predict a limitation of further heart period decreases. The new basal locus (open arrowhead) remains remote from the autonomic boundaries, however, and further decreases in heart period (either from sympathetic activation or vagal withdrawal) would not be precluded. The law of initial values cannot distinguish between the basal changes depicted by the solid and open arrows despite the fact that these movements are associated with dramatically different autonomic constraints. This has undoubtedly contributed to the inconsistency in the empirical manifestations of the law of initial values. Again, however, this distinction is inherent in the autonomic space model and in the law of dynamic range.

As discussed above, psychophysiological relationships in the autonomic domain entail two general classes of transforms: (a) between antecedent conditions and autonomic outflows and (b) between autonomic outflows and end-organ consequences. The examples of autonomic constraints considered above are based on the latter set of transforms. Nonlinearities in the transformation between antecedent conditions and autonomic outflows may also impose constraints on autonomic response, as considered above for the baroreflex (Figure 8). In this case, however, constraints may be seen remotely from autonomic boundaries. Although the lower asymptote of the baroreflex

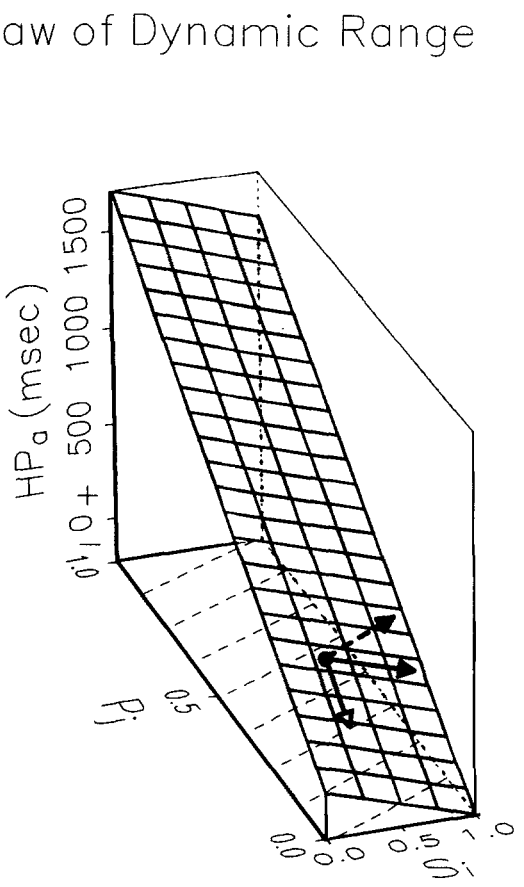

Figure 10. Law of dynamic range versus the law of initial values. (Arrows illustrate potential classes of alterations in basal autonomic loci. The solid arrow depicts an uncoupled sympathetic shift in basal state, associated with a change in baseline heart period that yields a corresponding constraint on subsequent phasic sympathetic activation. The dashed arrow illustrates a coactive shift in basal state, which is not associated with an alteration in baseline heart period but yields an equivalent constraint on sympathetic activation. The open arrow illustrates an uncoupled parasympathetic shift in basal autonomic state, which yields a change in baseline heart period equivalent to that of the solid arrow but is not associated with a further constraint on phasic sympathetic response. HP_a = autonomic contribution to heart period as a change from the intrinsic period, β. s_i and p_j are the independent activities of the sympathetic and parasympathetic innnervations at point *ij*.)

(lower right corner of autonomic space of Figure 8) may be due in part to limits of autonomic control, the upper asymptote does not approach autonomic boundaries. Thus, constraints on autonomic reactivity can arise either from the absolute limits of physiological action or from nonlinearities in activation functions within the dynamic range of response (e.g., baroreceptor nonlinearities). Although both of these general classes of constraints are subsumed by the laws of autonomic constraint, they are optimally illustrated by alternate autonomic and functional space representations. These representations afford a powerful platform for distinguishing and further exploring alternate sources of autonomic constraint.

Individual Differences in Cardiac Reactivity

Chronotropic responses to brief psychological stressors generally exceed metabolic demands and vary considerably as a function of age, genetic, dietary, task, and social factors. Cardiac responses to laboratory stressors have been shown to correlate with cardiac adjustments in real-world settings, and to predict risk for cardiovascular disease (Kamarck, in press; Matthews et al., 1986; Turner, 1989). This research is usually interpreted as reflecting individual differences in behaviorally evoked sympathetic nervous system activation. Individual differences in cardiac reactivity have been conceptualized, at least implicitly, as an unidimensional construct ranging from low to high sympathetic reactivity, even though active coping tasks are now known to affect vagal as well as sympathetic outflow to the heart (Allen & Crowell, 1989; Grossman & Svebak, 1987; Lane, Adcock, & Burnett, 1992). This is important because an individual's classification as a low cardiac reactor could stem from low sympathetic reactivity or from low to high coactivation of both autonomic branches, and classification as a high reactor could arise from elevated sympathetic reactivity, potent vagal withdrawal, or both. Investigators heretofore have relegated potential variations in the autonomic mode of chronotropic control to the error term, a practice that may obscure the relationship between cardiac sympathetic reactivity and humoral (e.g., sympathoadrenal) responses, immunological changes, and health outcomes. This practice also ignores the potential beneficial or ameliorative effect of vagal activity in adaptive reactions to stressors and health outcomes (e.g., Billman, Schwartz, & Stone, 1982). Quantifying these individual differences requires expansion of the unidimensional concept of sympathetic reactivity to a bivariate autonomic space with separate vagal and sympathetic activation dimensions. The autonomic space model presented here represents an important step toward this quantification.

The importance of the autonomic origins of cardiac reactivity is apparent when considering the putative relationship between individual differences in cardiac response and changes in catecholamine levels under stress or disease. Cardiac reactivity is thought to be positively related to changes in circulating catecholamines to a stressor (e.g., Krantz & Manuck, 1984), although this relationship is notoriously noisy. Much of this variance may be due to individual differences in vagal chronotropic response, which would degrade the relationship between cardiac reactivity and catecholamine responses. An individual who is classified as a low cardiac reactor due to a potent autonomic coactivation, for example, may show a higher catecholamine response than an individual who is classed as a high cardiac reactor due to a strong vagal withdrawal. Any such individual differences in modes of cardiac control are again relegated to the error term in contemporary conceptualizations of cardiac reactivity. To determine whether stable individual differences exist in autonomic modes of response, large-scale psychometric studies are needed in which the modes of autonomic control underlying cardiac reactivity to acute psychological stressors are examined longitudinally. Research of this form becomes feasible once valid noninvasive indices of vagal and sympathetic responses are available.

Applications

The functional (e.g., chronotropic) state of a dually innervated organ such as the heart is ambiguous with regard to its autonomic origins. Modeling the various modes of autonomic control offers a means of differentiating among similarly appearing functional states, and consequently reducing the statistical error term in psychophysiological studies. Equation 4 and its associated autonomic space, therefore, should have considerable utility for psychophysiological studies and concepts.

The autonomic space model is based on the single premise of the existence of multiple modes autonomic control (see Berntson et al., 1991; Berntson et al., in press; Koizumi & Kollai, 1992). The bivariate autonomic plane and three-dimensional effector and functional surfaces are logical consequences of these multiple modes of autonomic control. Pharmacological manipulations have provided powerful tools for confirming the existence of multiple modes of control of cardiac chronotropy, and for elucidating specific features and parameters of autonomic space. The autonomic space model is not about pharmacological blockades, however, but about autonomic organization and control. Pharmacological manipulations may not always be possible or even desirable in human psychophysiological studies. This does not detract from the conceptual implications of the multiple modes of autonomic control. Noninvasive indices of the activity of the autonomic branches, for instance, are continually under development and refinement. Although discussion of these indices is beyond the scope of this article, excellent reviews can be found in Porges (1986); Larsen, Schneiderman, and Pasin (1986); and Berntson, Cacioppo, and Quigley (1993). An illustrative study, however, serves to underscore their application from the standpoint of autonomic space.

As discussed in the previous section, individual differences in cardiovascular reactivity are associated with differential risk factors for cardiovascular disease. If subjects at risk could be identified, early intervention programs that would be infeasible for the entire population could be developed. Unfortunately, the subset of high cardiovascular reactors may be more inclusive than necessary, and this category may not be sufficiently predictive to justify such a program. Hence, it may be important to further differentiate risk factors within this group. As suggested above, one relevant dimension may be the autonomic bases of exaggerated cardiovascular reactivity. In a recent study, Cacioppo, Uchino, and Berntson (1993) examined the cardiovascular reactivity of a large groups of subjects ($N = 67$). Dependent measures included heart rate, blood pressure, catecholamine responses, and putative noninvasive indices of the parasympathetic (respiratory sinus arrhythmia, RSA) and sympathetic (pre-ejection period, PEP) control of the heart. Subsequent analyses revealed that the subset of high heart rate reactors (highest 50%) could be further differentiated based on the autonomic origins of this reactivity. Specifically, 8 of these subjects appeared to be high reactors because of parasympathetic withdrawal, as indexed by a potent stress-induced decrease in RSA, without significant change in PEP. For 7 additional subjects, high heart rate reactivity appeared to arise from a notable sympathetic activation, as evidenced by a significant decrease in PEP, without alteration of RSA. The remaining subjects displayed indications of reciprocal sympathetic activation coupled with parasympathetic withdrawal. These distinct subgroups more closely correspond to the specific modes of autonomic control, and are not adequately differentiated by heart rate measures alone. As discussed above, the cardiovascular literature suggests that risk factors for these subgroups may be widely divergent. Although noninvasive measures in this case do not permit a precise placement of basal state on the autonomic effector surface, they clearly reveal the pattern of autonomic response on the autonomic plane.

Summary

Autonomic space and its overlying effector surface offer a starting point for the development of a quantitative psychophysiology of cardiac chronotropy. Earlier studies using direct neural stimulation revealed that effector state could be represented as a surface (Levy & Zieske, 1969). The significance of the present model, however, does not revolve around the fact that the functional state of a target organ can be depicted as a surface. The surface feature is a necessary consequence of a bivariate model and merely offers a convenient graphic method of representing the modes of autonomic control. Rather, the significance of the present model is that natural behavioral stimuli can evoke a range of autonomic modes, which dictates a bivariate model of autonomic control. The specific parameters of Equation 4 and the details of the chronotropic effector surface are, of course, subject to empirical refinement. Of particular importance are normative studies of individual differences in the parameters of Equation 4, including the values and determinants of β and γ, which may permit their specification without the need for autonomic blockade. Similarly, individual differences may exist in the dynamic range of autonomic control, as cardiac responsiveness to adrenergic agonists is known to decline with age (Lakatta, 1984; Montamat & Davies, 1989). Hence, parametric studies of the values of the coefficients (c_s and c_p) across age, sex, and other factors would permit a more precise tailoring of autonomic space to individual subjects and groups. Of particular importance in future studies will be the development and further refinement of noninvasive indices of activities of the autonomic branches, which will permit a broader application of the autonomic space model.

Although the quantitative details of the effector surface are subject to refinement, the general principles and theoretical perspectives derived above are largely independent of specific parameter estimates. Clearly, in view of the multiple modes of autonomic control, the bivariate autonomic space model can provide a more accurate representation of psychophysiological relationships than can a single autonomic continuum.

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