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Social neuroscience: Autonomic, neuroendocrine, and immune responses to stress

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Abstract

The immune system is influenced by central nervous system processes that are shaped by social and psychological factors. Considerations of social factors, intrapersonal processes, and autonomic psychophysiology therefore may contribute to a fuller understanding of both immune and brain function. Research reviewed here (a) examines the socioemotional factors that contribute to, or moderate, responses to brief and chronic stressors, (b) determines whether or not stable individual differences in heart rate reactivity predict neuroendocrine and immune responses to a brief psychological stressor and to an influenza virus vaccine, and (c) investigates the autonomic origins of individual differences in low and high heart rate reactivity and their relationship to neuroendocrine and immune responses to chronic and acute stressors. Among our findings are: (a) acute psychological stressors activate the sympathetic adrenomedullary system across individuals and affect immune function; and (b) individuals characterized by high sympathetic cardiac reactivity to acute psychological stressors also show a relative activation of the hypothalamic pituitary adrenocortical system and altered immune function.

Descriptors: Psychological stressor, Individual differences, Aging, Autonomic reactivity, Neuroendocrine response, Immune response, Impedance cardiography, Respiratory sinus arrhythmia

Recent epidemiological studies have established a relationship between such social factors as social isolation, the stress of caring for a terminally ill loved one, and health. In a recent review of prospective studies, for instance, House, Landis, and Umberson (1988) found social isolation to be a major risk factor for morbidity and mortality from widely varying causes, even after statistically controlling for known biological risk factors, social status, and baseline measures of health. The negative health consequences of social isolation were particularly strong among the elderly, the poor, and blacks. Indeed, the strength of social isolation as a risk factor is comparable with health risk factors such as smoking, blood pressure, obesity, and physical activity (House et al., 1988).

Investigators have begun to address how social relationships produce these health outcomes. Friends and family, for instance, may contribute to better health by providing tangible aid and promoting better health-related behaviors (e.g., physical activity and diet). These direct effects do not appear to be sufficient, however, to account for the association between social relationships and health, nor do all social relationships promote good health (Ewart, Taylor, Kraemer, & Agras, 1991; Kiecolt-Glaser et al., 1993). Simply changing the social context, or the way in which a person thinks about or interacts with others around them, can also influence an individual's physiological reactivity (e.g., Cacioppo et al., 1990; Geen & Gage, 1977; Snydersmith & Cacioppo, 1992) and immune response (e.g., Kiecolt-Glaser et al., 1993) to psychological stressors.

Understanding the ways in which social factors impact on the brain, physiological processes, and health is becoming increasingly important for at least three reasons. First, the costs of health care are soaring, especially for the elderly who are no longer active. Finding ways to improve the quality as well as extend the length of people's lives, therefore, is consequential on both

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humanitarian and economic grounds. Second, House et al. (1988) noted that:

> Changes in marital and child bearing patterns and in the age structure of our society will produce in the 21st century a steady increase in the number of older people who lack spouses or children—the people to whom older people must often turn for relatedness and support. . . . Thus, just as we discover the importance of social relationships for health, and see an increasing need for them, their prevalence and availability may be declining. (p. 544)

Given these impending sociodemographic changes, it is important to find ways of reducing the risks faced by individuals who do not enjoy the benefits of nurturant or supportive families. Finally, the human brain has been characterized as an information-processing organ, but it is also a social brain (Gazzaniga, 1985). Research on the influence of social psychological factors on physiological processes and health may, therefore, contribute to our understanding of basic brain mechanisms (Cacioppo & Berntson, 1992).

We have been studying ways in which social factors affect intrapersonal processes and cardiac reactivity and, in turn, how individual differences in cardiac reactivity are related to neuroendocrinologic and immunologic responses to stress and health outcomes. I will focus on interindividual variations in cardiac reactivity as a means of illuminating the mechanisms underlying interactions among the autonomic, neuroendocrinologic, and immune systems. I will begin, however, by briefly illustrating how people's constructs of personal relationships can predict, if not impact directly on, cardiovascular reactivity.

Cardiovascular Activity as a Function of a Salient Interpersonal Relationship

We began our investigations by examining how an important interpersonal relationship might affect or predict cardiovascular activity and reactivity. Genetic, dietary, and behavioral factors have been found to predispose individuals to express high or low heart rate (HR) reactivity to psychological stressors (e.g., Carroll, Hewitt, Last, Turner, & Sims, 1985; Ditto & France, 1990; McIlhany, Shaffer, & Hines, 1975; Rose, 1992). There is a growing literature showing that social psychological factors also can have a strong impact on cardiovascular responses (Cacioppo & Petty, 1983; Kamarck, 1992) as well as potentiate the cardiovascular effects of factors such as sodium intake (e.g., Haythornthwaite, Pratley, & Anderson, 1992; see related studies by Bland, Krough, Winkelstein, & Trevisan, 1991; Dressler, 1983). In our initial research, we studied the social relationships and perceptions of caregivers for a family member with Alzheimer disease. The chronic stress of caregiving for a family member with Alzheimer disease has been associated with negative changes in psychological and immune function (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Not all caregivers are affected equally by this stressor, however. For example, we previously found that a caregiver's perceptions of social support moderates the negative impact of caregiving, as indexed by cardiovascular reactivity (Uchino, Kiecolt-Glaser, & Cacioppo, 1992) and immune function (Kiecolt-Glaser et al., 1991).

As part of this research, we investigated the prediction of a family caregiver's cardiovascular response by two features of the interpersonal relationship between the caregiver and the Alzheimer patient: (a) the caregiver's affection for the patient before illness, and (b) the caregiver's cohesiveness with the patient before illness (Uchino, Kiecolt-Glaser, & Cacioppo, in press). Affection before illness represents the caregiver's prior emotional bond, or the extent to which the caregiver felt strong positive emotions toward the patient prior to the onset of Alzheimer disease. Cohesion before illness represents the time spent and number of activities performed with the patient prior to the onset of Alzheimer disease. These features of interpersonal relationships are, of course, correlated, so the analyses summarized here were based on the prediction of cardiovascular activity by measures of each of these constructs while statistically controlling contributions of the other. Family caregivers' constructs of their affection for and cohesiveness with a patient before illness were measured by questionnaires during the second year of their participation in a longitudinal study. Two years later, these family caregivers performed a structured interview and a mental arithmetic task while HR and blood pressure were recorded.

Our expectations in this study were straightforward: caregiving for a patient with Alzheimer disease is a consuming task, leaving little time for caregivers to establish new social contacts or friends. Caregivers who spent relatively large amounts of their free time with the patients prior to the onset of Alzheimer disease therefore have suffered greater disruptions in their social lives. Accordingly, we reasoned that caregivers who scored high on cohesiveness before illness would show greater evidence of cardiovascular stress than caregivers who scored low on cohesiveness.

In contrast, we reasoned that caregivers who remembered the relationship before illness as being particularly affectionate may draw sustenance from the perception that they are helping a loved one in need. Consistent with this reasoning, a close caregiver–patient relationship forms an impression that caregiving is less burdensome (Williamson & Schulz, 1990) and stressful (Horowitz & Shindelman, 1983). Therefore, we reasoned that such caregivers would have less subsequent cardiovascular reactivity (Uchino et al., in press).

The results of the causal path analyses conducted to examine these hypotheses are illustrated in Figure 1. Statistically significant path coefficients confirmed that a person's construct of an important interpersonal relationship can have both positive and negative effects on cardiovascular function. Caregivers who had reported relatively high levels of cohesiveness before illness were characterized by higher resting systolic blood pressure (SBP) and diastolic blood pressure (DBP), whereas caregivers who reported relatively high levels of affection before illness were characterized by lower resting DBP and lower HR reactivity. Ancillary analyses indicated that these results could not be explained in terms of differences in the caregiver's task performance, task affect or effort, various lifestyle variables, patient status, depression, or mood (Uchino et al., in press). These data are consistent with the notion that social relations play an important, although not always beneficial, role in cardiovascular regulation and health and suggest that, across time, important interpersonal relationships may alter people's psychophysiological responses to daily irritations and stressors generally.

To understand more fully the impact of the social world on physiology and health, we are investigating how that world is realized through individual differences in cognition (e.g., interpretation, coping), physiology, and personality; how these factors change over time; and how these factors interact when individuals are confronted with a social or psychological challenge. In the remainder of this paper, I will focus on our research on interindividual variations in cardiac reactivity as a means of

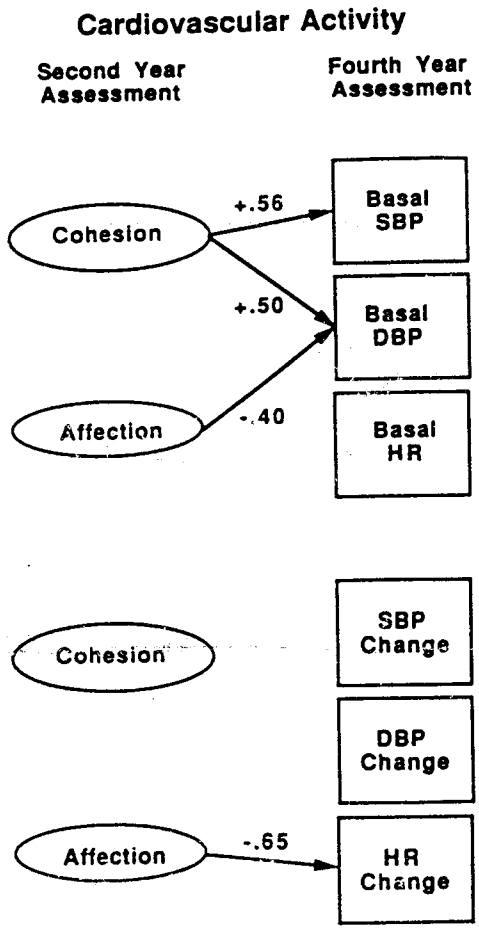

Figure 1. Top: Path analysis between family caregivers' ratings of affection and cohesiveness for the patient before illness and resting cardiovascular activity. Bottom: Path analysis between family caregivers' ratings of affection and cohesiveness for the patient before illness and cardiovascular reactivity (i.e., residualized change scores). Only statistically significant ($p < .05$) path coefficients are depicted. (From "Contruals of Pre-Illness Relationship Quality Predict Cardiovascular Response in Family Caregivers of Alzheimer's Disease Victims" by B. N. Uchino, J. K. Giecolt-Glaser, and J. T. Cacioppo, in press, *Psychology and Aging*. Copyright 1994 by the American Psychological Association. Adapted by permission.)

illuminating the mechanisms underlying interactions among the autonomic, neuroendocrinologic, and immune systems in response to acute psychological stressors. I will conclude with a study demonstrating that interindividual variations in the autonomic origins of HR reactivity are related to the cellular immune response to an influenza vaccine.

Measurement Properties of the Cardiovascular Reactivity Assessment

Prior research using cardiovascular measures has been plagued occasionally by relatively poor reliabilities. We therefore sought to develop a battery of psychological stressors that allowed us to assess people's characteristic reactions to the stressors and irritations that they confront in their daily lives. Previous research in psychophysiology proved to be helpful in this research and development work.

Kasprowicz, Manuck, Malkoff, and Krantz (1990), Kamark et al. (1992), Fahrenberg, Foerster, Schneider, Muller, and Myrtek (1986), and Sherwood, Dolan, and Light (1990), for instance, have demonstrated that the reliabilities of cardiovascular reactivity assessments are enhanced considerably by aggregation over repeated measures within measurement periods (e.g., pretask baseline, task) and across psychological stressors. This is the approach we adopted in our research. Seventy elderly subjects (36 family caregivers of patients with Alzheimer disease and 34 matched controls) performed two psychological stressors (i.e., mental arithmetic and a structured interview in counterbalanced order) while repeated measures of cardiovascular activity were recorded. The cardiovascular measures were aggregated within pretask baseline periods and within task periods with a consequent enhancement of measurement reliability. Although the purpose in using multiple stressors was to allow further aggregation and to enhance generality, we treated psychological stressor as a within-subjects factor to examine the comparability of the psychological stressors.

If interindividual variations in HR reactivity to brief psychological stressors are to be predictive of the development and/or clinical expression of disease, the cardiovascular reactions to these tasks should reflect reliable individual differences and should show significant reproducibility across time and across behavioral challenges (Manuck, Kasprowicz, Monroe, Larkin, & Kaplan, 1989; Matthews et al., 1986; Turner, 1989). The calculation of Cronbach's alphas revealed high internal consistencies. The four periods included in the analyses were baseline prior to the mental arithmetic task, mental arithmetic task, baseline prior to the structured interview, and the structured interview task. The Cronbach's alphas for the measure of HR, SBP, and DBP were .96, .96, and .97, respectively, and these internal consistency estimates were comparable for caregiver and control subjects.[1]

To determine the consistency in the cardiovascular assessments across brief psychological stressors, we correlated the levels observed prior to and during the two tasks. (Preliminary analyses indicated that the intertask correlations were not significantly different for caregivers and control subjects.) Intertask correlations for baselines, task periods, and reactivity indices were .97, .87, and .53, respectively, for HR; .82, .86, and .29, respectively, for SBP; and .83, .82, and −.27, respectively, for DBP, with all but the last correlation representing statistically significant associations. Thus, with the exception of the pres-

[1] Although heart rate is the most common index of cardiac chronotropy in this area, Berntson, Cacioppo, Quigley, and Fabro (1994) reviewed cross-species physiological evidence that both sympathetic activation and vagal activation of the heart are linearly related to heart period, at least until asymptotic levels are reached or arrhythmias occur. This linearity was also verified by direct neural stimulation of the vagus in the Sprague-Dawley rat (Berntson, Quigley, Fabro, & Cacioppo, 1992). These functions were not linear when cardiac chronometry was expressed in terms of heart rate. Moreover, nonlinearities between stimuli (e.g., blood pressure) and heart period were explicable in terms of nonlinearities within higher neural mechanisms (e.g., the baroreceptors). Although we will continue to focus on heart rate and heart rate reactivity in this article for didactic purposes and to facilitate comparisons with prior research, the results are presented in terms of heart period when discrepancies in results between the metrics occur. See Berntson, Cacioppo, and Quigley (1993c) for a detailed review of the appropriateness of the cardiac metrics of heart rate and heart period.

sor reactivity measures, the intertask correlations for the baseline, task, and reactivity measures were statistically significant and adequate.

The same cardiovascular reactivity assessment was administered to subjects 1 year later as part of a longitudinal study of caregivers. The 1-year test-retest correlations for baselines, task periods, and reactivity indices were .75, .76, and .58, respectively, for HR; .66, .62, and .55, respectively, for SBP; and .72, .70, and .25, respectively, for DBP. Thus, the baseline and task test-retest correlations were all above .60 and most were above .70, and with the exception of DBP, the test-retest reliabilities for the reactivity scores were statistically significant.

To summarize, HR and HR reactivity measures were generally stable across time and psychological stressors, SBP and reactivity measures were stable although somewhat less so than for the HR and HR reactivity measures, and DBP and reactivity measures were relatively instable across tasks and time. These data are consistent with those reported previously in the literature (Fahrenberg et al., 1986; Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991; Manuck et al., 1989).

The 1-year follow-up also revealed that subjects showed some habituation to the structured interview stressor but none to the mental arithmetic stressor. Therefore, we replaced the structured interview task with a speech stressor because it is an example of a real-world stressor that can be implemented in the lab, and additional research confirmed (a) high intertask correlations across a set of psychological stressors including the speech stressor, a modified Stroop test, and the mental arithmetic task, and (b) the largest mean and range in HR reactivity were found in response to the speech and mental arithmetic stressors.[2]

Given that our cardiac reactivity protocol was suitable for studying interindividual variations in cardiac chronotropic responses to brief psychological challenges, we investigated the differences between high and low HR reactors in their neuroendocrine and immune responses to stress potential mechanisms that warranted further scrutiny.

Neuroendocrine and Immune Responses to Stress by Low and High HR Reactors

Chronic or long-term psychological stressors such as caregiving for a family member with Alzheimer disease (Kiecolt-Glaser et al., 1991), marital strife (Kiecolt-Glaser et al., 1987), and bereavement (Schleifer, Keller, Camerino, Thornton, & Stein, 1983) are associated with immunological down-regulation. Chronic stressors, however, are not a ubiquitous part of nearly everyone's daily life. They therefore may provide an important but limited model for examining the mechanisms underlying the heterogeneity in people's response to psychological stressors and their susceptibility to disease. On the other hand, brief psychological stressors are commonplace and, as demonstrated earlier, can be implemented in the laboratory. The immunological consequences of brief psychological stressors have been studied only recently (see review by Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992). Although the results from the few studies that exist on acute stress and immune function suggest some consistency in effects, different subsets of immune measures have been used, making comparisons across studies difficult. The first aim of our study, therefore, was to examine more comprehensively the effects of a brief psychological stressor on multiple aspects of autonomic, neuroendocrinologic, and immunologic responses (Sgoutas-Emch et al., in press).

Studies by Manuck, Rabin, and colleagues have provided preliminary evidence that individuals who exhibit relatively high cardiovascular and/or catecholaminergic reactivity also exhibit larger immune responses to stress (Bachen et al., 1992; Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991). These studies are important because they bear on possible autonomic and neuroendocrine mechanisms that contribute to the immunological changes to psychological stressors. For instance, these researchers posited that acute psychological stress activates the sympathetic adrenomedullary axis but not the hypothalamic pituitary adrenocortical axis. Consistent with the involvement of the sympathetic adrenomedullary system in immunological regulation, epinephrine infusions in vivo have similar consequences to those observed following acute psychological stress, including decreases in blastogenic responses to mitogens and increases in natural killer (NK) cell number and cytotoxicity (Crary et al., 1983).

The hypothalamic pituitary adrenocortical system also has been shown to have immunoregulatory effects (Rupprecht et al., 1991). Although the pituitary adrenocortical system is governed by hypothalamic mechanisms that can affect autonomic activity (Sternberg, Chrousos, Wilder, & Gold, 1992), the extant research is unclear about the involvement of the hypothalamic pituitary adrenocortical system in response to brief psychological stressors (e.g., Lovallo, Pincomb, Brackett, & Wilson, 1990; Manuck et al., 1991). Therefore, our second aim was to track catecholaminergic and cortisol responses to brief psychological stressors in high and low HR reactors.

In light of the data demonstrating that catecholamine infusion decreases blastogenic responses to mitogen and increases NK cell number and cytotoxicity, we were less interested in studying individual differences in catecholaminergic activation than in determining whether interindividual variability in HR reactivity would predict differences in neuroendocrinological and immunological responses.

HR reactivity was selected primarily for two reasons. First, Knapp et al. (1992) examined autonomic and immunological responses while subjects recalled and relived maximally disturbing and maximally pleasurable emotional experiences. Correlational analyses between changes in autonomic and immunological variables during the negative emotional task revealed that HR correlated negatively and significantly with blastogenic responses to a mitogen (phytohemagglutinin) and positively and significantly with NK cell numbers and total lymphocyte cell numbers. These correlational data suggest that HR reactivity may be a marker or outcome of a common mechanism triggered by an acute psychological stressor that contributes to the regulation of cellular immune responsivity.

[2]Nonverbal forms of the mental arithmetic task have been developed, based on the assumption that the verbal component adds error variance in cardiovascular assessments (see Kamarck, 1992). However, we have retained the verbal form of the mental arithmetic stressor, with minute-by-minute adjustments in task difficulty to equate performance and to maximize involvement because (a) mental arithmetic demands continued concentration but involves minimal physical effort and metabolic requirements (Turner, 1989) and the public nature of the response may enhance its generality to interpersonal stressors in real-world settings (Snydersmith & Cacioppo, 1992), (b) there is extensive literature on verbal mental arithmetic as an active coping task (e.g., see Matthews, Weiss, Detre, Dembroski, Falkner, Manuck, & Williams, 1986), and (c) our studies indicate that it produces heart rate reactivity assessments that are internally consistent, reliable over at least 1 year, and generalizable to other brief experimental stressors.

Second, stable and generalizable individual differences in HR reactivity are identifiable when the reactivity assessment is based on multiple measures of HR during baseline and stressor periods (e.g., Kamarck et al., 1992; Kasprowicz et al., 1990; Sherwood et al., 1990; Turner, 1989). As shown above, this stability and generalizability contrasts with the high variability typically associated with catecholaminergic reactivity within and across individuals.

On a related point, in prior research investigators have relied on internal analyses to examine individual differences in neuroendocrine and immune responses to acute psychological stressors. To address whether our experimental observations represented stable characteristics of individuals, subjects who were characterized by very high or very low HR reactivity to a speech stressor in our laboratory were recruited to participate in the main study 3 weeks later at the Ohio State University Hospital, where cardiovascular, neuroendocrine, and immune responses to a speech stressor were determined.

Forty-four healthy undergraduate men ranging in age from 18 to 31 years participated in a prescreening study in which HR reactivity to a brief speech stressor was assessed. Strict inclusion criteria were applied to ensure subjects were in good health, were not dealing with a significant life or academic stressor (e.g., course exam) at the time of their participation, and were not speech, math, or needle phobic (Sgoutas-Emch et al., in press). Following adaptation to the lab, HR and blood pressure were recorded continuously over a 3-min baseline period and in response to a speech stressor (Saab, Matthews, Stoney, & McDonald, 1989). We first examined the internal consistency of HR, SBP, and DBP from the prescreening component. The two sets of data included in the analyses were baseline and speech periods. Cronbach's alphas for the measure of HR, SBP, and DBP over these periods were .80, .73, and .72, respectively. In addition, a repeated measures analysis of variance (ANOVA) confirmed that the speech stressor elevated HR ($M_{baseline}$ = 70.31, $M_{stressor}$ = 88.22), SBP ($M_{baseline}$ = 128.11, $M_{stressor}$ = 132.95), and DBP ($M_{baseline}$ = 72.57, $M_{stressor}$ = 78.77). We next identified individuals in the top or bottom quartiles in HR reactivity ($M_{HR\ reactivity}$ = 30.1 and 5.3 bpm, respectively) and conducted ancillary analyses to ensure high and low HR reactors were comparable in terms of basal HR and health-related behaviors. High and low HR reactors were then recruited to participate in the follow-up study in the Ohio State University Hospital.

The main study was run in the morning and consisted of four components: informed consent, explanation of task, and insertion of an in-dwelling catheter into the antecubital vein; a 30-min supine adaptation period followed by a blood draw; a 5-min baseline period (subsequent measurements verified that the prestress baseline produced as low a mean HR reading for low and high reactors as those taken as long as 1 hr after completion of the stressor); and a 12-min mental arithmetic task followed by a poststress blood draw. During the last 6 min of the stressor, subjects were exposed also to random 100-dB noise blasts. The subjects were told that the noise blasts were designed to make the task more challenging. HR and blood pressure were recorded continuously during the 5-min resting baseline and during the 12-min mental arithmetic task. The blood draws prior to and following the experimental stressor provided the materials for the neuroendocrine and immune assays.

Preliminary analyses confirmed that individual differences in HR reactivity were reliable across the testing sessions and stressors. Test–retest correlations showed that the HR reactivity to the speech stressor predicted well the HR reactivity to the mental arithmetic stressor 3 weeks later (r = +.62, p < .01). Furthermore, high HR reactors, as defined by their HR response to the speech stressor in the prescreening, displayed larger HR increases to the mental arithmetic stressor in the subsequent session.

As illustrated in Figure 2, we replicated prior research showing that the brief psychological stressor increased norepinephrine and epinephrine activity but not cortisol levels. It is this observation that has led others to suggest that brief psychological stressors activate the sympathetic adrenomedullary system but not the hypothalamic pituitary adrenocortical system. I will examine this conclusion after summarizing the effects of our stressor on immune function.

As outlined by Kennedy, Glaser, and Kiecolt-Glaser (1990), the immune system is comprised of different cell types, each with its own effects yet orchestrated to defend the body from antigens and pathogens. The human immune response can be divided functionally into two categories: nonspecific and specific responses. By nonspecific responses we refer to the general bodily defenses that result from exposure to a pathogen and include the activation of NK cells, which monitor the body and destroy virally infected and tumor cells, and the activation of macrophages, which engulf and destroy foreign substances. Specific immune responses include T-lymphocyte-mediated responses involving helper/inducer and suppressor/cytotoxic T lymphocytes (i.e., cellular immune response) and antibody production by B lymphocytes (i.e., humoral immune response). Among the actions of helper/inducer T lymphocytes are the activation of antibody production by B lymphocytes, stimulation (by the release of lymphokines) of T-helper cell and cytolytic T-cell production, and enhancement (via the release of gamma-interferon) in the lytic power of NK cells. Suppressor/cytotoxic help regulate the magnitude or duration of an immune response by suppressing T-helper cells and antibody production by B lymphocytes. Because the cells of the immune system are pooled in

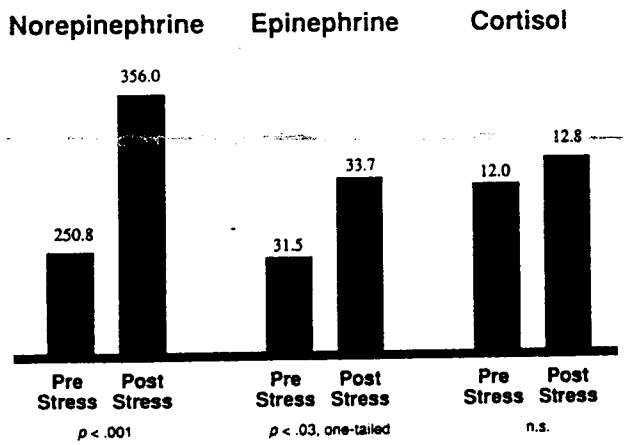

Figure 2. Mean neuroendocrine reactivity to acute psychological stress. Norepinephrine and epinephrine are expressed as pg/ml; cortisol is expressed as μg/dl. (From "The Effects of an Acute Psychological Stressor on Cardiovascular, Endocrine, and Cellular Immune Response: A Prospective Study of Individuals High and Low in Heart Rate Reactivity" by S. A. Sgoutas-Emch, J. T. Cacioppo, B. N. Uchino, W. Malarkey, D. Pearl, J. K. Giecolt-Glaser, and R. Glaser, in press, *Psychophysiology*. Copyright 1994 by the Society for Psychophysiological Research. Adapted by permission.)

diverse locations throughout the body, circulating blood plays an important role in transporting the immune cells among organs (e.g., spleen, thymus, bone marrow) and sites of antigens.

Two methods commonly are used to interrogate cellular immune status. The percentage of various kinds of blood cells can be quantified in vitro by using commercially available monoclonal antibodies. For instance, the CD4+ marker on the cell surface identifies helper/inducer lymphocytes, whereas the CD8+ marker identifies suppressor/cytotoxic lymphocytes (Kennedy et al., 1990). Because a balance of helper/inducer and suppressor/cytotoxic T lymphocytes is important in mounting an effective immune response (Herbert & Cohen, 1993), the ratio of CD4+/CD8+ cells is often of interest. As illustrated in the top panel of Figure 3, the brief psychological stressor resulted in more circulating suppressor/cytotoxic T (CD8+) cells, a reduction in the ratio of circulating helper to suppressor/cytotoxic T cells (CD4+/CD8+), and more circulating NK cells.

The functional status of cellular immunity typically is examined by quantifying the blastogenic response to mitogens in vitro, a procedure thought to model how cells respond to antigens in vivo (Kennedy et al., 1990). The most commonly used mitogens are concanavalin A (Con A) and phytohemagglutinin (PHA), which can stimulate T-lymphocyte proliferation, and pokeweed mitogen, which can stimulate B-lymphocyte proliferation. In addition, NK cytotoxicity can be measured by incubating NK cells with radioactively labeled target (e.g., tumor) cells and, following incubation and harvest, measuring the radioactivity released from the lysed cells (Kennedy et al., 1990). As illustrated in the bottom panel of Figure 3, analyses of T-lymphocyte and NK cell function confirmed that the blastogenic response to Con A decreased and NK cell cytotoxicity increased as a result of exposure to the psychological stressor. Although the pattern of results for PHA paralleled that observed for Con A, this test was not significant.

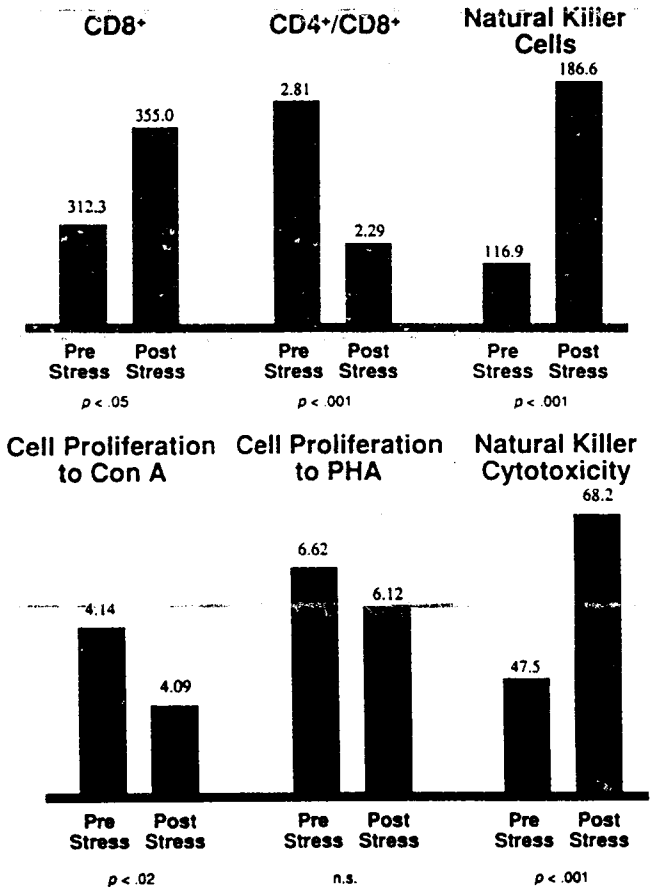

Figure 3. Cellular immune response to acute psychological stress. Top: Mean cell numbers (cells/m^3) as a function of stress. Bottom: Mean blastogenic response (expressed as average logarithms of the counts/min values) as a function of stress. (From "The Effects of an Acute Psychological Stressor on Cardiovascular, Endocrine, and Cellular Immune Response: A Prospective Study of Individuals High and Low in Heart Rate Reactivity" by S. A. Sgoutas-Emch, J. T. Cacioppo, B. N. Uchino, W. Malarkey, D. Pearl, J. K. Giecolt-Glaser, and R. Glaser, in press, *Psychophysiology*. Copyright 1994 by the Society for Psychophysiological Research. Adapted by permission.)

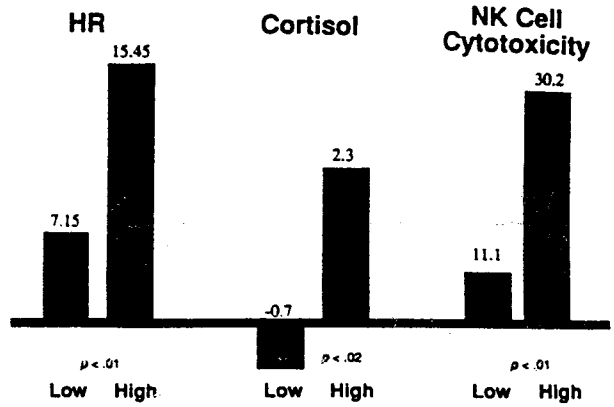

Figure 4. Heart rate (bpm), plasma cortisol concentration (μg/dl), and natural killer cell response (% lysis) to acute psychological stress in high and low heart rate reactors. (From "The Effects of an Acute Psychological Stressor on Cardiovascular, Endocrine, and Cellular Immune Response: A Prospective Study of Individuals High and Low in Heart Rate Reactivity" by S. A. Sgoutas-Emch, J. T. Cacioppo, B. N. Uchino, W. Malarkey, D. Pearl, J. K. Giecolt-Glaser, and R. Glaser, in press, *Psychophysiology*. Copyright 1994 by the Society for Psychophysiological Research. Adapted by permission.)

Thus, the analyses of the cellular immune response to the psychological stressor produced a consistent picture, revealing a pattern of immune response that is in accord with the activation and immunoregulatory effects of the sympathetic-adrenomedullary axis.

Importantly, when we contrasted the high and low HR reactors' neuroendocrine and immune responses to stressors, a different pattern emerged. For instance, the stressor comparably elevated plasma catecholamine levels in high and low HR reactors, but high HR reactors in contrast to low HR reactors showed higher stress-related levels of plasma cortisol. As illustrated in Figure 4, analyses also indicated that the high HR reactors showed larger stress-related increases in NK cell lysis. These data suggested to us that the hypothalamic-pituitary-adrenocortical axis should not be ignored and that interindividual variation in hypothalamic-pituitary-adrenocortical activation by brief psychological stressors may help explain why daily irritations and stressors have greater health consequences for some individuals than others. The hypothalamic-pituitary-adrenocortical system is governed by hypothalamic mechanisms that can also affect autonomic activity (Sternberg et al., 1992), but the present data showed clearly that cortisol is elevated by brief psychological stressors in high but not low reactors

(Sgoutas-Emch et al., in press). The finding that cortisol concentration was heightened in high reactors is particularly provocative in view of the extensive literature linking cortisol with the down-regulation of multiple aspects of cellular immune function.

Although hypothalamic mechanisms and corticotropin-releasing hormone can affect HR reactivity by altering the sympathetic and/or parasympathetic activation of the heart, an individual's classification as high in HR reactivity ignores possible individual differences in the autonomic origins of this reactivity. An individual's classification as high in HR reactivity could originate in elevated sympathetic reactivity, vagal withdrawal, or reciprocal activation of the sympathetic and vagal outflows to the heart. Conversely, an individual's classification as low in HR reactivity could stem from low sympathetic (and vagal) reactivity or from low-to-high coactivation of the sympathetic and vagal controls on cardiac chronotropy. Although psychophysiologists have long recognized these issues (e.g., Pollak & Obrist, 1988), research on cardiac reactivity generally has emphasized variations in HR reactivity rather than variations in the autonomic origins of HR reactivity. The classification of subjects in terms of HR reactivity relegates variations in the autonomic origins of HR reactivity to the error term, a practice that may obscure the relationship between autonomic responses to stressors and behavioral, humoral, or clinical outcomes. In the following section, we summarize a series of experiments on the effects of brief psychological stressors on the autonomic determinants of cardiac response. We then return to reexamine our observations that acute psychological stressors activated the sympathetic adrenomedullary system across individuals and affected immune function, and that individuals characterized by high cardiac reactivity additionally showed a relative activation of the hypothalamic-pituitary-adrenocortical system and altered immune function.

Individual Differences in the Autonomic Origins of HR Reactivity

Quantifying individual differences in the autonomic determinants of HR reactivity requires replacing the conceptualization of HR reactivity as a unidimensional (e.g., sympathetic activation) vector with a bivariate autonomic space. We recently outlined such a bivariate autonomic space (Berntson, Cacioppo, & Quigley, 1991) and reviewed the evidence consistent with the notion that HR reactivity can be derived from multiple modes of autonomic control (Berntson, Cacioppo, & Quigley, 1993b). According to this conceptualization, reliable interindividual variations may exist not only in HR reactivity to psychological stressors but also in sympathetic cardiac reactivity and in vagal cardiac reactivity. Furthermore, because grouping individuals by sympathetic cardiac reactivity and by vagal cardiac reactivity represent two separate autonomic determinants of HR reactivity, each should moderately predict individual differences in HR reactivity but may be only weakly related to each other. Unfortunately, there is a paucity of research in the contemporary literature on individual differences in the autonomic origins of HR reactivity. The purpose of our next study, therefore, was to go beyond HR reactivity to investigate individual differences in its autonomic origins.

Healthy undergraduate women volunteered to participate in this study (M_{age} = 18.8 years), and complete data were obtained from a sample of 67 subjects (Cacioppo, Uchino, & Berntson, in press). Following adaptation, cardiovascular and respiratory measures were made during a 2-min standing baseline and a 2-min sitting baseline. The order of postural testing was counterbalanced across subjects, and 30 s were allowed after the assumption of a given posture before baseline measures were initiated. After baseline testing, subjects were given 4 min to prepare and 4–5 min to present their speeches; recordings were obtained only during speech presentation. Approximately half (2 min) of the speech was delivered while seated, and approximately half (2 min) of the speech was delivered while standing. The same counterbalance order for postural testing used during baseline was used during the presentation of the speech. Subjects assumed the initial posture (sitting or standing) during the final 30 s of the speech preparation. Recordings were not initiated, however, until subjects began their speech. After speaking for 2 min, the recordings were paused surreptitiously, and subjects were instructed to change posture and to continue their speech. Subjects assumed the alternate posture (standing or sitting) and continued speaking. Thirty seconds later, the recordings were again surreptitiously initiated and continued for another 2 min, at which point recordings were stopped and subjects were instructed that they had done well and could stop (Cacioppo et al., in press). The postural manipulation allowed us to examine the reliabilities of respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) reactivity at two different levels of the autonomic activation of the heart.

The measures of RSA and PEP were selected because they represent two of the most promising noninvasive measures of the autonomic control of the heart currently available. The high-frequency (i.e., RSA: 0.12–0.40 Hz) component of the oscillations of heart periods provides a marker of vagal control as long as significant variations in respiratory activity are controlled or accounted for (Berntson, Cacioppo, & Quigley, 1993a; Grossman, Karemaker, & Wieling, 1991). The PEP, on the other hand, is inversely related to sympathetic inotropy (Binkley & Boudoulas, 1986). Shortenings in PEP accompany increases in HR resulting from adrenergic cardiostimulation but not from vagal blockade or atrial pacing (e.g., Harris, Schoenfeld, & Weissler, 1967). Studies further suggest that HR per se does not influence the PEP unless changes in HR are associated with inotropic changes or are accompanied by changes in preload or afterload (Lewis, Leighton, Forester, & Weissler, 1974).

Recall that subjects in the preceding study were categorized as high or low reactors based on their extreme HR reactivity scores to a speech stressor while sitting (Sgoutas-Emch et al., in press). As illustrated in Figure 5, nomothetic analyses indicated that the HR responses to the speech task were the result of the reciprocal activation of the sympathetic and parasympathetic branches: the speech stressor led to an elevation in HR, a reduction in RSA (depicting vagal cardiac withdrawal), and a shortening of PEP (indicating sympathetic cardiac activation; Cacioppo, Uchino, & Berntson, in press).

Idiographic analyses of these data, however, revealed considerable individual differences, with an exaggerated HR response to the stressor arising from various modes of control, ranging from strong parasympathetic withdrawal to reciprocal increases in sympathetic activation and decreases in parasympathetic activation to large increases in sympathetic activation. Among the high HR reactors, for instance, were three subgroups of individuals who showed either primarily vagal cardiac withdrawal, primarily sympathetic cardiac activation, or both vagal cardiac withdrawal and sympathetic cardiac activation.

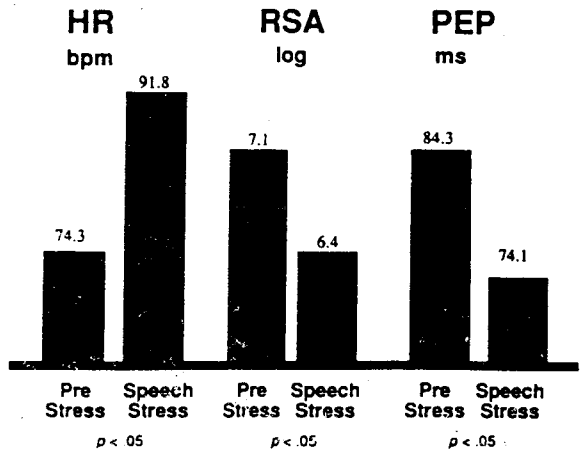

Figure 5. Mean cardiac response to the speech stressor while sitting. (From "Individual Differences in the Autonomic Origins of Heart Rate Reactivity: The Psychometrics of Respiratory Sinus Arrhythmia and Pre-ejection Period" by J. T. Cacioppo, B. N. Uchino, and G. G. Berntson, in press, *Psychophysiology*. Copyright 1994 by the Society for Psychophysiological Research. Adapted by permission.)

We next determined the measurement properties of our baseline, task, and reactivity (simple and residualized change) measures of HR, PEP, and RSA. We examined the internal consistency of each of these indices by calculating Cronbach's alphas across baseline and task periods within each posture, and again after aggregating across postures. Cronbach's alphas for the entire sample of 67 subjects ranged from .79 to .91, with aggregation improving modestly Cronbach's alpha for each index ($ps < .001$).

If individuals are to be classified not only by their HR reactivity but also by vagal and sympathetic cardiac reactivity, then HR reactivity, RSA reactivity, and PEP reactivity ideally should yield consistent classifications of individuals by their level of reactivity. To examine this question, we constructed three rank orderings of subjects by their HR, RSA, and PEP reactivity in the sitting posture, and we constructed corresponding rank orderings by their reactivity in the standing posture. We then computed the Spearman correlation for each measure to determine the stability of the rank orderings across posture—that is, at two different levels of tonic autonomic control of the heart. We then repeated these analyses using residualized change scores. In every instance, the Spearman coefficient was statistically significant at the $p < .01$ level despite differences in basal autonomic tonus across posture. Furthermore, the reliability statistics for classifying individuals by stress-induced RSA reactivity and by PEP reactivity are comparable with those for HR reactivity ($ps < .01$).

Next, we correlated basal HR, task HR, and HR reactivity (calculated as a simple change score and as a residualized change score) during sitting with the corresponding index during standing to determine test-retest reliabilities, and we performed comparable analyses for the indices based on RSA and on PEP. Results revealed that these test-retest correlations ranged from .53 to .82 ($ps < .01$). The finding that HR, RSA, and PEP reactivity indices during sitting were highly predictive of the corresponding reactivity measures during standing was encouraging because of our interest in individual differences in the autonomic substrates of cardiac reactivity.

We also sought to determine whether the interrelationships among the reactivity measures were consistent with the use of RSA and PEP reactivity as noninvasive indices of the vagal and sympathetic determinants, respectively, of stress-induced HR reactivity. Whether we used simple change scores or residualized change scores, we found the following correlations.

1. The correlations between stressed-induced changes in RSA and in HR were all negative, reflecting the negative chronotropic effects of vagal input to the heart. That is, individuals who displayed stress-induced increases in RSA also were likely to show small increases in HR, whereas individuals who showed stressed-induced decreases in RSA (reflecting vagal withdrawal) also displayed large increases in HR. Furthermore, the median correlation among these measures was statistically significant (median $r = -.53$, $p < .01$).
2. The correlations among stressed-induced changes in PEP and in HR were uniformly large and negative, consistent with the notion that stress-induced sympathetic cardiac activation shortens PEP and elevates HR. The median correlation among these measures was also statistically significant (median $r = -.54$, $p < .01$).
3. The correlations between the RSA and PEP reactivity measures revealed that these indices did not consistently covary across individuals, and the median correlation among these measures was not significant (median $r = .29$, n.s.).

The results of this study, therefore, were consistent with the notion that stress-induced changes in RSA and in PEP can vary independently and that each predicts unique autonomic determinants of HR reactivity.

The use of RSA and PEP to index stress-induced changes in the autonomic control of the heart is not without controversy, of course, and alternative indices (e.g., rate-corrected PEP, low-frequency heart-period variability) have been proposed in the psychophysiological and cardiologic literatures (e.g., see Berntson et al., 1993b; Binkley & Boudoulas, 1986). Therefore, we undertook a single and double autonomic blockade study to evaluate PEP as an index of sympathetic control of cardiac chronotropy and RSA as an index of parasympathetic control of the heart, as well as a number of other indices (Berntson, Cacioppo, Binkley, et al., 1993; Cacioppo et al., 1993). Although autonomic blockades can help illuminate the underlying autonomic origins of cardiac indices, systematic biases in estimates of the contributions of the autonomic branches can arise from both methodological and physiological factors (e.g., due to interactions among the autonomic branches at the level of the organ; indirect or reflexive alterations in the unblocked branch; nonselective actions of the blocker agents). Consequently, we developed autonomic estimates that were based on data from single and double blockade conditions and that allowed quantification of systematic biases (Berntson, Cacioppo, & Quigley, 1993c).

Subjects were tested under three drug conditions (saline, atropine sulfate, metoprolol) on 3 consecutive days in the Ohio State University Hospital; drug condition was counterbalanced across subjects and days. Cardiovascular and respiratory measures were obtained before and after infusion of either saline (saline condition), atropine sulfate (atropine condition), or metoprolol (metoprolol condition). Subjects who qualified for participation in the study were tested under all three drug conditions, and the order of drug administration was counterbalanced across sub-

jects. Following venipuncture at each session, subjects rested quietly for 30 min to allow adaptation to the laboratory, and initial baseline recordings were made during the final 3 min of this adaptation period. Intravenous infusion of saline, metoprolol (14 mg), or atropine sulfate (2 mg) followed (using a double-blind procedure), and subjects sat quietly for 15 min. Recordings were taken during the final 3 min of this postinfusion baseline and in response to an orthostatic stressor (3-min standing, 3-min sitting, order counterbalanced). Subjects then were exposed to a 3-min reaction time, mental arithmetic, and speech stressors, with a resting 3-min baseline preceding each stressor, and the order of stressors counterbalanced across days and subjects. At the end of the metoprolol session, atropine sulfate was infused and responses were monitored during the postinfusion (i.e., double blockade) baseline and during orthostatic stressor (Berntson, Cacioppo, Binkley, et al., 1993; Cacioppo et al., 1993).

Analyses revealed that drug condition was unrelated to the cardiovascular measures at preinfusion baseline, as would be expected given the counterbalancing and double-blind procedures that were used. As illustrated in the left panel of Figure 6, HR during the postinfusion baseline varied significantly as a function of autonomic blockade, with mean HR being about 72 bpm under saline, about 119 bpm under atropine, about 61 bpm under metoprolol, and 101 bpm under double blockade ($ps < .01$). Quantitative analyses indicated that sympathetic contributions to basal HR averaged 14 bpm whereas parasympathetic contributions to basal HR averaged −43.5 bpm (Cacioppo et al., 1993).

Analyses of the blockade data further revealed that PEP reflected sympathetic but not vagal influences on the heart, and RSA reflected vagal and only nominal sympathetic influences on the heart. Quantitative analyses of the postinfusion baseline data, for instance, indicated that sympathetic contributions to RSA averaged less than 0.5 log units whereas parasympathetic contributions averaged over 5.5 log units. The quantitative analyses revealed the opposite to hold for PEP: sympathetic contributions averaged −9.6 ms whereas parasympathetic contributions averaged −0.5 ms and fell within the range of error bias (see Figure 6, middle and right panels, respectively). Analyses of the cardiac responses to the orthostatic stressor under single and double autonomic blockade replicated these results (Cacioppo et al., 1993).

The basal autonomic control of the heart, and postural effects on basal autonomic control, can be depicted in a bivariate (Sympathetic Activation × Parasympathetic Activation) autonomic space (Berntson et al., 1991, 1993b). As illustrated in Figure 7, the sympathetic and parasympathetic axes are scaled relative to the dynamic ranges of the autonomic divisions so that a given displacement along either of the axes represents an equivalent millisecond change in heart period. The cardiac effector surface in the left panel of Figure 7 represents the chronotropic state of the heart associated with all possible physiological loci in autonomic space (Berntson, Cacioppo, Binkley, et al., 1993). Because the same basal heart period may be achieved by multiple combinations of sympathetic and parasympathetic activation, basal heart period (or HR) alone does not identify a specific autonomic origin, even though knowledge of the location on the autonomic plane uniquely defines a basal chronotropic state. However, the tonic heart periods associated with the autonomic blockades provide the information needed to determine these locations on the autonomic plane (Berntson et al., 1993b).

The effects of standing on basal cardiac states is depicted by the open circle and arrow in the left panel of Figure 7, and the autonomic determinants of the cardiac response to the psychological stressors are depicted by the solid circle and arrow in the left panel. Note that (a) the loci lie generally within the lower one third of the vagal dynamic range and within the middle two

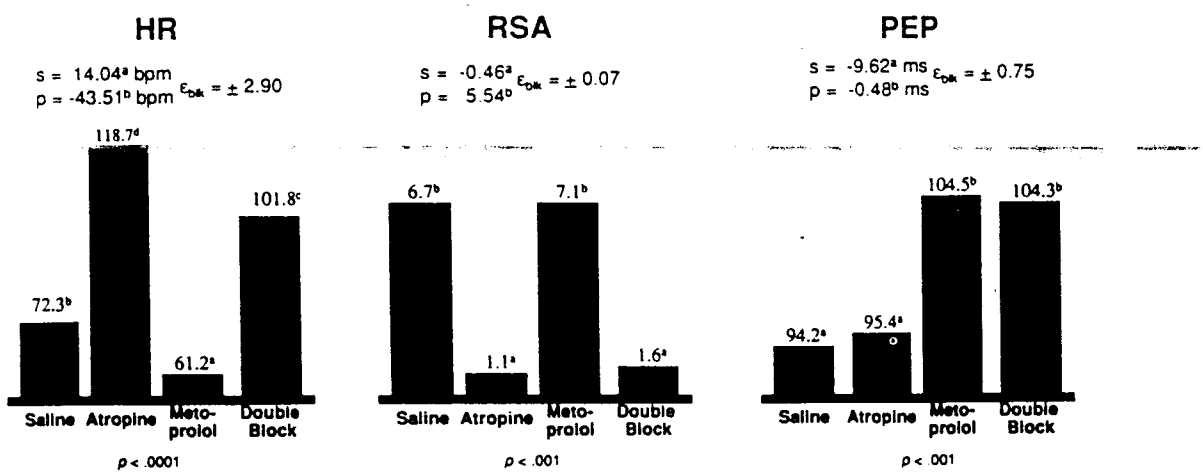

Figure 6. Autonomic cardiac control during postinfusion baseline period as revealed by autonomic blockades. Left: Mean heart rate under saline, atropine sulfate, metoprolol, and double blockade. Middle: Mean RSA under saline, atropine sulfate, metoprolol, and double blockade. Right: Mean PEP under saline, atropine sulfate, metoprolol, and double blockade. The terms at the top of each panel represent quantitative estimates of the sympathetic (s) and parasympathetic (p) contributions, respectively, to the corresponding cardiac index. The term ϵ_{blk} represents a estimate of the range of error in the quantitative estimates based on autonomic blockades. Quantitative estimates with dissimilar superscripts differ at $p < .05$. (From *Autonomic Cardiac Control: II. Basal Response, Noninvasive Indices, and Autonomic Space as Revealed by Autonomic Blockade* by J. T. Cacioppo, G. G. Berntson, P. F. Binkley, K. S. Quigley, B. N. Uchino, and A. Fieldstone, 1993. Adapted by permission.)

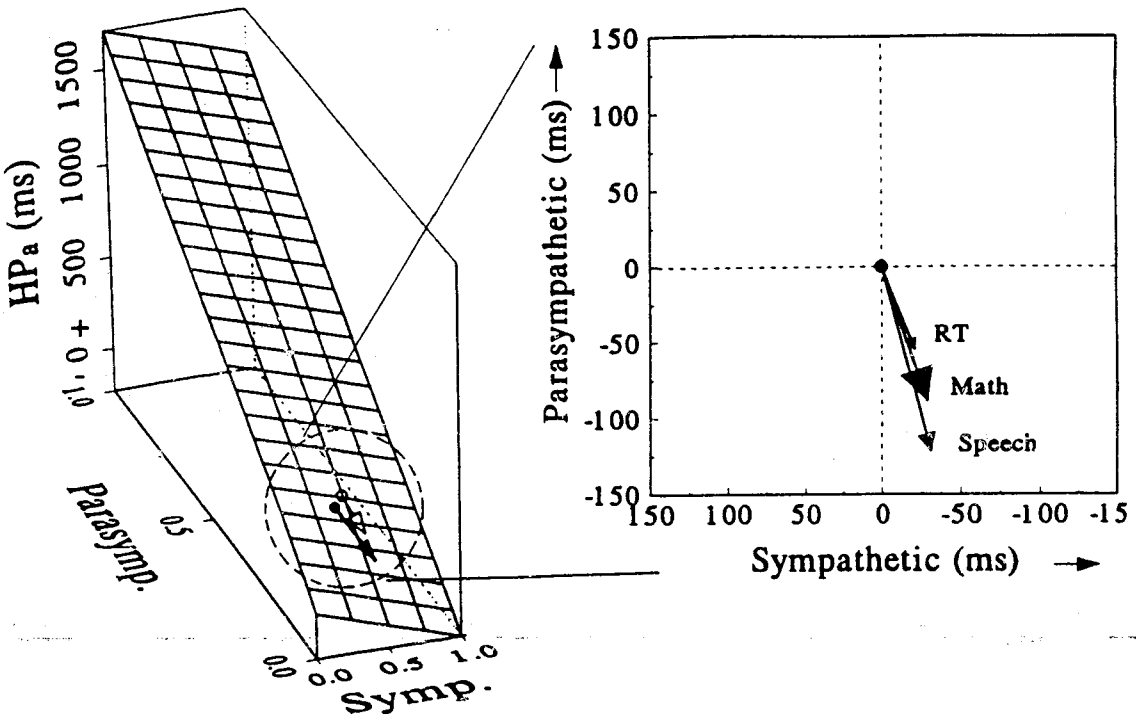

Figure 7. Cardiac responses to stress as depicted in autonomic space. Left: Autonomic space and its associated cardiac effector surface for the human. The sympathetic and parasympathetic axes are expressed in proportional units of activation. The length of the axes are scaled relative to the dynamic ranges of the autonomic divisions (see Berntson, Cacioppo, & Quigley, 1993a) such that a given displacement along either of the axes represents an equivalent millisecond change in heart period. The z-axis represents the autonomic contribution to cardiac chronotropy as a change from the intrinsic period in the absence of autonomic control (double blockade). The cardiac effector surface overlying the autonomic axes represents the chronotropic state of the heart for all loci within autonomic space (see Berntson, Cacioppo, & Quigley, 1993a). The open arrow indicates the response vector for these subjects to a change in posture from sitting to standing. The solid arrow on the effector surface depicts the mean response vector to the psychological stressors. The baseline preceding the psychological stressors is indicated by the solid dot, and the maximal response is indicated by the solid arrowhead. Right: The relevant segment of the cardiac effector surface. The axes' units are expressed in millisecond changes in heart period. The expanded inserts depict the cardiac response as movements along the two autonomic axes, expressed in milliseconds of heart period as defined by equations outlined in Berntson, Cacioppo, Binkley, Uchino, Quigley, and Fieldstone (1993). The large dot at the center of the right panel is the basal starting point, and the arrows extending from this basal point depict the overall autonomic responses to the reaction time, mental arithmetic, and speech stressors. The width of the arrowheads illustrate the size of the bias estimate (ϵ_{blk}), corresponding to the confidence range of the autonomic blockade analyses. (From *Autonomic Cardiac Control: III. Psychological Stress and Cardiac Response in Autonomic Space as Revealed by Pharmacological Blockades* by G. G. Berntson, J. T. Cacioppo, P. F. Binkley, B. N. Uchino, K. S. Quigley, and A. Fieldstone, 1993. Adapted by permission.)

thirds of the sympathetic range; and (b) as expected, vagal control is lower and sympathetic control is higher during standing than sitting and during the stressor than baseline periods. The nomothetic analyses suggest that the cardiac effects of the orthostatic stressor as well as the effects of the acute psychological stressors are implemented primarily by reciprocal activation of the sympathetic and parasympathetic branches of the autonomic nervous system.

Based on the known physiology, the postural effect depicted in the left panel of Figure 7 is largely attributable to reciprocal autonomic control by the baroreflex. Indeed, the correlation between our quantitative estimates of sympathetic and parasympathetic contributions to the cardiac response to orthostatic stressor was large and significant ($r = -.70$), confirming reciprocal cardiac activation at the idiographic level. The autonomic control of the cardiac effects of each of the psychological stressors, however, are thought to be modulated by more rostral brain systems and, therefore, were expected to reveal more interindividual variation in the mode of cardiac control.

The autonomic determinants of the cardiac responses to each of the psychological stressors is depicted in the right panel of Figure 7 (Berntson, Cacioppo, Binkley, et al., 1993). The large dot at the center is the basal starting point and the arrows extending from this basal point depict the overall autonomic responses to the reaction time, mental arithmetic, and speech stressors (Berntson, Cacioppo, Binkley, et al., 1993). This nomothetic depiction suggests that the HR reactivity evoked by each of the psychological stressors differed slightly in magnitude but were consistent with reciprocal autonomic activation. However, we also observed large and reliable individual differences

in the sympathetic and parasympathetic determinants of the cardiac response to the psychological stressors (Berntson, Cacioppo, Binkley, et al., 1993). Indeed, unlike what we found for posture, the correlation between our quantitative estimates of sympathetic and parasympathetic contributions to the cardiac response to psychological stressors was nonsignificant and opposite in sign ($r = +.09$).

These individual differences are depicted in autonomic space in Figure 8. Each arrow represents the mean cardiac response of a given subject across all three tasks, and the horizontal and vertical error bars at each arrowhead depict the standard errors of the sympathetic and parasympathetic responses, respectively, across the three tasks for a given subject. Note that (a) subjects can be grouped by their HR reactivity, their sympathetic cardiac reactivity, or their parasympathetic cardiac reactivity to the stressors; and (b) as suggested by the nonsignificant ($r = +.09$) correlation between sympathetic and parasympathetic contributions to the cardiac response to psychological stress, these rank-orderings are not simply redundant representations of interindividual variation.

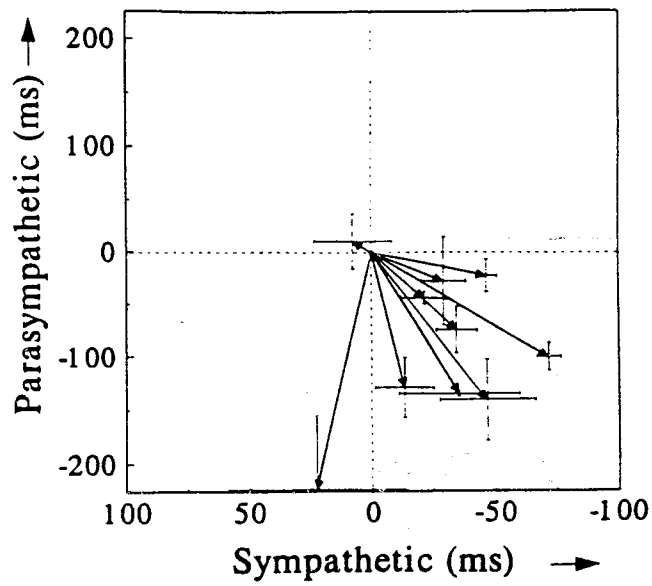

Figure 8. Interindividual variations in cardiac responses to psychological stressors as depicted in autonomic space. The arrows represent individual autonomic responses (from baseline) along the sympathetic and parasympathetic axes, expressed in milliseconds of heart period as derived from the equations in Berntson, Cacioppo, Binkley, Uchino, Quigley, and Fieldstone (1993). Each arrow represents the mean response of a given subject across all three psychological stressors. The horizontal and vertical error bars at each arrowhead depict the standard errors of the sympathetic and parasympathetic responses, respectively, across the three tasks for that subjects. (From *Autonomic Cardiac Control: III. Psychological Stress and Cardiac Response in Autonomic Space as Revealed by Pharmacological Blockades* by G. G. Berntson, J. T. Cacioppo, P. F. Binkley, B. N. Uchino, K. S. Quigley, and A. Fieldstone, 1993. Adapted by permission.)

Neuroendocrine and Immune Response to Acute Psychological Stressors in the Elderly as a Function of HR, RSA, and PEP Reactivity

Our autonomic blockade research, like our earlier research using RSA and PEP (Cacioppo, Uchino, & Berntson, in press), suggests that when individual differences in HR reactivity are based on extreme scores from the HR reactivity distribution (as in our initial study of neuroendocrine and immune responses to brief stressors; Sgoutas-Emch et al., in press), high and low HR reactors are likely to also differ in terms of sympathetic cardiac reactivity and in terms of vagal cardiac reactivity. However, if sympathetic cardiac reactivity is the better marker of hypothalamic-pituitary-adrenocortical activation by brief psychological stressors, as we have posited, then interindividual variation in sympathetic cardiac reactivity should be related more strongly than HR reactivity to stress-induced changes in plasma cortisol concentrations. As before, we further expected that this interindividual variation would add to the effects of psychological stressors on sympathetic adrenomedullary activation and would be related to cellular immune responses to brief psychological stressors. The final study discussed here tested this hypothesis. In addition, in a part of this research project directed by Jan Kiecolt-Glaser, we investigated the immunological differences of high and low reactors by tracking their immunologic response to influenza vaccine over a 3-month period.

Twenty-two elderly women ($M_{age} = 66.9$ years) participated in the study. The study was run in the morning and consisted of a 30-min supine adaptation period followed by a blood draw, a 5-min baseline period, and a 6-min mental arithmetic task and 6-min speech task (counterbalanced order). Impedance cardiovascular and ECG measurements were made during baseline and stressor periods, and blood draws were obtained during baseline, and at 6 and 12 min following onset of the stressors (i.e., mid- and poststressor). Immunological data were obtained from the pre- and poststress blood draws, and neuroendocrine measures were obtained from pre-, mid-, and poststress blood draws. That afternoon, a subset of the subjects received an influenza vaccine, and blood was drawn that afternoon, 2 weeks later, and 3 months later, to determine their response to the vaccine.

Recall that these laboratory stressors were developed to assess how individuals respond to the irritations and stress they face numerous times in their daily lives. As illustrated in Figure 9 (top panel), the psychological stressors evoked a large increase in HR that was maintained across the 12 min stress period.[3] Furthermore, just as we had observed in our prior studies (Cacioppo et al., in press; Berntson, Cacioppo, Binkley, et al., 1993), these psychological stressors resulted in a diminution of PEP and RSA, suggesting, at least at the group level, that the stressors produced a reciprocal sympathetic activation and parasympathetic withdrawal.

The mean neuroendocrine response to the stressors are depicted in the bottom panel of Figure 9. The psychological stressors produced an increase in the norepinephrine and epinephrine plasma levels but appeared to have no effect on cortisol levels. This is the same pattern of neuroendocrine response we observed in our earlier study of undergraduate men (Sgoutas-Emch et al., in press). However, in that study, neuroendocrine activity was only measured pre- and poststressor. These data suggest that epinephrine levels were maximal midstressor.

[3] The psychological stressors evoked statistically equivalent responses; therefore, the results were averaged across psychological stressors.

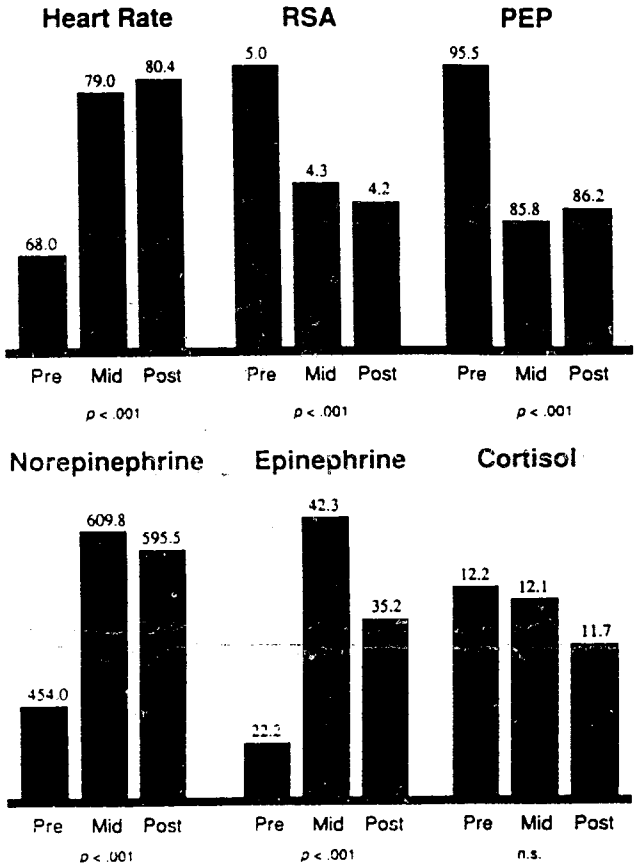

Figure 9. Top: Mean autonomic response to acute psychological stress. Heart rate is expressed as bpm, RSA as log units, and PEP as ms. Bottom: Mean neuroendocrine response to acute psychological stress. Norepinephrine and epinephrine are expressed as pg/ml, and cortisol as μg dl.

Analyses of the lymphocyte and NK cell numbers also revealed the same pattern of results as found in our study of undergraduate men. The psychological stressors resulted in more circulating suppressor/cytotoxic (CD8+) cells, a reduction in the ratio of circulating helper to suppressor/cytotoxic T cells (CD4+/CD8+), and more circulating NK cells (Figure 10, top panel). Analyses of the functional measures of cellular immune response also revealed a similar pattern of results. The acute psychological stressors decreased the blastogenic response to Con A and increased NK cell cytotoxicity (Figure 10, bottom panel). The magnitude of the effects of stress on cellular immune responses is especially impressive given cellular immune activity is diminished in the elderly.

Regression analyses (treating HR, PEP, and RSA reactivity indices as continuous rather than as dichotomous individual-difference variables) were performed to examine our hypothesis that the sympathetic substrate of HR reactivity (as indexed by PEP reactivity) rather than HR reactivity per se would be more strongly related to stress-related neuroendocrine and immune changes. Recall that in our prior study (Sgoutas-Emch et al., in press), the pre- and poststress levels of plasma cortisol were comparable, but that interindividual variations in HR reactivity predicted stress-related changes in plasma cortisol levels. Inspection of the upper left panel of Figure 11 confirms that we found the same pattern in this study: the higher an individual's HR reactivity, the greater the stress-induced change in cortisol tended to be.

The PEP and RSA measures extended these results by unveiling the autonomic substrates of the association between stress-induced changes in HR and cortisol. As indicated in the bottom panel of Figure 11, sympathetic cardiac reactivity (as marked by PEP reactivity in this paradigm; cf. Cacioppo & Tassinary, 1990) predicted well the stress-induced changes in plasma cortisol concentrations. On the other hand, vagal cardiac reactivity (as indexed by RSA changes) was unrelated to cortisol concentrations (Figure 11, middle panel). This is precisely the pattern of results one would expect if sympathetic reactivity were underlying the relationship between HR reactivity and cortisol. To further test this hypothesis, we conducted hierarchical regression analyses. Results confirmed that the relationship between stress-induced PEP and cortisol changes was highly significant ($p < .01$), and that the relationship between HR reactivity and cortisol changes was completely eliminated when statistically controlled for PEP reactivity ($F < 1$). These data, therefore, indicate

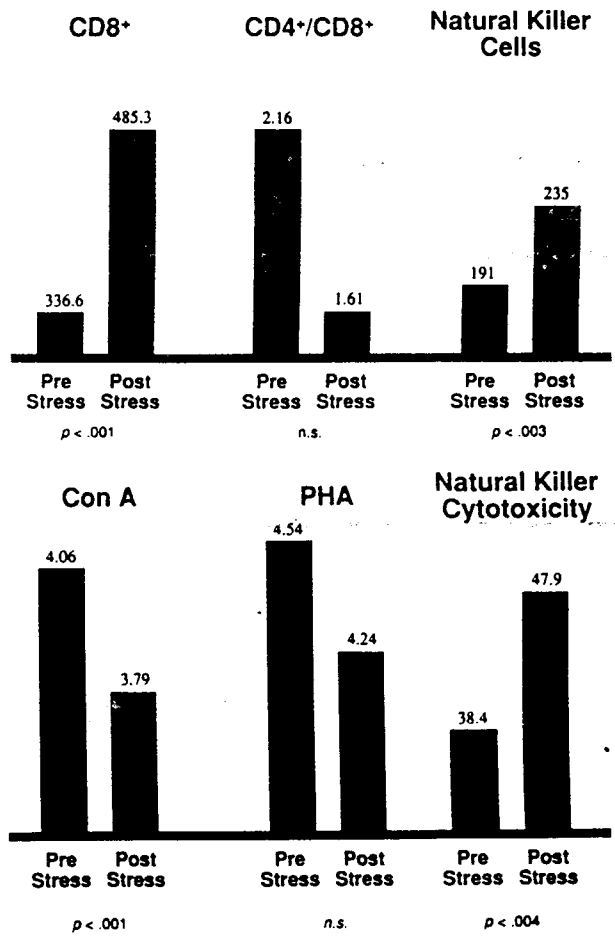

Figure 10. Cellular immune response to acute psychological stress. Top: Mean cell numbers (cells/m^3) as a function of stress. Bottom: Mean blastogenic response (average logarithms of counts/min) as a function of stress.

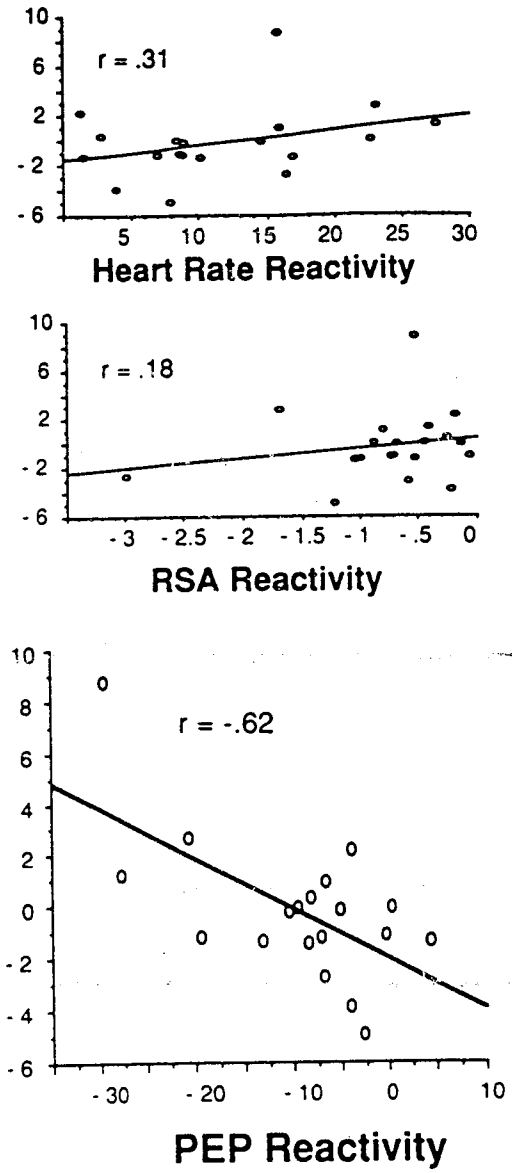

Figure 11. Cortisol response as a function of interindividual variations in heart rate reactivity (top), vagal cardiac reactivity (middle), and sympathetic cardiac reactivity (bottom).

that brief psychological stressors clearly have an impact on the hypothalamic pituitary adrenocortical axis in some individuals—specifically, individuals who are characterized by high sympathetic cardiac reactivity.

Recall that the psychological stressors used in this study had strong effects on epinephrine activity (see Figure 9). Regression analyses revealed that the increases in epinephrine concentrations evoked by the stressors were unrelated to HR reactivity ($r = +.02$) and were only modestly and differentially related to cardiac sympathetic reactivity ($r = -.37$) and vagal reactivity ($r = +.38$). These results indicate that interindividual variation in sympathetic cardiac reactivity does not simply reflect general sympathetic arousal but rather is a more specific marker of hypothalamic pituitary adrenocortical activation, possibly reflecting the common effects of corticotropin-releasing hormone on sympathetic cardiac activation and cortisol levels. As expected, we found that PEP reactivity was as strongly associated with stress-induced plasma adrenocorticotrophic hormone concentrations as it was with cortisol levels ($ps < .01$).

Finally, a subset of these subjects received an influenza vaccine 7–8 months earlier, as part of a larger study on stress and vaccine response. The T-cell response to this vaccine was measured by an influenza-virus-specific interleukin-2 (IL-2) response in vitro. Analyses of the IL-2 response revealed the expected inverted-U-shaped cellular immune response across time, with a decline in the T-cell response clearly evident by 3 months following vaccination (see Figure 12). The persistent immunological down-regulation in aged individuals, its possible attenuation (along with HR reactivity) by socioemotional processes, and its possible magnification in sympathetically reactive individuals are important because aged individuals already exhibit diminished immune function involving T cells and cytokine response, and respiratory and viral infections remain a major cause of morbidity and mortality among older adults (McGlone & Arden, 1987). Therefore, differences in the maintenance of an immune response to an influenza vaccine may be quite significant.

Our idiographic analyses provided support for the notion that individuals characterized by high sympathetic cardiac reactivity were especially at risk. Specifically, the IL-2 levels at 3 months are depicted in Figure 13. Inspection of the bottom panel of Figure 13 confirms that the T-cell response declined more quickly in individuals characterized by high sympathetic cardiac reactivity. Neither HR reactivity nor cardiac vagal reactivity predicted IL-2 levels (Figure 13, top panels). Obviously, the autonomic and neuroendocrine changes we assessed 3 months earlier did not produce these effects, but we believe that the autonomic and neuroendocrine changes we assessed in the lab at that time accurately indexed how these individuals respond on a daily basis to irritations and stressors. Thus, poorer T-cell response at 3 months is most likely the result of more frequent hypothalamic-pituitary-adrenocortical activation in the high reactors.

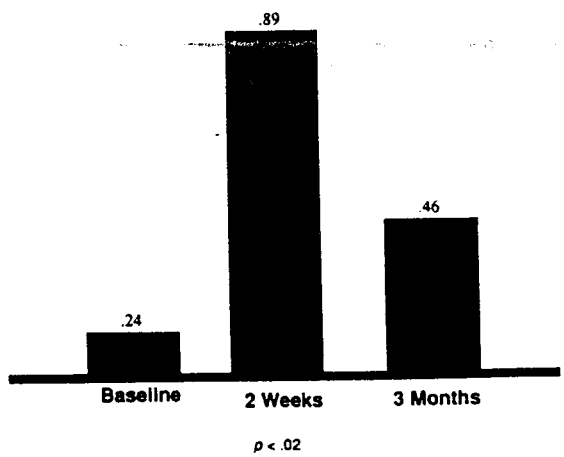

Figure 12. Influenza virus induced interleukin-2 levels in vitro the day of the inoculation of the vaccine, 2 weeks following the inoculation, and 3 months following the vaccine.

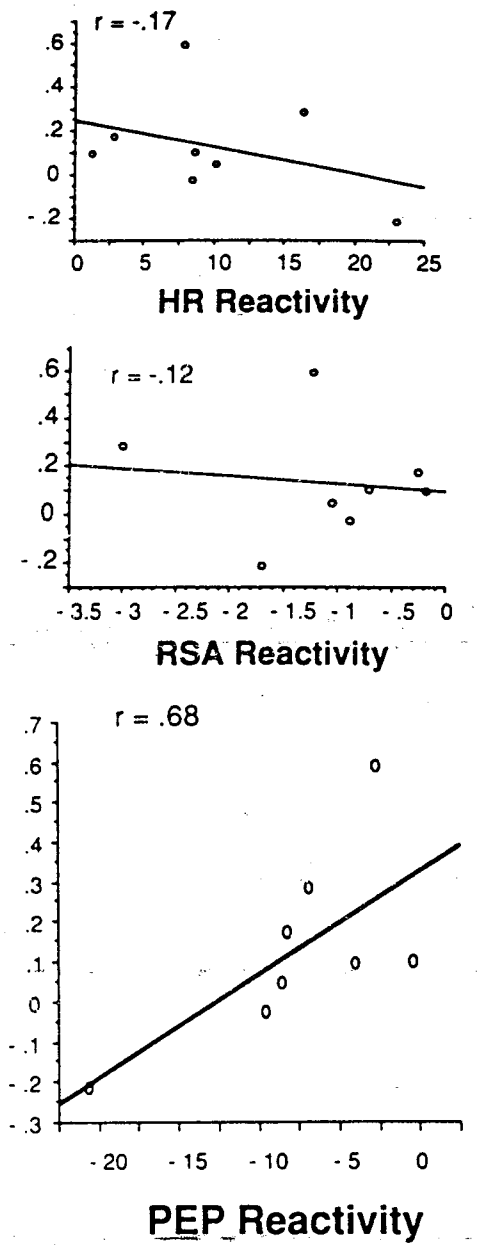

Figure 13. Influenza induced interleukin-2 levels in vitro 3 months following an influenza vaccine inoculation as a function of interindividual variations in heart rate reactivity (top), vagal cardiac reactivity (middle), and sympathetic cardiac reactivity (bottom).

Is there any additional evidence for this interpretation? We have suggested that, although brief psychological stressors can elevate catecholamine levels generally, the interindividual variation in sympathetic cardiac reactivity is a more specific marker of the activation of the hypothalamic-pituitary-adrenocortical axis than for the more general activation of the sympathetic adrenomedullary axis. If sympathetic cardiac reactivity to brief laboratory stressors reflects individual differences in the impact of daily stressors on the activation of the hypothalamic-pituitary-adrenocortical axis, then interindividual variation in the changes in plasma cortisol, in contrast to plasma epinephrine, should better predict the virus-specific T-cell response (IL-2 production) to the vaccine 3 months later. Analyses provided preliminary support for this reasoning. Stress-induced changes in plasma cortisol levels predicted IL-2 levels 3 months later, with individuals showing stress-related increases in plasma cortisol characterized by lower IL-2 levels ($r = -.56$). In contrast, stress-induced plasma epinephrine levels were positively and only weakly related to IL-2 levels ($r = +.13$). Thus, although the psychological stressors activated the sympathetic adrenomedullary system in the elderly subjects generally, these stress-induced plasma epinephrine levels were unrelated to the virus-specific T-cell response to the influenza vaccine 3 months later; the hypothalamic-pituitary-adrenocortical system, however, was particularly activated in individuals who were characterized by high sympathetic cardiac reactivity to acute psychological stressors, and both PEP reactivity and stress-induced plasma cortisol concentrations predicted maintenance of the T-cell response to the viral antigen.

To summarize, traditional views of the immune system have emphasized specific and nonspecific cellular and humoral responses to pathogens and tissue damage. However, it is now clear that the immune system is influenced by central nervous system processes that are shaped by social psychological factors. It is also becoming apparent that an understanding of immune function will be incomplete without considerations of social psychological processes and autonomic psychophysiology. For instance, we have found orderly relationships among autonomic, neuroendocrinologic, and immunologic responses to acute psychological stressors, with different mediating roles played by the hypothalamic-pituitary-adrenocortical and the sympathetic adrenomedullary systems. Although we have much more to do before we fully understand the psychological processes and brain mechanisms responsible for these relationships, psychophysiology clearly has much to contribute to the explication of the impact of social and psychological processes on neuroendocrine and immune function and health.

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