Autonomic, Neuroendocrine, and Immune Responses to Psychological Stress: The Reactivity Hypothesis[a]

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ABSTRACT: We examined the effects of brief psychological stressors on cardiovascular, neuroendocrine, and cellular immune response in 22 older women to investigate the common effects of stress across systems. Results revealed that psychological stressors heightened cardiac sympathetic activation, elevated plasma catecholamine concentrations, and affected the cellular immune response (*ps* < 0.05). In a replication and extension, 27 women caring for a spouse with a progressive dementia (high chronic stress) and 37 controls category matched for age and family income (low chronic stress) performed the 12-min laboratory stressor. Measures were taken before (low acute stress) and immediately following (high acute stress) exposure to the laboratory stressors as well as 30 min after termination of the stressor (recovery period). Acute stress again heightened cardiac sympathetic activation, elevated plasma catecholamine concentrations, and affected cellular immune responses (*ps* < 0.05), whereas chronic stress was associated with higher reports of negative affect, enhanced cardiac sympathetic activation, elevated blood pressure and plasma levels of ACTH, and diminished production of interleukin-1β (*ps* < 0.05). Correlational analyses in both studies further suggested that individuals who showed the greatest stress-related changes in HPA activation also exhibited the greatest diminution in cellular immune response.

The concept of stress connotes the exposure of an individual to a threatening stimulus or overwhelming event. Autonomic activation in response to stressors is beneficial up to a point, but excessive autonomic activation may also have hidden costs. Autonomic and neuroendocrine activation in response to stressors serves to mobilize metabolic resources to support the requirements of fight or flight. The stressors of contemporary society, however, often do not require or even allow behavioral

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fight or flight, and the autonomic and neuroendocrine reactions shown in response to acute psychological stressors substantially exceed metabolic requirements.[1] Thus, a design for the brain and stress physiology that worked well in human evolution may have maladaptive aspects that manifest as civilizations developed and life expectancy increased well beyond the reproductive years. According to the disposable soma theory of aging, for instance, it may be "disadvantageous to increase maintenance beyond a level sufficient to keep the organism in good shape through its natural life expectancy in the wild, because the extra cost will eat into resources that in terms of natural selection are better used to boost other functions that will enhance fitness" (Lithgow and Kirkwood,[2] p. 80). Given the metabolic requirements posed by the psychological stressors in today's society are often minimal, the differential responses of high versus low reactors may shed light on what these long-term costs might be and on possible mechanisms underlying the effects of stress on cellular senescence and health.

Prior research on stress and health has tended to contrast persons who are high versus low in basal physiological activation or high versus low in their exposure to a stressor. The study of autonomic, neuroendocrine, and immune response as a function of *stress-reactivity* represents a complementary approach. The same excitatory stimulus (e.g., stressor) can have profoundly different effects on physiological activation across individuals or life circumstances even when coping, performance, and perceived stress are comparable.[3] This heterogeneity in stress response may hold a key to understanding what makes some persons (or persons in some circumstances) susceptible to disease and others (or the same persons at other times) resilient to disease. Higher levels of stress are associated with susceptibility to disease.[4,5] We hypothesized that persons who show relatively large physiological stress responses to the threats and irritations of everyday life (high stress reactivity) may be at greater risk for disease susceptibility even though their affect and perceptions of coping and stress are comparable to persons who show relatively muted physiological stress responses (low stress reactivity). To examine this hypothesis, we developed a set of brief laboratory stressors representative of everyday events that were tailored to hold performance constant and to be perceived as moderately engaging and stressful by all participants (see Refs. 1, 6).

In our initial study, 44 healthy undergraduate men participated in a prescreening study in which heart rate (HR) reactivity to a brief speech stressor was assessed.[7] 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.[8] We 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.

Recordings were obtained from participants in the follow-up study during a 5-min baseline period and during a 12-min mental arithmetic task. During the last 6 min of the stressor, participants were also exposed to random 100-dB noise blasts, which the participants were told were designed to make the task more challenging. Blood draws were obtained before and following the psychological stressor and provided the materials for the neuroendocrine and immune assays.

Test–retest correlations showed that the HR reactivity to the speech stressor in the prescreen predicted well the HR reactivity to the mental arithmetic stressor 3 weeks later ($r = +0.62$, $p < 0.01$). 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.[7] Thus, participants differed reliably in terms of HR reactivity.

Analyses of cellular immune responses showed that 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 natural killer (NK) cells. Analyses of several functional immune measures revealed that the proliferation of peripheral blood leukocytes (PBLs) to conconavolin A (Con A) decreased and NK cell lysis increased as a result of exposure to the acute psychological stressors.[7] Results also replicated prior research showing that brief psychological stressors increase norepinephrine and epinephrine activity but not cortisol levels. The pattern of neuroimmune responses found in response to acute psychological stressors (e.g., Ref. 9; see Ref. 10) can be explained in terms of the activation and immunoregulatory effects of the sympathetic adrenomedullary system (SAM) axis (e.g., Refs. 11, 12). This has led to the suggestion that brief psychological stressors activate the SAM system but *not* the (hypothalamic–pituitary–adrenocortical) HPA system.

Further analyses, however, revealed HPA activation, and its associated glucocorticoid reactivity, to be a component of some individuals' response to stressors requiring active coping. Specifically, when we contrasted the high and low HR reactors' neuroendocrine and immune response to stressors in our initial study of low and high reactors, another pattern emerged.[7] The stressor elevated plasma catecholamine levels comparably in high- and low-HR reactors, but high-HR reactors showed higher stress-related levels of plasma cortisol than low-HR reactors. Analyses also indicated that the high-HR reactors showed larger stress-related increases in NK cell lysis. The finding that cortisol concentration was heightened in high reactors is particularly provocative in view of the extensive literature linking cortisol with the downregulation of multiple aspects of cellular immune function *in vitro*.[13]

Our initial investigation was based on persons who showed very low or very high heart rate reactivity to our active coping tasks. An individual's classification as high or low in HR reactivity in a given situation ignores possible differences in the autonomic origins of this reactivity, however. An individual's classification as high in HR reactivity in a given situation could originate in elevated sympathetic reactivity, vagal withdrawal, or reciprocal activation of the sympathetic and vagal outflows to the heart. Research on cardiac reactivity has generally emphasized variations in HR reactivity rather than variations in the autonomic origins of HR reactivity.[14] This classification of participants in terms of HR reactivity ignores variations in the autonomic origins of this reactivity, a practice that may obscure the relationship between autonomic responses to stressors and behavioral, hormonal, or clinical outcomes.

Quantifying differences in the autonomic determinants of HR reactivity across situations or individuals requires replacing the conceptualization of HR reactivity as a unidimensional (e.g., sympathetic activation) vector with a two-dimensional autonomic space. We recently outlined such an autonomic space model[15] and reviewed the evidence consistent with the notion that HR reactivity can derive from multiple modes of autonomic control.[16] According to this conceptualization, reliable differences exist not only in HR reactivity to psychological stressors, but perhaps even more so in sympathetic cardiac reactivity and in vagal cardiac reactivity. This conceptualization also requires a means of measuring the separable autonomic origins of HR reactivity. We have relied on the noninvasive measures of respiratory sinus arrhythmia (RSA) and cardiac preejection period (PEP) because

both psychometric (e.g., Ref. 14; cf. Ref. 17) and autonomic blockade research (e.g., Ref. 18, 19) indicate that these measures represent noninvasive indices of the autonomic control of the heart in the context of our stress-reactivity protocol.

The corticotropin releasing hormone response to stress influences autonomic as well as HPA activation.[20] This raises the possibility that variations in sympathetic cardiac reactivity might be related more strongly to stress-induced changes in plasma cortisol concentrations than vagal reactivity. In a test of this reasoning, 24 healthy undergraduate women participated in a study of psychological stress.[21] The study was run in the morning and consisted of a 30-min adaptation period followed by a blood draw, a 6-min baseline (prestress) period, and a 12-min mental arithmetic task, during the last 6 min of which participants were exposed to 100-dB noise blasts. Autonomic measurements were made during baseline and stressor periods, and blood draws were obtained during baseline and following the stressor.

Recall that the laboratory stressors were developed to assess reactions to the irritations and stressors people face numerous times in their daily lives. The psychological stressors evoked a large increase in HR that was accompanied by a diminution of PEP (reflecting increased sympathetic activation) and RSA (reflecting vagal withdrawal). The brief psychological stressor also elevated SBP and DBP. Together, these data suggest that, at least at the group level, the stressors produced a reciprocal sympathetic activation and parasympathetic withdrawal.

Nomethetic (group) analyses again suggested that the acute psychological stressor produced an increase in the norepinephrine and epinephrine plasma levels but appeared to have no effect on HPA activation. However, when we focused on stress reactivity, we again found evidence for differential HPA activation by the stressor: HR reactivity was significantly correlated with stress-related changes in plasma ACTH and cortisol (rs = + 0.50 & + 0.62, respectively, $ps < 0.02$). Furthermore, and consistent with our hypothesis, it was sympathetic cardiac reactivity that was underlying these relationships: Cardiac sympathetic activation, as measured by PEP reactivity, was significantly correlated with cortisol reactivity (r = - 0.45, $p < 0.05$), whereas cardiac vagal withdrawal, as indexed by RSA reactivity, was unrelated to cortisol changes (r = - 0.18, n.s.). Neither of these autonomic measures was correlated with plasma catecholamine reactivity to the psychological stressor (- 0.35 < rs < 0.20, n.s.).

Analyses of NK cell lysis replicated the elevation in NK lysis that we observed previously in response to the brief stressor. Analyses aimed at examining the autonomic substrates of this association confirmed our expectation that stress-induced PEP reactivity was a strong predictor of NK cell activity (r = - 0.56, $p < .01$) whereas RSA reactivity was uncorrelated with changes in NK cell activity (r = - 0.12, n.s.). As might be expected, we also observed a positive correlation between cortisol and NK cell activity changes (r = 0.51, $p < 0.02$).

Considerable evidence has now accumulated suggesting that sympathetic cardiac reactivity marks HPA activation to brief psychological stressors.[6,21–24] If stress reactivity is related to health in part through its association with cellular senescence, the health consequences of these differences may be more evident in older than younger individuals. Therefore, we studied 22 elderly women to examine the generalizability of the acute effects we have observed and to explore possible differences in response to an influenza vaccine in high and low reactors.[23] 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. Autonomic measurements were made during baseline

and stressor periods, and blood draws were obtained at baseline, midstressor, and poststressor. Immunological data were obtained from the pre- and post-stress blood draws, and neuroendocrine measures were obtained from pre-, mid-, and post-stress blood draws. That afternoon, a subset of the participants received an influenza vaccine, and blood was drawn that afternoon, 2 weeks later, and 3 months later to determine their response to the vaccine.[25]

As in our prior research, the psychological stressor evoked a large increase in HR that was maintained across the 12-min stress period. Furthermore, just as we had observed in our prior studies, the psychological stressor resulted in a diminution of PEP and RSA. Analyses of blood pressure again revealed significant pressor responses, consistent with the notion that brief psychological challenges that require active coping can produce what at the nomethetic level of analysis appears as a reciprocal sympathetic activation and parasympathetic withdrawal. In addition, we again found that the psychological stressor elevated epinephrine and norepinephrine plasma levels, and we found that the stressor also elevated ACTH levels.

Analyses of the lymphocyte and NK cell numbers in these elderly women also revealed the same pattern of results as found in our study of undergraduate men. The psychological stressor increased the number of circulating T cells and NK cells, elevated the number of circulating suppressor/cytotoxic ($CD8^+$) cells, and reduced the ratio of circulating helper to suppressor/cytotoxic T cells ($CD4^+/CD8^+$). Analyses of the functional measures of cellular immune response also revealed a similar pattern of results: The acute psychological stressor decreased the blastogenic response of PBLs to Con A and increased NK cell activity. The magnitude of the effects of stress on the cellular immune response measures is especially impressive given that cellular immune activity is diminished in the elderly.

Although nomethetically we observed reciprocal sympathetic activation and parasympathetic withdrawal, dramatic individual differences were also evident, with some persons showing little cardiac sympathetic activation or vagal withdrawal, some showing cardiac sympathetic activation but no change in vagal activity, some showing little change in cardiac sympathetic activation but significant vagal withdrawal, and still others showing both cardiac sympathetic activation and vagal withdrawal.[6] We next investigated how these individual differences related to HPA activation.

Limited *in vivo* samples of plasma cortisol may not be an optimal approach for investigating the relationships among autonomic, neuroendocrine, and immune function because not all plasma cortisol is biologically active (free) and because cortisol varies in a pulsate fashion and is subject to large diurnal variations. Given this caveat, we conducted regression analyses to examine whether the sympathetic substrate of HR reactivity (as indexed by PEP reactivity) might be more strongly related to stress-related neuroendocrine and immune changes than the vagal substrate of HR reactivity. In our prior studies,[7,21] the pre- and post-stress levels of plasma cortisol were comparable, but variations in cardiac reactivity predicted stress-related changes in plasma cortisol levels. We again found that the higher the HR reactivity, the greater tended to be the stress-induced change in cortisol ($r = 0.31$). More interestingly, sympathetic cardiac reactivity again predicted the stress-induced changes in plasma cortisol concentrations ($r = -0.62$, $p < 0.05$), and vagal cardiac reactivity was again unrelated to cortisol responses ($r = 0.18$, n.s.). This is the relationship we observed in our prior study of undergraduate men[21] and is 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 ($p < 0.01$), and that the relationship between HR reactivity and cortisol changes was completely eliminated when statistically controlling for PEP reactivity ($F < 1$). These data, therefore, indicate that brief psychological stressors have an impact on the HPA axis in *some* situations and individuals—specifically, when sympathetic cardiac reactivity is also high, possibly due to the common effects of the corticotropin releasing hormone (CRH) system.[26]

To the extent that catecholamines and glucocorticoids can have long-term suppressive effects on the immune response to infectious agents, low reactors may show superior immunosurveillance. In a pilot study to examine this hypothesis, a subset of these participants received an influenza vaccine the afternoon of their participation in our reactivity protocol. The T-cell response to this vaccine was measured by an influenza virus-specific interleuken-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.

Differences in the maintenance of an immune response to an influenza vaccine may have health relevance because the elderly already exhibit diminished cellular immune function involving T cells and cytokine responses, and respiratory and viral infections remain a major cause of morbidity and mortality among older adults.[27] Consistent with the stress-reactivity hypothesis, high sympathetic cardiac reactivity was associated with diminished immune response in this pilot study. The T-cell response declined more 3 months following the vaccination in individuals who exhibited high sympathetic cardiac reactivity to representative psychological hassles and challenges in our laboratory stress test ($r = 0.68$, $p < 0.05$). HR and cardiac vagal reactivity, on the other hand, did not predict IL-2 levels ($rs = -0.17$ and -0.12, respectively, n.s.).[6] These data, while preliminary, suggest that the autonomic and neuroendocrine changes we assessed in the lab 3 months earlier indexed how these persons responded on a daily basis to irritations and stressors given their life circumstances over this period.

If sympathetic cardiac reactivity to brief laboratory stressors reflects differences in the impact of daily stressors on the activation of the HPA axis, stress-related variations in plasma cortisol may predict the virus-specific T-cell response (IL-2 production) to the vaccine three months later better than changes in plasma epinephrine. Although results should be considered tentative given our small sample size, the analyses are consistent with this reasoning: Stress-induced changes in plasma cortisol levels predicted IL-2 levels three months later, with individuals showing stress-related increases in plasma cortisol characterized by lower IL-2 levels ($r = -0.56$, $p < 0.05$); in contrast, stress-induced plasma epinephrine levels were positively and nonsignificantly related to IL-2 levels ($r = +0.13$, n.s.). That is, the psychological stressors activated the SAM system in the elderly participants generally, but these stress-induced plasma epinephrine levels were unrelated to the virus-specific T-cell response to the influenza vaccine three months later.[6]

The studies presented thus far have demonstrated that psychological stressors can activate the autonomic nervous system and promote the release of pituitary and adrenal hormones. To the extent that catecholamines and glucocorticoids can have long-term suppressive effects on the immune response to viral and infectious agents, low reactors may show superior immunosurveil-

lance. The results of our pilot study of responses to an influenza vaccine in an aged population were consistent with this hypothesis. In a follow-up test of our hypothesis that high reactivity is associated with immunosuppression, we recently examined the association between reactivity and the steady-state expression of latent Epstein-Barr Virus (EBV) by measuring antibody titers to EBV virus capsid antigen (VCA) IgG.[28]

The competence of the cellular immune response is a critical factor in controlling primary herpesvirus infections such as EBV and maintaining virus latency.[29] Considerable evidence has accumulated linking stress with the appearance, duration, and intensity of herpesvirus infections, and the modulation of the steady-state expression of latent EBV (e.g., Refs. 29, 30). When latent EBV is reactivated, the memory immune response reacts to the increased synthesis of viral proteins resulting in heightened antibody levels to the virus. Reliable changes in antibody titers to EBV VCA IgG have been found concomitant with the downregulation of different aspects of the cellular immune response.[30-32]

Data were obtained from 54 elderly women who participated in a larger study.[28] The study was run in the morning and consisted of a 30 min adaptation period followed by a blood draw, a 6-min baseline (prestress) period, and a 12-min psychological stressor that again consisted of a 6-min mental arithmetic task and a 6-min speech task. Autonomic measurements were made during baseline and stressor periods, and blood draws were obtained during baseline, immediately after the stressor, and 30 mins after the stressor.

As in the previous studies, the psychological stressors evoked a large increase in HR that was accompanied by a diminution of PEP and RSA. The analyses of blood pressure again provided converging evidence that the brief psychological stressor activated the cardiovascular system, and analyses of the recovery period showed that these changes were short-term.

To examine what immune changes covaried with cardiac sympathetic reactivity, we conducted a median split on stress-related PEP changes. Recall that the laboratory stressors were designed to be comparably and moderately engaging for all participants. Consistent with this design, high and low reactors rated the laboratory stressor as equally unpleasant, mentally effortful, and fearful. High and low reactors also expressed comparable basal levels in state anxiety and changes in state anxiety following exposure to the laboratory stressor.

Because high and low reactors were defined based on a median split on PEP reactivity, PEP reactivity was, of course, larger in the high reactors than low reactors. High and low reactors did *not* differ in terms of basal cardiac sympathetic activation, as indexed by prestress PEP; basal cardiac parasympathetic activation, as indexed by prestress RSA; or basal HR or blood pressure. More interestingly, analyses of autonomic reactivity revealed that (a) the laboratory stressor produced significant cardiac sympathetic activation (i.e., reduction of PEP) in the high reactor group but no significant change in cardiac sympathetic activation in the low reactor group; (b) these autonomic differences in high and low reactors were also evident in HR reactivity, systolic blood pressure reactivity, and diastolic blood pressure reactivity; and (c) these autonomic differences were not manifest in cardiac parasympathetic (RSA) activity. Together, these results indicate that the laboratory stressor produced large and significant increases in the sympathetic activation of the autonomic nervous system in high reactors, whereas the stressor did not alter sympathetic activation in low reactors. Furthermore, the effect of the stressors on parasympathetic activation was comparable for high and low reactors.

The relatively long half-life of IgG of approximately 20 days suggests that differences between low and high reactors in the steady-state expression of latent EBV reflect biologically significant changes in the status of the latent EBV genome and perhaps differences in the cellular immune response in high and low reactors rather than transient reactions to the laboratory stressor *per se*. In earlier research, no relationship was found between EBV VCA IgG antibody titers and basal plasma cortisol levels,[33] even though glucocorticoids can reactivate latent EBV *in vitro*.[33,34] Because plasma cortisol fluctuates, we explored the possibility that the pulsing characteristic of glucocorticoid hormones in high- versus low-reactive individuals might reveal the relationship of these hormones and the steady-state expression of latent EBV *in vivo*. Results confirmed that high reactors showed higher EBV antibody titers than low reactors.

Previous studies from our laboratories showing the induction of EBV from latently infected cells have been performed using single concentrations of a given hormone over time. Results showed that glucocorticoids but not catecholamines reactivated latent EBV.[33] Given the prior work linking cortisol and sympathetic cardiac reactivity to psychological stressors[7,21-24] and the association found in this study between sympathetic cardiac reactivity and the steady-state expression of latent EBV, we explored the possibility that varying dexamethasone concentrations over a 72-hour period might influence the expression of the latent EBV genome in cells in a different way.[28] In some cultures, the concentration of dexamethasone was varied from 10^{-5} M to 10^{-9} M every 24 hours for 3 days. The control cells were exposed to medium or a single concentration of the hormone for 3 days.

Confirming previous reports, we found cells grown in medium without hormone showed approximately 3–5% antigen-positive cells, and a progressive enhancement of the percentage of EBV antigen-positive cells when the cells were exposed to 10^{-9} M dexamethasone (7%), 10^{-7} M dexamethasone (8%), or 10^{-5} M dexamethasone (12%) after 72 hours of incubation. This dose-response curve replicates prior research. Extending this research, we found that the cultures that were exposed to the varying concentrations of dexamethasone over a 24-hour period for three days showed approximately 36% EBV antigen-positive cells.

To summarize, previous research examining candidate stress hormones, *in vitro*, found that glucocorticoids but not epinephrine or norepinephrine reactivated EBV.[33] On the basis of our prior research on reactivity, we reasoned that changing glucocorticoid concentrations could elicit more EBV reactivation than steady-state levels. Consistent with our reactivity hypothesis, we observed three- to 10-fold greater reactivation of virus in the cells exposed to varying dexamethasone concentrations when compared to a constant level of one concentration of dexamethasone. These results suggest that autonomic reactions may mark, if not play a role in, modulating the expression of latent EBV *in vivo* and that phasic changes in glucocorticoids over time may be partly responsible for this reactivation.

The effects of stress on health have been traditionally conceptualized as operating through tonic (e.g., basal) autonomic and neuroendocrine states (e.g., Ref. 26). The thesis outlined here is that *stress-reactivity* represents an important, complementary perspective in this area. The same stressor can have profoundly different effects on physiological activation across individuals or in individuals across different life circumstances even when comparable levels of coping, performance, and perceived stress are expressed. This heterogeneity in stress response may help explain what makes some persons susceptible and others resilient to disease. Although higher levels of stress are associated with susceptibility to disease (e.g., Refs. 4, 5), the series of studies described here suggest that persons who show relatively large physiological

stress responses to the hassles, challenges, and frustrations of everyday life (high stress reactivity) may be at higher risk for disease susceptibility even when their affect and perceptions of coping and stress are comparable to individuals who show relatively muted physiological stress responses (low stress reactivity). These data also provide clues for understanding how the modulation of physiological responses induced by psychological stress can mediate immune function and health. Both low and high reactors exhibited stress-related elevations in SAM activity, but the elevations shown by low reactors tended to be smaller. More strikingly, low reactors showed little or no stress-related change in HPA activation compared to high reactors. High reactors may therefore show selected signs of diminished immunosurveillance because of the long-term suppressive effects of sympathetic activation and stress hormones on the immune response to viral and infectious agents.

REFERENCES

1. TURNER, R. J. 1989. Individual differences in heart rate response during behavioral challenge. Psychophysiology **26**: 497–505.
2. LITHGOW, G. J. & T. B. L. KIRKWOOD. 1996. Mechanisms and evolution of aging. Science **273**: 80–81.
3. CACIOPPO, J. T., B. N. UCHINO, S. L. CRITES JR., M. A. SNYDERSMITH, G. SMITH, G. BERNTSON & P. J. LANG. 1992. Relationship between facial expressiveness and sympathetic activation in emotion: A critical review, with emphasis on modeling underlying mechanisms and individual differences. J. Pers. Soc. Psychol. **62**: 110–128.
4. COHEN, S., D. A. J. TYRRELL & A. P. SMITH. 1991. Psychological stress and susceptibility to the common cold. N. Engl. J. Med. **325**: 606–612.
5. COHEN, S., D. A. J. TYRRELL & A. P. SMITH. 1993. Life events, perceived stress, negative affect and susceptibility to the common cold. J. Pers. Soc. Psychol. **64**: 131–140.
6. CACIOPPO, J. T. 1994. Social neuroscience: Autonomic, neuroendocrine, and immune response to stress. Psychophysiology **31**: 113–128.
7. SGOUTAS-EMCH, S. A., J. T. CACIOPPO, B. N. UCHINO, W. MALARKEY, D. PEARL, J. K. KIECOLT-GLASER & R. GLASER. 1994. 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. Psychophysiology **31**: 264–271.
8. SAAB, P.G., K. A. MATTHEWS, C. M. STONEY & R. J. MCDONALD. 1989. Premenopausal and postmenopausal women differ in their cardiovascular and neuroendocrine responses to behavioral stressors. Psychophysiology **26**: 270–280.
9. BACHEN, E. A., S. B. MANUCK, A. L. MARSLAND, S. COHEN, S. B. MALKOFF, M. F. MULDOON & B. S. RABIN. 1992. Lymphocyte subset and cellular immune responses to brief experimental stress. Psychosom. Med. **54**: 673–679.
10. KIECOLT-GLASER, J. K., J. T. CACIOPPO, W. B. MALARKEY & R. GLASER. 1992. Acute psychological stressors and short-term immune changes: What, why, for whom, and to what extent? Psychosom. Med. **54**: 680–685.
11. BENSCHOP, R. J., M. RODRIGUEZ-FEUERHAHN & M. SCHEDLOWSKI. 1996. Catecholamine-induced leukocytes: Early observations, current research, and future directions. Brain Behav. Immun. **10**: 77–91.
12. CRARY, B., M. BORYSENKO, D. C. SUTHERLAND, I. KUTZ, J. Z. BORYSENKO & H. BENSON. 1983. Decrease in mitogen responsiveness of mononuclear cells from peripheral blood after epinephrine administration in humans. J. Immunol. **130**: 694–697.
13. COHEN, S., G. W. EVANS, D. STOKOLS & D. KRANTZ. 1986. Behavior, Health, and Environmental Stress. Plenum Press. New York.
14. CACIOPPO, J. T., B. N. UCHINO & G. G. BERNTSON. 1994. Individual differences in the autonomic origins of heart rate reactivity: The psychometrics of respiratory sinus arrhythmia and pre-ejection period. Psychophysiology **31**: 412–419.

15. BERNTSON, G. G., J. T. CACIOPPO & K. S. QUIGLEY. 1991. Autonomic determinism: The modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. Psychol. Rev. **98**: 459–487.
16. BERNTSON, G. G., J. T. CACIOPPO & K. S. QUIGLEY. 1993. Cardiac psychophysiology and autonomic space in humans: Empirical perspectives and conceptual implications. Psychol. Bull. **114**: 296–322.
17. BERNTSON, G. G., J. T. CACIOPPO & K. S. QUIGLEY. 1993. Respiratory sinus arrhythmia: Autonomic origins, physiological mechanisms, and psychophysiological implications. Psychophysiology **30**: 183–196.
18. BERNTSON, G. G., J. T. CACIOPPO, P. F. BINKLEY, B. N. UCHINO, K. S. QUIGLEY & A. FIELDSTONE. 1994. Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by autonomic blockades. Psychophysiology **31**: 599–608.
19. CACIOPPO, J. T., G. G. BERNTSON, P. F. BINKLEY, K. S. QUIGLEY, B. N. UCHINO & A. FIELDSTONE. 1994. Autonomic cardiac control. II. Basal response, noninvasive indices, and autonomic space as revealed by autonomic blockades. Psychophysiology **31**: 586–598.
20. IRWIN, M. 1992. Central corticotropin-releasing hormone activates the sympathetic nervous system and reduces immune function: Increased responsivity of the aged rat. Endocrinology **31**: 1047–1053.
21. UCHINO, B. N., J. T. CACIOPPO, W. B. MALARKEY & R. GLASER. 1995. Individual differences in cardiac sympathetic control predict endocrine and immune responses to acute psychological stress. J. Pers. Soc. Psychol. **69**: 736–741.
22. AL' ABSI, M., S. BONGARD, T. BUCHANAN, G. A. PINCOMB, J. LICINIO & W. R. LOVALLO. 1997. Cardiovascular and neuroendocrine adjustment to public-speaking and mental arithmetic stressors. Psychophysiology, in press.
23. CACIOPPO, J. T., W. B. MALARKEY, J. K. KIECOLT-GLASER, B. N. UCHINO, S. A. SGOUTAS-EMCH, J. F. SHERIDAN, G. G. BERNTSON & R. GLASER. 1995. Cardiac autonomic substrates as a novel approach to explore heterogeneity in neuroendocrine and immune responses to brief psychological stressors. Psychosom. Med. **57**: 154–164.
24. LOVALLO, W. R., G. A. PINCOMB, D. J. BRACKETT & M. F. WILSON. 1990. Heart rate reactivity as a predictor of neuroendocrine responses to aversive and appetitive challenges. Psychosom. Med. **52**: 17–26.
25. KIECOLT-GLASER, J. K., R. GLASER, S. GRAVENSTEIN, W. B. MALARKEY & J. SHERIDAN. 1996. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc. Nat. Acad. Sci. USA **93**: 3043–3047.
26. CHROUSAS, G. P. & K. P. W. GOLD. 1992. The concepts of stress and stress system disorders. J. Am. Med. Assoc. **267**: 1244–1252.
27. MCGLONE, F. B. & N. H. ARDEN. 1987. Impact of influenza in geriatrics and an action plan for prevention and treatment. Am. J. Med. **82**: 55–57.
28. CACIOPPO, J. T., J. K. KIECOLT-GLASER, W. B. MALARKEY, L. A. KUTZ, K. M. POEHLMANN, M. H. BURLESON & R. GLASER. 1996. Autonomic modulation of the steady-state expression of latent Epstein-Barr virus. Manuscript under review.
29. GLASER, R. & J. K. KIECOLT-GLASER. 1994. Handbook of Human Stress and Immunity. Academic Press. San Diego.
30. GLASER, R., J. RICE, J. SHERIDAN, R. FERTEL, J. STOUT, C. E. SPEICHER, D. PINKSY, M. KOTUR, A. POST, M. BECK & J. K. KIECOLT-GLASER. 1987. Stress-related immune suppression: Health implications. Brain Behav. & Immun. **1**: 7–20.
31. GLASER, R., G. R. PEARSON, J. F. JONES, J. HILLHOUSE, S. KENNEDY, H. MAO & J. K. KIECOLT-GLASER. 1991. Stress related activation of Epstein-Barr virus. Brain Behav. & Immun. **5**: 219–232.
32. KIECOLT-GLASER, J. K., W. GARNER, C. E. SPEICHER, G. M. PENN, J. HOLLIDAY & R. GLASER. 1984. Psychosocial modifiers of immunocompetence in medical students. Psychosom. Med. **46**: 7–14.
33. GLASER, R., L. A. KUTZ, R. C. MACCALLUM & W. B. MALARKEY. 1995. Hormonal modulation of Epstein-Barr virus replication. Neuroendocrinology **62**: 356–361.
34. BAUER, G. 1983. Induction of Epstein-Barr virus early antigens by corticosteroids: Inhibition by TPA and retinoic acid. Int. J. Cancer **31**: 291–295.