



Invited minireview

# Stable individual differences in physiological response to stressors: implications for stress-elicited changes in immune related health<sup>☆</sup>

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## Abstract

Stress reactivity refers to a stable individual difference in response to stressors. This article addresses three questions about reactivity: (1) Are cardiovascular, endocrine, and immune responses to acute laboratory stressors stable over time and across stressor tasks? (2) Are cardiovascular, endocrine, and immune reactors the same people? and (3) Are reactive people more vulnerable to stressor-induced effects on susceptibility to infectious disease? We conclude that for many individual indicators of physiological responsiveness to stressors there is moderate stability over time and across stressor tasks indicating the possible existence of underlying dispositional characteristics; the commonality of immune and cardiovascular and hormonal responses to stress depend on the nature of regulation of the immune response being assessed; reactivity appears to have implications for vulnerability to stressor-associated disease risk (stress-by-reactivity interaction) in the natural environment, but the exact nature of this vulnerability is not as yet entirely clear.

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## 1. Introduction

There is considerable evidence that naturalistic stressors are associated with greater incidence of upper respiratory illness. However, only a fraction of those with high stress develop illness. Stress reactivity—a stable (trait-like) individual difference in physiological response to stressors, may be an important factor for explaining variability in stress-induced susceptibility. Reactivity was originally conceived of in relation to cardiovascular disease with persons showing a disposition toward greater cardiovascular response (reactors) thought to be at greater risk for stressor-induced hypertension and heart disease. More recently, reactivity has been applied to susceptibility to infectious diseases. In short, dispositions to respond to stressors with greater sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal axis (HPA) activation are

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thought to be associated with greater stressor-induced alterations (mostly suppression) of immunity. In turn, the tendency to show more extreme immune reactions to stressors is thought to characterize vulnerability to stress-induced changes in host resistance to infectious agents. Those typically responding with substantial immunoenhancement would be less susceptible to disease when exposed to naturalistic stressors, while those typically responding with greater immunosuppression would be more vulnerable to stressor-elicited disease. This hypothesis predicts a stress-by-reactivity interaction (see Fig. 1). The importance of reactivity of a specific immune marker should depend on its relevance for the host resistance to a specific infectious agent.

This paper summarizes evidence on the plausibility that cardiovascular, endocrine, and immune reactivity are stable markers of people's vulnerability to stressor-induced risk for infectious disease. We address three questions: (1) Are cardiovascular, endocrine, and immune responses to acute stressors consistent across time and stressor tasks? (2) Are cardiovascular and endocrine responders also immune responders? and (3) Are reactive people more or less vulnerable to stressor-induced effects on susceptibility to infectious disease? The mini-review format does not allow for a comprehensive review of this literature, instead we attempt to present evidence representative of the relevant literatures and our interpretations of these literatures.

### 1.1. Assessing reactivity

Mostly, reactivity is assessed in the laboratory. The underlying assumption here is that the way people respond to stressors in the lab reflects the pattern and

magnitude of physiological responses they exhibit when confronted with stressors in naturalistic settings. Traditional research paradigms in this area have determined reactivity from a single response to an acute stressor in the laboratory. However, reactivity is thought to be an enduring trait and one-shot measures do not provide information about the stability of response over time (Kamarck and Lovallo, 2003; Manuck, 1994). Studies averaging responses to a single stressor across multiple assessments are a substantial improvement. However, physiological response to stressors may vary according to the type of stressor (e.g., social conflicts versus achievement tasks) as well. To address the issue of stressor differences, other studies have averaged responses to multiple stressors during a single assessment. The optimal (but seldom used) procedure to assess a stable disposition to react to stressors would combine these strategies—averaging across both time (multiple assessment sessions) and stressor tasks (multiple stressors) (Kamarck and Lovallo, 2003).

## 2. Are physiological responses to stressors in the laboratory consistent across time and task?

If there are stable dispositions to react to stressors with greater or less response, one would expect that physiological responses to stressors (within a specific domain, e.g., blood pressure or natural killer cell cytotoxicity) would correlate across time and across stressors. That is, reactors will be reactive whether tested today or next month, and irrespective of whether the stressor is a social conflict or a demanding cognitive task. There is considerable evidence on stability of

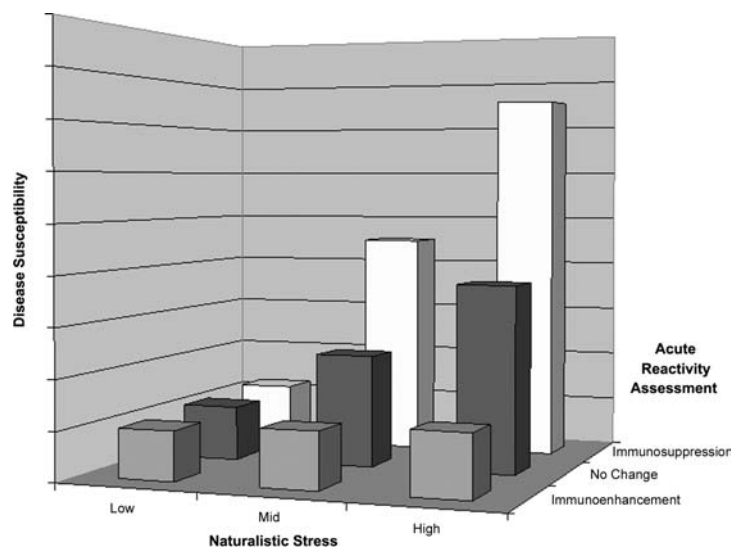


Fig. 1. Predicted role of immune reactivity in moderating stressor-induced risk for infectious disease.

response to the same task over time and more limited evidence on stability of response across different tasks.

### 2.1. Cardiovascular response

Evidence for the stability of cardiovascular response is provided by research on effects of acute laboratory stressors. In a review of 21 studies with intervals ranging from 2 days to a few months, Manuck (1994) reported average correlations of .60 for heart rate (HR) response, .51 for systolic (SBP), and .34 for diastolic blood pressure (DBP) response. Our own recent work (Cohen et al., 2000) has found similar correlations between responses to public speaking tasks given two weeks apart (.64 for HR; .67 for SBP; and .50 for DBP). However, even higher correlations have been obtained with aggregation of responses over multiple tasks and occasions of measurement (Kamarck and Lovallo, 2003). Even though these responses are reliable in the laboratory, less clear is whether laboratory cardiovascular reactivity assessments predict patterns of cardiovascular response in naturalistic settings (Kamarck and Lovallo, 2003).

### 2.2. Hormones

Acute stressors have also been found to produce changes in concentrations of circulating hormones. The hormones that have been studied in acute laboratory stress–reactivity paradigms are epinephrine and norepinephrine—products of SNS activation, and ACTH and cortisol—products of the HPA. All four hormones are commonly found to increase in response to acute psychological stressors and all are known to regulate immune response (Rabin et al., 1989). A handful of studies have addressed the stability of catecholamine reactivity. For example, Mills et al. (1993) found participants exhibited stable stressor-induced increases in both epinephrine ( $r = .41$ ) and norepinephrine ( $r = .36$ ) to the same acute laboratory stressor given 10 days apart. Cohen et al. (2000) found similar consistency across two-weeks for norepinephrine ( $r = .32$ ) but not epinephrine ( $r = -.05$ ) and Adler et al. (2002) found responsivity to acute laboratory stressors separated by 6-weeks correlated  $r = .40$  or greater for both hormones. Lundberg and colleagues (1990) compared both catecholamine and cortisol reactivities taken in the laboratory to those taken in a naturalistic (workplace) setting, separated by four months. Catecholamine inter-session correlations across the same time of day (done to control for diurnal variation) were comparable to those found in other studies (epinephrine:  $r = .47$ ; norepinephrine:  $r = .37$ ). Yet cortisol inter-session reactivity correlations across the same time of day did not reach significance ( $r = .10$ , n.s.). In contrast, Cohen et al. (2000) did find a moderate inter-session correlation for cortisol response across the same time of day ( $r = .37$ ). Similarly,

Kirschbaum et al. (1995) found cortisol levels were elevated in response to an acute laboratory stressor on each of five days with inter-session reliability of cortisol response ranging from  $r = .38$  to  $.60$ . Hawkley and colleagues (2001) also found acute stressor-induced increases in both cortisol and ACTH levels to be stable across a public speaking and math tasks on the same occasion of testing ( $r = .75$  for both). In sum, findings suggest that there are moderately stable individual differences in the magnitude of SNS and HPA hormone response to acute stressors.

### 2.3. Immune response

There are considerably fewer data on the stability of functional immune response to an acute stressor task across testing periods. Marsland et al. (1995) reported diminished proliferative response to phytohemagglutinin (PHA) and concanavalin A (ConA) when subjects gave a public speech. Although stress-induced changes in PHA response were stable across two testing periods ( $r = .50$ ), ConA response was not ( $r = .04$ ). Cohen et al. (2000) found increased natural killer cell (NK) cytotoxic response (after controlling for NK number) in reaction to a public speaking task with consistency ( $r = .52$ ) across tasks given two-weeks apart.

Several studies have reported test–retest correlations of changes in enumerative measures of immunity (circulating white blood cell populations) in response to acute stressors (e.g., Adler et al., 2002; Cohen et al., 2000, 2002; Marsland et al., 1995; Mills et al., 1995a,b). Subjects vary from college students to elderly caregivers for Alzheimer patients. These studies found that acute laboratory stressors elicited changes in the numbers and percentages of a variety of types of circulating white blood cells. However, overall significant correlations across sessions were found consistently only for increases in circulating natural killer (CD56+) cells (e.g., Adler:  $r = .22$ – $.40$ ; Cohen et al.:  $r = .69$ ; Marsland et al.:  $r = .42$ ; Mills, Haeri and Dimsdale:  $r = .41$ ; and Mills et al.:  $r = .49$ ) and T-cytotoxic/suppressor (CD8+) cells (e.g., Adler:  $r = .30$ – $.51$ ; Cohen:  $r = .50$ ; Marsland:  $r = .53$ ) and for a decrease in the helper–suppressor (CD4+:CD8+) ratio (Cohen:  $r = .39$ ; Mills, Haeri, and Dimsdale:  $r = .60$ ; Mills et al.:  $r = .55$ ).

In contrast, there is only one study examining the stability of immune reactivity *across stressors* (Marsland et al., 2002). Subjects were exposed to two different laboratory stressors, a speech task and a mental arithmetic task, on the same occasion of testing. Here, inter-task correlations were significant for the magnitude of decrease in proliferative response to PHA ( $r = .76$ ) and increase in the number of circulating NK cells ( $r = .46$ ). Stressor-induced changes in circulating numbers of CD3+, CD4+, CD8+, and CD19+ lymphocytes were not correlated across tasks.

Taken together, the results of these studies suggest that individuals are relatively consistent across time in the magnitude of several immune responses to acute stress. These include PHA stimulated proliferation, NK cell cytotoxicity, and numbers of CD56+, CD8+, and the CD4+/CD8+ ratio. Limited evidence supports similar consistency across cognitive stressor tasks, however further work (including generalizations across more varied types of tasks) is necessary.

### 3. Are cardiovascular and endocrine responders also immune responders?

An integrated view of reactivity was suggested by Boyce et al. (1995; see related discussion by Cacioppo et al., 1995) who proposed a unified biological response to stressors. This was referred to as “psychobiological” reactivity. Such an approach suggests that there are close interrelations between cardiovascular, endocrine, and immune responses to stress. Consequently, persons reactive on one of these measures will be reactive on the others as well. It follows that such persons would be at risk for stress-induced disease across multiple physiological systems.

Although Boyce and his colleagues used cardiovascular and immune reactivities interchangeably to characterize individual differences in children’s susceptibility to upper respiratory infection (discussed below), they did not report relations between cardiovascular and immune response or aggregate across domains. There is evidence, however, that some (but not other) immune responses to stress are moderately correlated with concomitant cardiovascular and plasma catecholamine responses. Stress-induced changes in immunity associated with greater cardiovascular and catecholamine response include decreased PHA (Herbert et al., 1994; Manuck et al., 1991; but not Zakowski et al., 1992) and ConA (Zakowski et al., 1992) stimulated lymphocyte proliferation, increased natural killer cell cytotoxicity, and increased numbers of CD8+ and CD16+/56+ or CD56+ cells in circulation (e.g., Cacioppo, 1994; Cohen et al., 2000; Herbert et al., 1994; Manuck et al., 1991). Adreno-receptor blocking studies have also provided support for the coordination of cardiovascular and immune response. These studies demonstrate that laboratory stressor induced changes in mitogen stimulated lymphocyte proliferation, natural killer cell activity, and numbers of circulating lymphocytes do not occur with inhibition of adrenergic stimulation of lymphocytes (Bachen et al., 1995; Benschop et al., 1994).

Although this evidence suggests that certain immune outcomes are at least partially mediated by sympathetic responses, there have been relatively few studies assessing cortisol as a potential mediator of immune reactivity

outcomes. This is because in most existing studies blood is drawn for immune measures during or immediately after stressor tasks lasting 4–10 min, whereas maximum cortisol response does not occur until approximately 20–30 min after initiation of the stressor. This negates the potential to address the possible mediating role of cortisol within the time-frame used in most reactivity studies (Cohen et al., 2000; Manuck et al., 1991). Further, many reactivity studies are conducted in the morning hours when it is difficult to detect task-induced increases in cortisol due to a rapid decline in the diurnal cortisol rhythm at that time of day. None-the-less, one study by Caudell and Gallucci (1995) found stress-induced increases in cortisol assessed one hour after stressor-task termination to be associated with concomitant decreases in NK cell activity ( $r = -.47$ ,  $p = .04$ ).

In sum, because there are few studies that have simultaneously assessed responses from multiple physiological systems, it is difficult at this point to identify which response domains cohere across a common dimension and which represent partly or entirely independent systems. However, it is likely that immune responders of certain sorts (e.g., PHA is suppressed and NK cell numbers increase) are also SNS (cardiovascular and catecholamine) responders. In short, it is our best guess that there may be several different types of “unified psychobiological response” with each type reflecting different sources of regulation of immune response for different immune measures.

### 4. Are reactive people more vulnerable to stress-induced effects on susceptibility to infectious disease?

In theory, immune reactivity might operate to distinguish between people more or less vulnerable to stress-elicited risk for any immune mediated disease (see Fig. 1). Similarly, differences in endocrine or cardiovascular reactivity would play a role if the particular response (e.g., release of epinephrine or cortisol, elevated blood pressure or heart rate) was thought to regulate an immune response that played a role in vulnerability to disease or in disease progression.

Although psychological stress has been found to be associated with greater incidence of upper respiratory infectious illness (URI), only a fraction of those with high stress develop illness. Individual differences in reactivity may be an important factor for explaining variability in stress-induced susceptibility to URI (Boyce et al., 1993, 1995; Cohen and Manuck, 1995, 2002). Because the stress-induced responses of the SNS, HPA, and immune system are thought to modulate host resistance to infectious agents, knowing the propensity of persons to respond to stressors in a specific way should increase our ability to predict if they will respond to

naturalistic stressors with increased or decreased susceptibility.

Boyce and his colleagues studied the roles of cardiovascular and immune reactivities in explaining individual vulnerability to stress-associated risk for URIs in young children. In one study, after cardiovascular reactivity to a series of acute stressors was assessed, the children were followed for 6 months for episodes of URI, which were diagnosed by a nurse practitioner, or reported by a parent or teacher (Boyce et al., 1995). Children who had responded to the acute stressors with greater increases in mean arterial blood pressure had higher rates of illness if their childcare situation was rated as high in stress, but lower rates if their childcare situation was rated as low in stress. Less understandable were the findings for the children whose blood pressures were less responsive to the acute stressor tasks. They had high rates of URIs under low childcare stress and slightly lower URI rates under high stress. Heart rate reactivity did not moderate the relation between stress and rates of illness.

In their first study of immune reactivity Boyce et al. (1993) found that immune responses to entering kindergarten predicted changes in rates of URI episodes occasioned by a major earthquake. Children who reacted to kindergarten entry with either increases in the ratio of CD4+ to CD8+ cells or increases in pokeweed-stimulated lymphocyte proliferation had higher rates of URI in response to the earthquake. Those who responded to kindergarten entry with decreases in these immune parameters showed a slight decrease in number of respiratory illnesses from pre- to post-earthquake. In their second study of immune reactivity Boyce et al. (1995) again assessed reactivity as the response to the acute stressor of entering kindergarten. This time naturalistic stress was assessed as the number of negative life events over the previous 12 months as reported by the child's parents. The investigators failed to replicate the CD4+/CD8+ reactivity effect, but did find marginal support for a similar effect of pokeweed mitogen stimulated proliferation. Moreover, they also reported that children who responded to entering kindergarten with greater increases in CD19+ (B-cell) number had more respiratory illnesses (based on parents report of symptoms) in the face of high levels of stressful life events, but lower rates of illness if they faced lower numbers of events. Overall, this work suggests that biological reactivity might moderate the stress-URI link. However, the results are complex and somewhat counterintuitive—at least in so far as responses that otherwise suggest activation of the immune system under stress (stressor-associated increases in CD4+/CD8+ cells or increases in pokeweed-stimulated lymphocyte proliferation) appear to confer heightened disease risk in individuals exposed to stress in their natural environments.

To gain a broader view of the role of reactivity in susceptibility to stress-elicited disease risk for respira-

tory infections, we undertook a study of 115 undergraduate students (Cohen et al., 2002). At baseline healthy subjects were administered a negative stressful life events checklist and were tested to assess their SNS (blood pressure, heart rate, and catecholamines), HPA (cortisol), and immune (NK cell cytotoxicity and lymphocyte subsets) reactivities to two laboratory speech tasks administered two weeks apart. The reactivity markers that were evaluated were all found to be reliable measures of response across the two week interval (Cohen et al., 2000) hence responses were averaged across the laboratory assessments to create “stable” reactivity scores. After the assessments were completed, participants were followed weekly for 12 consecutive weeks during “cold” season. At each follow-up they completed a measure of perceived stress experienced over the last week. They were also instructed to contact the study coordinator if they had a cold or flu at any time during follow-up. A health care worker verified reported illnesses using a standard protocol.

In a traditional prospective analysis, high cortisol reactors with high levels of life events had a greater incidence of verified URI during the 12-week follow-up than high reactors with low levels of life events and low reactors irrespective of their life event scores. If we assume that higher levels of cortisol response suppress host resistance to upper respiratory pathogens, these data are consistent with what one would expect. In a within subject analysis (using hierarchical linear modeling), CD8+ number, NK cell number, and NK cell cytotoxicity reactivities each interacted with weekly-perceived stress levels in predicting concurrent occurrences of *self-reported* URIs. (URIs that were not presented for verification were also used here to increase the number of illnesses for this more intensive analysis). For these outcomes, high immune reactors (greater stressor-induced increases in NK, CD8+ numbers, and NK cytotoxicity) were *less* likely to experience an URI during high stress than low stress weeks. In contrast, low immune reactors were at greater risk for URI as a function of weekly stress level. One might argue that for these immune outcomes increased response can be viewed as immunoenhancing and hence greater response should be associated with greater host resistance. The SNS reactivity markers did not moderate the association of stress and URI incidence in either analysis.

Why did we find differences between reactivity as a moderator of stressful life events and reactivity as a moderator of weekly perceived stress levels? Although we did not find significant interactions between stressful life events and NK or CD8+ number or NK cytotoxicity reactivities in the traditional prospective analysis, the patterns of illness rates were all consistent with those found in the within subject (HLM) analyses. For example, as in the within subject analyses, persons with high life events and low immune reactivity had

substantially higher rates of illness than the remaining subjects in all three cases. It is not surprising that these effects did not reach statistical significance since there is a substantial loss of power in the traditional (relative to the within-subject) analyses. This is because of the elimination of between subject error in within-subject analyses and because the traditional prospective analyses focused on verified (by health care worker) incidence, which has a much lower base rate of occurrence than the unverified self-reported episodes used in the within-subject analyses.

In contrast, the interaction between negative life events and cortisol reactivity that we found in the traditional prospective analysis was not found (even in terms of patterns of results) in the within-subject analyses. There are several potential reasons. In this case, it is possible that cortisol reactivity is more important in response to the more chronic and substantial background stressors represented by major stressful life events than the acute stressful conditions assessed on the weekly level.

Both we and Boyce found that stressor-elicited activation of a system that often suppresses immune response (elevated blood pressure as a marker of SNS for Boyce and elevated cortisol as a marker of HPA for us) were associated with increased risk for illness when exposed to naturalistic stressors. Although not a true replication, these results are consistent with the argument that a disposition toward stress-associated physiological activation is associated with a poorer outcome when people are exposed to naturalistic stressors. On the other hand, the evidence on the role of immune-reactivity in vulnerability from the different labs is clearly inconsistent. Boyce and colleagues found that elevated immune reactivity was associated with greater risk under stress. In contrast, we found that elevated immune reactivity was associated with less risk. There are, of course, many differences between this earlier work and our own. Some striking examples include that they studied young children while we studied young adults. They assessed the number of URIs experienced within a specific time frame, while we focused on incidence-based analyses that addressed whether stress was associated with at least one occurrence of URI within specific time frames. In their studies, immune reactivities were assessed as responses to a single naturalistic stressor-entering school, with pre- and post measures assessed two weeks apart. In contrast, we assessed the average response to two laboratory stressors, each over a 5–20 min period. Finally, Boyce's two studies and our study differ in the functional immune outcomes utilized. We did not assess mitogen-stimulated proliferation as a measure of reactivity. This measure was, in fact, the one that Boyce and his colleagues found to be a reliable moderator of the stress-illness effect across two studies (Boyce et al., 1993, 1995). In contrast, they did not assess natural

killer cell cytotoxicity reactivity; the functional measures we found to be associated with lower risk under stress. Because modulation of different immune parameters may have very different implications for host resistance, it is clearly possible that there is less inconsistency here than there seems. Moreover, stress-elicited changes in some immune parameters are biphasic—e.g., initially rising but after some time falling below basal levels. Hence the different direction of associations we found for immune reactivity might be attributable to our assessing immune response at different lags after stress initiation than Boyce and his colleagues.

Finally, in a recent (and as yet unpublished) paper, we have replicated the result that cortisol reactors experiencing high levels of naturalistic stress are at greater risk for colds than the three remaining groups (low stressed reactors and nonreactors and high stressed nonreactors). This study of older adults has increased our own confidence that cortisol responsiveness is a marker of vulnerability to stress-associated risk for developing respiratory infections.

## 5. Discussion

We began by raising three questions about physiological reactivity and its implications for stressor-associated risk for respiratory illness. First, are cardiovascular, endocrine, and immune responses to acute laboratory stressors consistent across time and stressor task? The answer is that there is considerable consistency at least across time and across similar tasks. The fact that the largest correlations are found for cardiovascular measures may merely reflect error in measurement rather than actual differences in stability. In these studies, heart rate and blood pressure are measured multiple times (in response to the same stressor) and averaged. In contrast, the endocrine and immune measures are usually assessed only once at baseline and once during or after the stressor task resulting in less reliable measurement. This is exacerbated by the fact that laboratory assay assessments are subject to substantially more procedurally related error than standard (usually automated) assessments of cardiovascular response.

There is reason, however, to think that responses to very different types of stressors (e.g., those eliciting psychological threat versus effort and attention) might not be correlated. Such differences suggest that a more sophisticated approach to this issue might attempt to distinguish between types of stressors associated with different physiological responses. For example, cognitive tasks that are demanding and result in increased effort and attention on the part of the subject seem to primarily drive SNS response, while those that are more of a psychological threat drive both SNS and HPA activation (Lundberg and Frankenhaeuser, 1980). Such task

typologies could be based on objective characteristics of the tasks but might also be based on the cognitive and emotional response of individual subjects. Relatedly, there is the issue of whether the types of stressor-tasks used in assessing laboratory reactivity are appropriate models for stressors occurring in the natural environment. For example, will a cognitively demanding laboratory task elicit the same physiological responses as a social conflict with one's spouse? Certainly a better understanding of the differential effects of different types of stressors could lead to better laboratory based prediction of response to stressors in naturalistic settings and consequently more sensitive measures of vulnerability to naturalistic stressors.

Second, are cardiovascular and endocrine responders also immune responders? It is likely that correlations between SNS or HPA reactivity and immune reactivity depend on the specific regulatory mechanisms for the immune measure(s) that are included. For example, it is fairly clear that the acute stressor-elicited increases in number of NK cells and in NK cytotoxicity are mediated by SNS response. In consequence, it is not surprising that reactivity as assessed by markers of sympathetic response (HR, BP, and catechols) are correlated with NK cell number and cytotoxicity reactivity. One broad psychobiologic cluster might include sensitive sympathetic markers as well as other immune responses that are known (or likely to be) responsive to sympathetic activation. Another might focus on HPA response and related immune responses. Another clustering strategy might differentiate between those responding with both SNS and HPA activation, those responding with only one, and those with relatively minimal responses in both systems. A better understanding of the mediators of acute stress elicited changes in immunity will result in a better understanding of which types of reactivity cluster together and which do not.

The current literature hints at the possibility that clustering may not be the only way to go. Specific measures (within a domain) are in some cases (e.g., blood pressure reactivity in Boyce's work) individually responsible for increased vulnerability. Although clusters may increase reliability of measurement, individual markers of reactivity increase specificity of effects. Work distinguishing between the autonomic (differentiating between vagal and sympathetic) origins of heart rate activity is an example of applying sophisticated analysis to a measure in an attempt to further increase specificity by breaking a measure down into components based on underlying processes (Cacioppo, 1994; Hawkey et al., 2001). In short, it seems unlikely that an undifferentiated aggregated measure including a wide range of physiological reactivity markers that are not theoretically associated will be a useful predictor of vulnerability. Further work developing clusters that make theoretical sense and prove to be reliable across time and across

clearly defined domains of stressors seems like the best bet for the future. Work focusing on individual markers of physiology that are thought to be central to regulating important immune processes may be helpful as well.

The data we have addressed above are based upon reactivity assessments collected during or immediately after task performance, when SNS activity is most heightened. However, when the immune responses to acute stressors are followed over longer periods they often turn out to be multiphasic, e.g., rising initially, returning to baseline, and sometimes falling below baseline. We need to do a better job in characterizing the longer-term nature of responses before we can more fully understand individual differences in response to naturalistic stressors. This requires longer post-stressor follow-ups in the laboratory and more sophisticated analyses of the data. For instance, Llabre and colleagues (2001) have utilized latent growth curve modeling of patterns of systolic blood pressure reactivity and recovery.

In order to make our argument about the importance of reactivity, we have oversimplified the predictions of the reactivity hypothesis. As stated, the hypothesis assumes that certain physiological states suppress or enhance host resistance to infectious disease. If "reactors" are more likely to be in these states when exposed to a stressor, stressor exposure would put them at greater (if suppressed) or lesser (if enhanced) risk of developing an infectious illness. The oversimplification has to do with the implications of the direction of immune response. For example, our own work (Cohen et al., 1999) suggests that illness expression among people infected with influenza viruses may be attributable to the production of "too much" pro-inflammatory cytokine (immuno-enhancement?). Consequently, the role of reactivity is best viewed within the context of the specific immune response and specific disease and disease stage.

In sum, are reactive people more or less vulnerable to stressor-induced effects on susceptibility to infectious disease? There is some evidence that persons inclined to respond to stressors with relatively high levels of activation of SNS and HPA are at greater risk for illness when exposed to a stressor. Although immune reactivity has also been associated with vulnerability to stressor-elicited risk, the exact nature of this relationship is still unclear.

The existing evidence does suggest a need to pursue the reactivity questions from several different perspectives including: (a) assessing the reliability of reactivity measures across time and stressor tasks; (b) assessing lab-to-life generalizability of reactivity, with special emphasis on the importance of similarity of the laboratory and real life stressors; (c) evaluating the usefulness of reactivity measures based on different types of stressors categorized by both objective stressor criteria

and in terms of individual psychological response; (d) evaluating the usefulness of reactivity measures based on different types (and clusters) of physiological response with special emphasis on responses suspected to play a role in disease susceptibility; and (e) characterizing reactivity over a longer period of time to include magnitude of response, time to recovery to baseline, and time to return to a stable baseline.

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