



Review

Do low levels of stress reactivity signal poor states of health?

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ABSTRACT

Studies of cardiovascular disease risk have explored the idea that exaggerated physiological responses to stress may signal increased risk of cardiovascular disease. We describe a neurophysiological model of brain structures and peripheral structures that may contribute to exaggerated reactivity. Level I in this model includes the limbic system and its interactions with the prefrontal cortex that determine stress appraisals and coping responses. Level II addresses the hypothalamus and brainstem that contribute outputs to the body and which also includes brainstem nuclei that feed back to Level I to modulate its functioning. Level III includes the peripheral tissues themselves. We then suggest that stress reactivity ranging from very low to very high has a normative midrange of intensity and present evidence that negative health outcomes may be associated with both exaggerated and diminished stress reactivity since both tendencies imply a loss of homeostatic regulation. In particular, dysregulation at Levels I and II in our heuristic model signify altered motivational function and an attendant alteration in outflow to the periphery and poor behavioral homeostasis. In consequence, poor affective and behavioral regulation would be expected to contribute to poor health behaviors therefore additionally impairing health. In conclusion, diminished as well as exaggerated physiological reactivity should be seen as nonoptimal functioning that can contribute to poor health outcomes. This conceptualization places physical health into the context of behavioral and physiological processes that contribute to homeostasis.

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1. Overview

The idea that biased emotional reactions and physiological responses are an indication of poor health is as old as Hippocrates. Under the Greek worldview, the balance of four vital humors controlled a person's temperament. States of imbalance would render the person prone to disease. The present paper will discuss altered states of health in light of emotions, brain mechanisms, temperament, and biases in physiological regulation. Our perspec-

tive is that reactions to stress should be seen as having a normal, or normative, magnitude, and that significant deviations in response, whether above or below normal, are indicative of biases in homeostasis. In consequence, both exaggerated and diminished reactivity to stress may signal vulnerabilities to psychosomatic diseases.

2. Historical perspective

Greek thinkers held that the body consisted of four humors that had an optimal balance that defined a state of health (Hart, 2001). Each humor could influence the individual's psychological and

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physiological disposition, and either an excess or a deficit would render the individual subject to particular behavioral traits and health outcomes dispositions. For example, yellow bile embodied the element of fire. It came from the gall bladder, and too much yellow bile made a person choleric (bad tempered and easily angered) and subject to inflammation and fevers. Therefore humoral imbalances were used to account for both personality characteristics and associated disease vulnerabilities. Seemingly outmoded, this model has a modern flavor as well. The humors are similar to the hormones and neurotransmitters that we now study in relation to our behaviors, moods, and health. For example, dopamine is viewed, a bit simplistically, as the brain's reward substance. Individual differences in central dopamine function are associated with variations in moods, food consumption tendencies, and also with addictions (Koob and Le Moal, 1997). In this sense, our modern psychosomatic theories still rely on imbalances in physiological substances as affecting how we respond to the world, and we see these altered responses as signaling health and disease.

The noted physiologist, Walter Cannon, talked frequently about emotional reactions originating in the brain areas later termed the limbic system. In particular, he commented on how strong emotional reactions could affect hormonal and nervous system outputs to the body, with the potential to cause significant physical symptoms including death (Cannon, 1928, 1957). Cannon also recognized that a tendency to be emotionally reactive could be a persistent tendency underlying what we think of as individual differences in temperament. This approach to emotional reactions and medical consequences reached its high point as an all-encompassing system of thinking in Franz Alexander's textbook of psychosomatic medicine (Alexander, 1950). In both Greek and more recent thinking, there is an interplay between unseen essential properties (the character of fire, for instance, or the emotional reactions to an event) and physiological counterparts or consequences. The historical parallels between the Greek system of medicine and the more recent history of psychosomatic thinking are therefore not so different in essential quality as they are in the details.

One outgrowth of this tradition is the *reactivity hypothesis* that traces its history to the early 1930s. Hines and Brown (1932, 1933), then at the Mayo Clinic, used the cold pressor test as a provocative challenge to investigate individual differences in risk for hypertension. These workers framed the hypothesis that immersing a hand or foot in ice water could cause a reflex rise in blood pressure that would be larger in persons who were at risk of future hypertension. This work provided the tester with a specific stressor and a simple measure of responsivity that proved to be reasonably reliable and predictive of disease risk. Larger blood pressure responses were found in children from families with hypertension (Hines, 1937; Matthews et al., 1988), and they predicted risk of future hypertension (Matthews et al., 2004). Such evidence provided an orientation for other studies of cardiovascular disease risk. In this tradition, studies of reactivity and disease all share the postulate that larger-than-normal responses are markers of subclinical disease or that they contribute to increased risk (Everson et al., 1996; Kaplan et al., 1985; Manuck et al., 1983). This paper will not review specific evidence for or against the predictive value of reactivity data as this has been done extensively elsewhere (Treiber et al., 2003). Instead we will discuss possible sources of large or small stress responses and present evidence that deviations from the norm may have prognostic value.

3. Sources of individual differences in reactivity

Studies of stress reactivity and disease risk have tended to avoid considerations of underlying mechanism and instead have focused on the chosen peripheral indicator of reactivity, such as blood

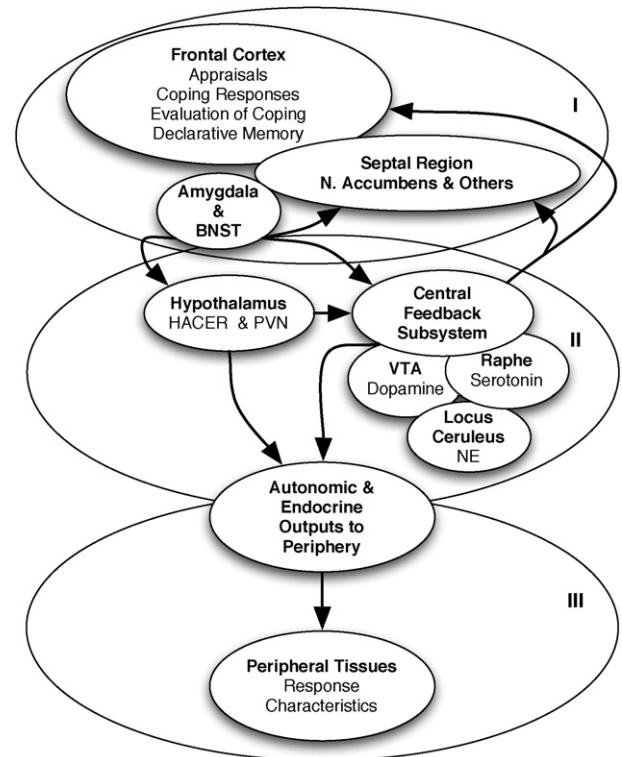


Fig. 1. Three levels of systems organization that may contribute to individual differences in stress reactivity. BNST: bed nuclei of the stria terminalis; HACER: hypothalamic area controlling emotional reactions, the lateral-hypothalamic-perifornical region; PVN: paraventricular nucleus of the hypothalamus, a nucleus that regulates both stress endocrine outputs to the pituitary and sympathetic outflow via the brainstem; VTA: ventral tegmental area, the source of ascending dopaminergic fibers to the limbic system and prefrontal cortex; NE: norepinephrine.

pressure response, and then examined its association with future disease. Although this is a valid approach to the question of association, it diminishes the potential for understanding how the altered response tendency might interact with disease pathophysiology. We have described in recent publications how altered functioning of brain systems and peripheral tissues could underlie individual differences in reactivity to psychological and physical stressors (Lovallo, 2005a,b; Lovallo and Gerin, 2003). Fig. 1 shows the system divided for heuristic purposes into three levels of organization, with each level being a possible source of altered response tendencies.

Level I in the system incorporates the brain's emotional apparatus and associated appraisal-based response system. Emotions are complex events that have four components: Emotions have cognitive inputs, and they can be evoked, heightened, and lessened by our thoughts (Schachter and Singer, 1962). Cognitive processes, including working memory and decision-making, underlie Lazarus's system of primary appraisals of the threat value of an event and secondary appraisals of coping options and resources that influence emotional and physiological responses (Folkman and Lazarus, 1988; Lazarus and Folkman, 1984). These cognitive reactions are further refined by limbic system inputs, arising at the amygdala and forwarded via the bed nuclei of the stria terminalis to the orbitofrontal cortex and anterior cingulate gyrus (Lovallo, 2005b; Rolls, 2000). Emotions also have skeletal motor components; we convey our emotions in facial expressions and emotions are action dispositions that prepare us for behaviors to avoid danger and obtain things needed for survival (Ekman, 1993). These action dispositions are accompanied by visceral changes that prepare us to sustain the behavioral efforts necessary

to accomplish the survival goals that are called for (Sinha et al., 1992). Finally, thoughts, visceral states, and muscle feedback together result in subjective sensations that we experience as the feeling of happiness, sadness, anxiety, etc.

These Level I interactions between the prefrontal cortex and the limbic system also establish the outflow to Level II, which includes the hypothalamus and brainstem.

Level II structures have two important functions. The hypothalamus and brainstem form the final common pathways for outputs to the body. They can be influence reactivity because of variations in homeostatic set points and output gain factors. For example studies in hypertension risk indicate that persons that have equivalent responses at Level I may differ in output to the cardiovascular and endocrine systems because of characteristics of the hypothalamic paraventricular nucleus (al'Absi and Lovallo, 1993; Goncharuk et al., 2002). In addition, Level II structures represent the brainstem's "central feedback subsystem," a term we have applied to the aminergic nuclei of the pons. Descending inputs from the hypothalamus and limbic system act on the brainstem's noradrenergic, serotonergic, and dopaminergic nuclei, and these in turn acutely and chronically alter the responsiveness of Level I structures and also influence peripheral outflow (Lovallo, 2005c).

Finally, at Level III are the peripheral tissues that can determine response magnitudes. Individual differences in response may reflect differences in autonomic outputs or intrinsic differences in tissue structure.

According to this model, individual differences at any of the three levels of systems organization could account for individual differences in response to stress and interact in different ways with disease mechanisms. In addition, appropriate study designs and use of emotion self-reports can help to identify which levels in the system are contributing to obtained reactivity differences (Lovallo, 2005a,b; Lovallo and Gerin, 2003).

4. Large and small responses to stress and possible disease associations

The typical view of stress reactivity and disease assumes that larger responses are worse and smaller responses are better. This unstated assumption seems to be self-evident and in no need of examination, however we have recently questioned this assumption and advanced the idea that biases toward both very large and very small stress reactions are both indicators of poor homeostasis and are signals of possible disease risk (Carroll et al., 2009; Carroll et al., in press). If we assume that larger-than-normal responses of the cardiovascular and endocrine systems can signal systemic dysfunction (Manuck et al., 1989), then it may be equally likely that smaller-than-normal responses can also signal systems dysfunction and contribute to pathophysiological processes.

The following example illustrates this point. A healthy young man in a seated position should have a heart rate of about 60–65 beats per minute and a blood pressure of perhaps 115/65 mmHg. If this person rises to a standing position, the blood would tend to pool in the legs, but this would be opposed by the baroreceptor system, which initiates a vigorous sympathetic nervous system response to maintain adequate return of blood to the heart by contracting peripheral blood vessels and stimulating the heart to increase cardiac output (Cacioppo et al., 1994; Guyton and Hall, 2000). Accordingly we might expect heart rate to go up to about 85 beats per minute, systolic blood pressure to rise slightly, and diastolic pressure to change very little. This response appears to be normative for the challenge of orthostasis.

Variations up or down from this normal response pattern are undesirable. If the heart rate were to go to 130 beats per minute or blood pressure to rise substantially, we might suspect a failure of the baroreceptors to have regulated the response appropriately (a

failure at Level II). Similarly, a prehypertensive person with altered blood vessel wall thickness might have an abnormally heightened blood pressure response that would signal persistently elevated peripheral resistance, a Level III response alteration common in prehypertensive states (Folkow, 1990). We might therefore assume that there is an existing pathophysiology and that the persistence of such dysregulated responses might have damaging consequences.

Consider the alternative scenario. Our young man rises to a standing position and promptly faints. Such an outcome could indicate that the baroreceptors failed to trigger the necessary sympathetic output (a failure in Level II of the system), or the sympathetic outflow failed to evoke the necessary peripheral responses (a failure at Level III). This not-uncommon failure to regulate blood pressure and flow under the simple demand of orthostasis is typically a signal of an autonomic neuropathy, among other possibilities.

These contrasting examples illustrate that response deviations from normal in either direction may signal a loss of homeostatic regulation and indicate disease risk. If the system is organized homeostatically, or we may say normatively, then the system's response and return to normal will be within normal limits and time parameters given the current demand. By definition responses that depart significantly from that norm in either direction could signal a potential systems dysregulation, pointing toward a reduced state of health. To illustrate this point, Fig. 2 presents a normal curve as representing the response of a regulated physiological variable, such as heart rate, blood pressure, or cortisol, in a large population of otherwise healthy persons. The center of the distribution may be seen as representing a presumed normative range of reactions that captures the reactivity tendencies of the majority of persons being tested. At the tails of the distribution are persons who, based on statistical principles, do not represent the normative range, but are in the extremes. This is an argument in principle that the concept of reactivity and its association with disease risk should include exaggerated responses and ones that are smaller than normal. The remainder of this discussion will focus on individual differences in emotional reactivity and coping and how these may affect stress reactivity and risk of disease.

5. Level I and II processes can determine exaggerated or diminished outputs from the brain to the periphery

As noted above, emotional responses formed at Level I in the system determine outputs to Level II and ultimately how the body responds to stress. Alterations in these Level I relationships will affect a person's emotional response characteristics, and it is likely that some alterations in emotional reactivity will result in diminished reactions to stress rather than larger ones. These

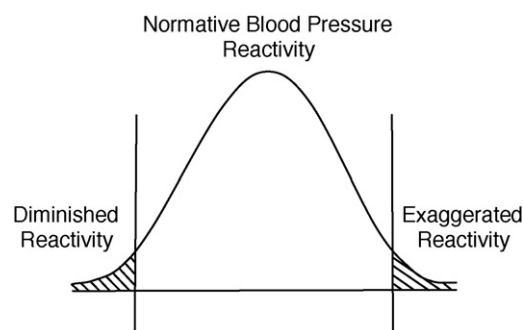


Fig. 2. A hypothetical cardiovascular response distribution with areas under the curve identifying highly reactive individuals along the right tail and highly unreactive individuals under the left tail.

diminished responses would then affect Levels II and III in the system with implications for physiological reactivity and health. In addition, altered emotional reactivity would affect motivational processes, and these would influence behavioral choices and habits that may have implications for health.

Damasio and colleagues have written persuasively about the impact of altered prefrontal–limbic integrations on cognition, behavior, emotional responses, and autonomic outflow (Anderson et al., 1999; Damasio, 1994; Damasio et al., 2000). The amygdala and its interactions with the striatum, orbitofrontal cortex, and anterior cingulate gyrus stand at the core of the brain's emotional response system (Rolls, 1972, 1999). The amygdala contains inborn neuronal pattern recognition systems that carry survival benefit to the developing animal. Primates' well-known innate fear of snakes is one such example, and this fear is known to depend on an intact amygdala. Young monkeys fear snakes on the first encounter, but amygdaloid ablation completely eliminates this fear response (Amaral et al., 1992; Prather et al., 2001). This example presents a case in which a small or absent response is clearly not adaptive and health promoting; young monkeys that are not afraid of snakes are at high risk of being bitten while those with large reactions are likely to avoid such a fate.

In addition to the amygdala's innate response repertoire, the amygdala is essential to the formation of Pavlovian conditioned associations; the amygdala receives highly processed sensory inputs from cortical association areas, and also receives inputs from the viscera via the anterior insula (Davis, 2000). This pairing permits bodily states to be associated with external events and permits development of normally motivated responses to those events. Destruction of the amygdala abolishes the ability to form Pavlovian conditioning (Campeau and Davis, 1995). Loss of the ability to form Pavlovian associations, or to properly express innate response tendencies, leaves the person unable to develop appropriately motivated behaviors in response to situational demands. In humans bilateral amygdala damage disrupts emotional responsivity and this disruption is most severe in persons sustaining damage early in life because of a failure to develop a normal experiential background of motivated responses (Anderson et al., 1999; Siebert et al., 2003; Tranel et al., 2006).

At least one study has shown that high levels of emotional stability and intelligence predict longer lifespan, suggesting that integrity of the central nervous system at Levels I and II can contribute to good health (Weiss et al., 2009). Damage to the amygdala or its connections to the prefrontal cortex impairs emotional responsivity and diminishes the person's ability to produce adequate behavioral coping strategies to challenges presented by external events. Recent neuroimaging work examining brain activity in relation to cardiovascular stress reactivity has provided substantial real-time evidence that amygdala connectivity is an important determinant of individual differences in cardiovascular response tendencies (Gianaros et al., 2007, 2005, 2008).

Given the central role of these amygdala–prefrontal connections, it is perhaps not difficult to view more subtle Level I deficits as causing diminished emotional reactivity and accordingly smaller physiological responses to stressor challenge. There are several lines of evidence that this is so. Psychopaths typically display a lack of emotional response to social cues, and this is accompanied by deficient activity of the amygdala during tasks designed to evoke such responses (Blair et al., 2001; Kiehl et al., 2001; Muller et al., 2003; Rilling et al., 2007). Such reactivity differences are mirrored in persons with varying numbers of alleles for a low-activity version of the catechol-O-methyltransferase (COMT) gene. Each person carries one copy from each parent and therefore can have 0, 1, or 2 copies of the low-activity variant or its high-activity counterpart allele. Persons with two copies of the

low-activity allele are highly reactive to unpleasant stimuli in relevant frontal and limbic system areas (Smolka et al., 2005). Persons with two copies of the high-activity allele are emotionally unreactive and have antisocial and disinhibitory behavioral characteristics (Goldman et al., 2005). Not surprisingly, persons with disinhibitory behavioral patterns also have smaller cardiovascular and cortisol reactions to threatening social situations, such as a public speaking task (Sorocco et al., 2006). The common factor tying behavioral disinhibition together with lack of emotional and physiological reactivity is that deficient inputs from the amygdala or inadequate connections to the prefrontal cortex would affect the person's ability to choose adaptive courses of action and would similarly influence Level II activity causing diminished physiological responsivity.

In addition to affecting Level II outputs to the periphery, altered amygdala–prefrontal communication have an impact on the actions of the brain's central feedback subsystem consisting of the serotonergic raphe nuclei, the dopaminergic ventral tegmental nuclei, and the noradrenergic locus ceruleus all located in the pons (Iversen et al., 2000; Swanson, 2000). These brainstem nuclei depend on inputs from higher centers to react to the external environment. Once they do react, they set the state of the central nervous system in response to such inputs, they also develop characteristic patterns of reaction that contribute to individual differences in relation to experience (Koob, 1992; Koob and Le Moal, 1997; Swanson, 2000). The serotonergic raphe nuclei have ascending fibers that affect the state of limbic system and prefrontal cortex communication. Alterations in their signaling would have an impact on long-term regulation of affect (Manuck et al., 1999, 2000, 2003). In similar fashion, the activity and response level of the locus ceruleus to external events depends on normal activation of the brain's corticotropin releasing factor neurons (Aston-Jones et al., 1986; Petrusz and Merchenthaler, 1992). The locus ceruleus is responsible for the global activational state of the central nervous system (Aston-Jones et al., 1986). Finally, the dopaminergic fibers arising from the ventral tegmental area of the pons, and arriving at critical striatal areas such as the nucleus accumbens, are necessary for maintaining normal attention to cues signaling reward and motivating approach behaviors and cognition more generally (Arnsten, 1997; Dellu-Hagedorn, 2006; Hakyemez et al., 2008; Murphy et al., 1996). Alterations in dopaminergic signaling to these areas are considered by many to be a source of altered approach-avoidance tendencies and differential response to reward signals. Accordingly, persons with deficient or excessive dopaminergic function may have altered behavioral tendencies and altered autonomic responses to environmental cues. Consequently, altered frontal–limbic interactions would alter the ability of the pontine nuclei to perform their functions and, in turn, altered pontine function would affect the background state of the central nervous system, both processes acting as neurophysiological underpinnings of individual differences in reactivity.

The evidence cited above indicates that significant motivational consequences occur when there are functional alterations of either prefrontal–limbic communication (providing inputs to Level II processes) or altered feedback from the Level II aminergic nuclei to Level I structures. These alterations in Level I and II interactions would therefore have an impact on outflow to the periphery via the brainstem and hypothalamus. Because these interactions affect coping processes and decision-making, they may also have significant consequences for health behaviors, including a tendency toward poor eating habits, risk-taking, smoking, and alcohol intake, among others.

There is no inherent reason why these alterations in peripheral outflow would only result in exaggerated outputs; they may equally well diminish normal physiological reactivity.

6. Health implications of reduced levels of physiological reactivity

We recently summarized research indicating that low stress reactivity may accompany biases in food intake and fuel homeostasis and also abnormal motivational states involving risk of alcoholism (Carroll et al., *in press*). Although a full accounting of existing evidence is beyond the scope of this paper, a few indications of the health context of reduced stress reactivity is in order. Briefly stated, we noted that persons with altered stress responses are shown to have changes in immune system response (Cacioppo et al., 1998; Sheridan et al., 2000). Persons with robust cortisol stress responses also have more vigorous antibody responses to antigen challenge while blunted cortisol responses signal poorer antibody response (Phillips et al., 2005). In this latter study, blunted stress cortisol responses were also accompanied by high levels of neuroticism, suggesting a poor regulation of affect in these persons, potentially implicating Levels I and II in our model. Other research shows that deficient stress cortisol responses may fail to keep immune activity in check, increasing the risk of autoimmune diseases. Women characteristically have diminished cortisol responsivity (but the same basal levels) relative to men, and they are about four times more likely to suffer from autoimmune disorders such as arthritis (Morell, 1995). The Lewis rat model of arthritis provides a mechanistically elaborated example of reduced stress reactivity and its implications for arthritis. The Lewis rat is genetically deficient in corticotropin releasing factor activity at the hypothalamic paraventricular nucleus. This leads to reduced cortisol activation to an immune system challenge such as injection of streptococcus bacteria cell wall preparations. Following such injections Lewis rats exhibit joint inflammation and deformation analogous to human arthritis (Sternberg et al., 1989, 1991).

Obesity research also suggests health implications of reduced stress reactivity in relation to Level I and II brain structures. One study examined central serotonergic reactivity to fenfluramine challenge and its relationship to the metabolic syndrome, a constellation of body mass index, abdominal obesity, hypertension, poor lipid profile, and insulin resistance, and found that low serotonergic responsivity was associated with greater prevalence of these metabolic risk factors (Muldoon et al., 2004). More direct evidence comes from a Scottish longitudinal study that found low levels of cardiovascular response to stress predicted higher levels of obesity at entry and greater five-year progression of obesity (Carroll et al., 2008). In a U.S. community-based study, perceived stress predicted a flattening of the diurnal cortisol curve, an indicator of reduced integrity of hypothalamic–pituitary–adrenocortical axis function (Farag et al., 2008). However, when obesity was taken into account, this relationship disappeared and obesity alone accounted for the flattening of the cortisol curve. One way to interpret this evidence is that a flattened diurnal cortisol pattern is either contributes to obesity or is a reflection of obesity (Dallman et al., 2003). An additional health consequence is that a flattening of the diurnal cortisol curve reduces the ability of peripheral cortisol to reset circadian cellular clocks in various tissues. A loss of this time signal could well be an indicator of poor systems integrity and poorer systems function (Buijs et al., 2003).

How might we interpret the connection of reduced cortisol responsivity to obesity as a behavioral trait? There is increasing evidence in the field of addiction research that persons prone to smoking, alcoholism, gambling and other forms of substance abuse are relatively antisocial and behaviorally disinhibited (perhaps evidence of Levels I and II having altered function) and that these same people also have reduced stress cortisol reactivity (Acton, 2003; Anker et al., 2009; Raine et al., 2000). Adolescent and young adult offspring of alcoholic or substance-abusing parents are

themselves at increased lifetime risk of substance abuse, with a significant genetic contribution to this risk (Cloninger et al., 1981). In addition, a tendency toward substance use disorders is significantly associated with antisocial tendencies accompanied by poor mood regulation (Cadoret et al., 1985; Lovallo et al., 2006; Shedler and Block, 1990; Vanyukov et al., 1993). In turn, antisocial and disinhibitory behavioral tendencies predict reduced cortisol stress reactivity which itself predicts experimentation with smoking in at-risk adolescents (Moss et al., 1999, 1995). A blunted stress cortisol response to stress is also seen in young adults with a family history of alcoholism (Sorocco et al., 2006) and in alcoholic and polysubstance-abusing patients (Lovallo et al., 2000). The blunted stress cortisol responses in these latter studies are accompanied by a diminished cardiovascular response to stress (Lovallo et al., 2000; Panknin et al., 2002).

These diminished endocrine and autonomic responses to stress are associated with poor regulation of affect and behavior in these family history positive persons. We have observed persons with a positive family history of alcoholism to have antisocial tendencies, to be high in neuroticism, and to have higher depression scores than persons with no such history (Sorocco et al., 2006). In addition, these same individuals have poorer working memory performance, and the males are biased toward attention to winnings in a gambling task (Lovallo et al., 2006). These persons also make more impulsive errors on a Go-NoGo reaction time task (Saunders et al., 2008). Neuroimaging work shows that otherwise healthy nonalcoholic young adults with a family history of alcoholism have reduced amygdala activation to emotional faces and that this blunted amygdala response is greater in persons with more antisocial tendencies (Glahn et al., 2007). During work on the Iowa Gambling Task, these same persons with a positive family history have greater activation of anterior cingulate gyrus and the dorsal striatum (caudate nucleus) (Acheson et al., 2009). We interpreted the striatal activation in the scanner as being associated with the greater attention to gains that we saw in the laboratory, an indication that the persons with a positive family history were playing the game more as a risky gamble, while the persons with a negative family history approached the game more as a cognitive challenge.

This evidence points to a connection between altered Level I and II systems functioning, reduced endocrine and autonomic stress reactivity, and behavioral dysregulation with consequences for health. The evidence for behavioral dysregulation includes standard tests of behavioral control in the lab, but it also seems to extend to dysregulated consummatory behaviors seen in obesity and addiction-proneness in daily life. A question worth asking is how does poor mood regulation accompanied by behavioral disinhibition relate to deficient cortisol and autonomic reactivity? We have discussed elsewhere that poor amygdala response to environmental challenge, and hence altered amygdala–prefrontal signaling, may result in risk-taking behavior and overly active approach tendencies and deficient avoidance tendencies (Lovallo, 2007). The amygdala plays in a key role in signaling the system that danger is present, and helping to generate a normal stress response, including cortisol and sympathetic activation, to support fight-or-flight behaviors. Persons lacking a normal amygdala response are more likely to be attracted to situations that others perceive as dangerous and to be focused on hedonic experience at the expense of longer term planning. This model therefore is consistent with overconsumption of alcohol, recreational drugs, and high-calorie foods. As noted in this connection, Mary Dallman has proposed a related example of food overconsumption resulting from high levels of cortisol secretion. In this model, high levels of cortisol signal the system that a homeostatic threat is present, food intake dampens this ongoing cortisol activity, and the return to homeostasis registers as a reward signal supporting future intake

behaviors (Dallman, 1993; Dallman et al., 2003). It may seem contradictory that both high levels of cortisol and reduced cortisol reactivity would be associated with increased consummatory behavior, but this may equally well exemplify our basic thesis that elevated and reduced stress reactivity both signal systems dysregulation and potential health risks.

The present paper has avoided a specific focus on cardiovascular disease in relation to subnormal response dispositions because examples from other health problems are now more prevalent and examples from cardiovascular disease are few. Future studies may well focus on cardiovascular disease risk as a further test of the hypothesis advanced here.

7. Final considerations and implications for research

The thrust of this discussion is that the study of stress reactivity and its implications for health should be broadened to incorporate both exaggerated and diminished physiological reactivity as candidates for predicting poorer health outcomes. Although there is good evidence that elevated reactivity may indicate greater cardiovascular disease risk, there is now a small but growing number of studies suggesting that reduced stress reactivity signals altered frontal–limbic integrations of behavior and physiological functioning. These latter alterations may be risk factors for altered eating behaviors and substance use disorders, among others.

In reference to Fig. 2, we might consider several points about the ideas expressed above. First, a frequently used strategy for studying reactivity is a median split of the data, with the goal of comparing the 50% above the median with the 50% below. Examination of Fig. 2 indicates that this could tend to wash out true effects operating at both ends of the distribution. Persons who are highly reactive are lumped in with many others near the median who represent the normative homeostatic range. Similarly, grouping those at the very low end with persons near the median obscures the consequences of low reactivity. A more fruitful research strategy would be to compare each end of the distribution against the middle.

Second, there are a several questions that come to mind when thinking about the people who inhabit these distribution extremes:

1. Who are they? An initial approach might be to do a multivariate analysis to identify the set of demographic or psychological characteristics that best define those low or high in reactivity without preconceptions about who they are.
2. What are the psychological or physiological characteristics of the low and high reactor groups?
3. Given the psychophysiological characteristics of the extreme groups, how do they differ from the normative middle group?
4. If we know the psychophysiological profile of persons at either extreme, we can then ask what disorders each extreme group might they be predisposed to, or protected against? Is it possible that persons with very small responses are disposed to risk-taking and consummatory disorders while high reactors are at risk of an entirely different set of disorders, such as hypertension? In this phase of the analysis, consideration of mechanisms operating at Levels I, II, vs. III of the model in Fig. 1 may be of help in sorting out the potential risks.

As an initial suggestion for research to test our hypothesis, researchers with ready access to large prospective cardiovascular disease databases may be positioned to test this hypothesis without the collection of new data. For example, any study of blood pressure reactivity at entry and with long-term follow-up of health outcomes could be reexamined with an emphasis on persons at both ends of the response distribution, as illustrated in Fig. 2.

Relevant questions are whether the putative outcomes for the groups at the two extremes are both within the cardiovascular domain or not. If not, then what sorts of disorders cluster at the lower end of the distribution?

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