

Cardiovascular reactivity: Mechanisms and pathways to cardiovascular disease

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Abstract

Researchers in physiology, psychology, and medicine have held the idea that risk for cardiovascular disease is increased by exaggerated responses to stress. Some epidemiological evidence supports this view and shows that exaggerated blood pressure responses to stress add to disease prediction beyond that provided by standard risk factors. Most studies of reactivity and disease risk have taken a correlational approach to the reactivity–disease relationship. This paper presents a model of central nervous system control over peripheral response systems that provides a way of designating three sources of exaggerated stress reactivity that may vary across individuals. The top level in the model consists of the limbic system and prefrontal cortex as interacting areas that form psychological stress responses. These frontal–limbic interactions are a means of translating experiential and affective processes into bodily responses. The middle level consists of hypothalamus and brainstem areas that translate descending influences into bodily outputs. Activation levels in these structures can lead to enhanced reactivity to many forms of challenge. The final level consists of the peripheral effectors that create the response itself; altered effector function can be a source of enhanced reactivity. Study designs that involve both psychological and physiological challenges and that take account of self-reports of affect and activation provide a basis for separating these sources of responsiveness. This organization may provide useful insights into the sources of stress reactivity that characterize specific groups at risk and allow inferences as to the source of the disease pathophysiology.

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1. Introduction

Cardiovascular disease contributes disproportionately to premature morbidity and mortality in the developed and developing worlds (Cooper et al., 2000; Domanski et al., 2002). Our ability to identify persons at greatest risk of cardiovascular disease is currently limited by the relatively poor sensitivity of traditional risk factors (Cooper et al., 2000). Most of the decline in cardiovascular disease mortality in recent years has been due to improved medical intervention and little has been due to primary prevention by risk factor modification (Cooper et al., 2000). The con-

stellation of contributors to both heart disease and hypertension suggests that behavioral factors play a role in the etiology of both. This has led to an interest in identifying lifestyle and psychological markers of increased risk. The search for psychophysiological risk factors has the potential to more specifically target persons at risk and also to elucidate interactions among risk factors.

Astute physicians have long suspected that risk for coronary artery disease was associated with an emotional temperament, especially a proneness to anger and confrontational behavior (Osler, 1892). Most prominent of these attempts was the pioneering work of Friedman and Rosenman in describing the Type A behavior pattern—a constellation of time orientation, an aggressive approach to life, and frequent experience of hostility (Friedman and Rosenman, 1959). Although this work attracted a great deal

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of attention, the Type A pattern inconsistently predicted outcomes in large epidemiological studies (Shekelle et al., 1985). However, positive indications that behavioral tendencies can be related to disease risk have been found. Specific speech patterns, and especially a hostile temperament, behaviors at the core of the Type A pattern, were found to predict negative outcomes, even in studies failing to show associations with the Type A pattern as a whole (Dembroski et al., 1989; Scherwitz et al., 1990). More recent work has also found that a lingering sense of hopelessness predicts increased risk of coronary artery disease, and like hostility, it too predicts greater risk of all causes of death (Everson et al., 1996b).

In response to these difficulties and limited successes, attention turned to a more empirical approach to the question; to identify persons who had the largest physiological responses when exposed to various stressors and then to examine disease risk factors and outcomes (Corse et al., 1982; Menkes et al., 1989). This effort supports the position that persons with the greatest response to stressors are at greater risk of future disease (Treiber et al., 2003). Treiber concluded that there is “reasonable evidence to suggest that cardiovascular reactivity can predict” development of cardiovascular disease signs and outcomes (Treiber et al., 2003). The involvement of hostile reactions with exaggerated disease risk and the question of affective reactions to stressor challenges as mediators of putative reactivity–disease relationships raises the question of how central nervous system processes can determine exaggerated reactions to psychological and nonpsychological challenges.

The objectives of this didactic review will be: to identify and briefly discuss brain structures regulating the emotions; to describe how different levels in the central nervous system and the periphery can affect cardiovascular reactions to stress; and to discuss these relationships to disease pathology. Our goal is to map out a model of reactivity and disease that can guide future research.

2. The reactivity concept

Physicians and physiologists have long advanced the idea that dysregulated physiological reactions to systemic challenges were signals of a vulnerability to disease or that disease was manifest in the dysregulation. In the 1930s Hines and Brown expressed the idea that a large blood pressure response to the immersion of a hand or foot in ice water signaled elevated risk of future hypertension (Hines and Brown, 1932). In keeping with the atheoretical origins of the reactivity hypothesis, epidemiological studies showing an association between reactivity and disease risk have deliberately taken a strictly empirical approach to the relationships in question (Everson et al., 1996a; Menkes et al., 1989). The present paper presents a model of the central and peripheral nervous system functions that may serve to tie together psychological processes, nervous system

response biases, and pathophysiological mechanisms. It is hoped that this may allow discrepancies between studies to be better understood and to contribute to a positive direction of this important research enterprise.

We present here a three-level model that begins with the actions of the central nervous system structures that form emotional states and give rise to conscious experience of motivations (Lovallo and Gerin, 2003). The model then describes interactions between these frontal–limbic actions and the hypothalamus and brainstem output channels. Finally, the model discusses sources of peripheral response biases.

3. The emotions

As background, it is useful to consider the close relationship between emotions, the formation of psychological stress reactions, and the ways that these may engage response systems that can affect the body (Lovallo, 2005). A simple definition of emotions is that they are complex neuropsychological events that ultimately serve to motivate adaptive behaviors and which have four components: (1) affects, the unique feeling states that convey a subjective sense of behavioral motivation and give judgmental–evaluative quality to our experiences, along with an appreciation of our visceral state; (2) cognitions, in the sense that our thoughts can shape our emotional reactions and our emotional reactions can direct our thoughts; (3) visceral outputs, that form the physiological substrate to support the behavior in question and that can shape the affective and motivational properties of the emotion itself; and (4) motor patterns that have social communicative and behavioral preparatory functions. Although the affective state is a sine qua non of an emotion, a lack of or significant alteration of any one of the other components is truly a distortion of the proper emotional character (Winkielman and Berridge, 2004). Perhaps most importantly, the cognitive state of the person is crucial for shaping the direction and intensity of the emotional experience (Cannon, 1928; Schachter and Singer, 1962).

3.1. Lazarus's model of psychological stress

The model of psychological stress developed by Richard Lazarus provides an intuitive, heuristically useful guide to the role of emotions in shaping stress responses (Folkman and Lazarus, 1988; Lazarus and Folkman, 1984). This model is diagrammed in Fig. 1. According to Lazarus's formulation, persons preconsciously or consciously appraise events as to their implications for the person's well being, and accordingly whether they require any coping resources to be expended to deal with them. The primary appraisal process compares each event against the person's beliefs about the world and commitments to a given course of action, including the most basic, biologically relevant

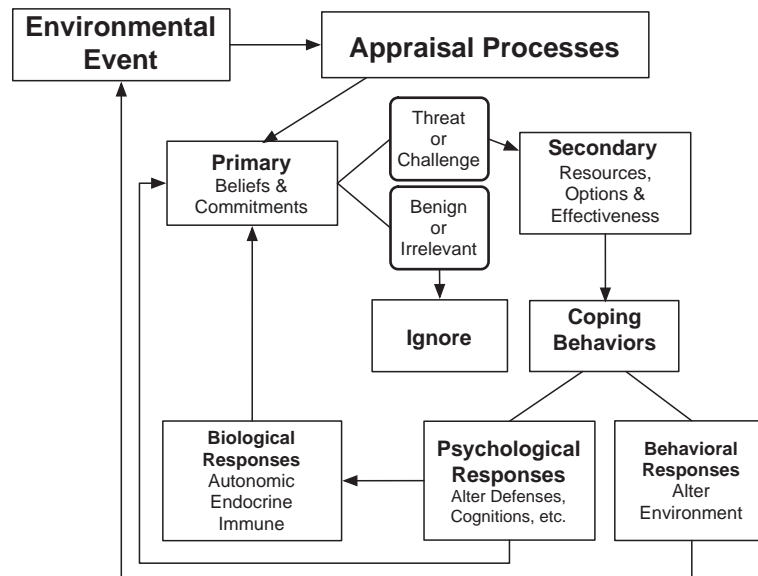


Fig. 1. Lazarus and Folkman's model of psychological stress. Environmental events are appraised as to threat value (primary appraisals). If an event is judged potentially harmful a secondary appraisal process determines the potential courses of action and their likelihood of successful coping with the event. Such appraisal processes are thought to underlie psychological stress responses. Adapted from Lovallo (2005). *Stress and Health: Biological and psychological interactions*. Sage Publications: Thousand Oaks, CA.

actions such as maintaining life. Events that are neutral or benign are by definition not threats to the person's beliefs and commitments and are accordingly safe to ignore. Events that pose an actual or implied threat require a second stage of appraisal to evaluate coping options and weighing the potential success of each of these.

The appraisal and coping processes play directly into each of the four elements of the emotions described above. The appraisal process itself is inherently cognitive, and the factors that play into it will determine the strength and valence of the emotional response. For example, persons with significantly different beliefs and commitments will accordingly have very different emotional responses to the same event, as a function of these cognitive appraisal steps. The cognitive processes accompanying the primary and secondary appraisals also shape the psychological responses accompanying the emerging emotional state including affective experience and revised evaluations as the process is shaped and reshaped in consciousness (Schachter and Singer, 1962). In accord with the processes already described, the behavioral responses of the person will be motorically shaped to express the person's feelings, and behavioral coping responses may come into play as well. Finally, the visceral state of the person will change as the appraisal and coping processes unfold. The appraisal model of Lazarus therefore allows a ready incorporation of affective, cognitive, visceral, and behavioral components of the emotions. This model is useful in another way, namely, it provides a guide for directing how we think about the development of stress responses, particularly psychological stress responses. It also gives us a way to think about individual differences in stress reactivity and how these differences might arise. As a result, we may arrive at a set of

hypotheses about stress reactivity based on a psychophysiological model derived from affective neuroscience (Davidson et al., 2002).

Lazarus's model is most useful in defining the steps by which stimuli become incorporated into thoughts and emotions, and therefore into reactions to stress. However, the model as put forth was not phrased in terms of neurophysiological activities, and it might be useful to do so here. As a guide to the remainder of this didactic lecture, I have developed Fig. 2, which is a model illustrating three levels in the system that participate in the shaping and executing responses to stressful situations. At the top level (Level I) is shown a set of brain structures and key elements in their interactions that determine how events are categorized and how emotional responses are formulated. At the middle level (Level II) is the hypothalamus and brainstem, two tightly integrated levels in the central nervous system at which physiological and behavioral responses are organized in forming outputs to the body. Finally, at Level III, the diagram refers to peripheral organs and tissues, targets of autonomic and endocrine outflow and behavioral response execution through which stress responses are enacted.

3.2. The cerebral hemispheres and control of motivated behavior

In considering levels in the central nervous system that contribute to forming emotions, motivations, and hence stress responses, it is instructive to return to the classic brain transection studies of Cannon and Bard (Bard, 1928; Cannon, 1929). Cat brains were transected just above the hypothalamus, and the cerebral hemispheres were removed. Still, the cats were able to display the classic diencephalic

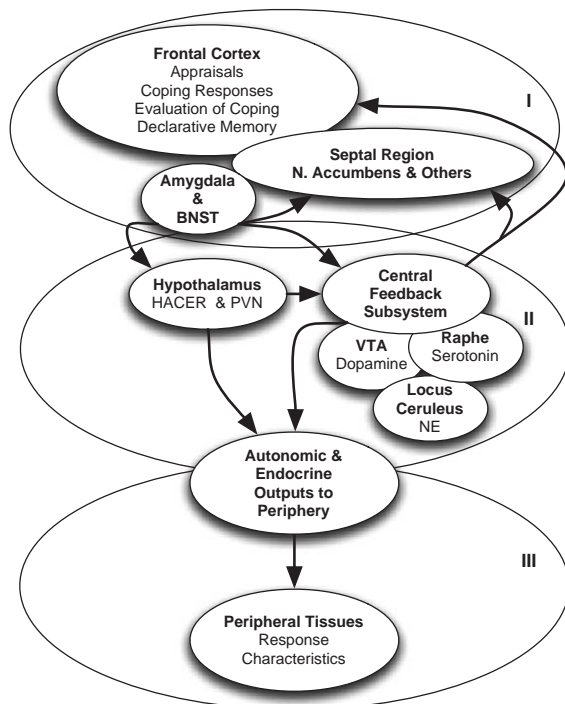


Fig. 2. Three levels of brain and peripheral functions that may be responsible for individual differences in cardiovascular and endocrine reactivity to stress.

rage response. With little or no provocation an animal might assume a defensive or attack posture and exhibit a fight-or-flight reaction. Recent work with such animals shows that they are able to survive quite well in a supportive environment, provided they are given ready access to food and water. The conclusion from this work is that the cerebral hemispheres are neither essential for survival under these circumstances nor are they required for display of emotional behaviors. The converse is that the hypothalamus and brainstem are necessary and sufficient for emotional displays (Swanson, 2000). Nevertheless, Bard's cats had emotional displays that were not goal directed; the animals lacked the ability to identify external threats or goals and to formulate appropriate behavioral strategies. Therefore, we say that the cerebral hemispheres have three functions, perceiving things outside the body, formulating response strategies, and executing the motor patterns to carry out these strategies. The processes of perceiving and classifying external events and formulating response strategies are different ways of characterizing Lazarus's processes of primary and secondary appraisals and coping responses.

3.3. The limbic system

The limbic system appears to have evolved to shape motivated behaviors in relation to external events. The system is comprised of a specialized set of brain structures that have as their unique role the assignment of approach-avoidance weighting and behavioral motivational value to inputs (Roesch and Olson, 2004). The primary structures of

the limbic system are the parahippocampal and cingulate gyri, the ventromedial prefrontal cortex, the amygdala and its rostral projections to the septal region, the hippocampus, and their elaborate connections. The single most critical structure in the assignment of affective weighting to inputs is the amygdala. The amygdala is exposed to highly processed inputs from all sense modalities (Rolls, 2000), and it possesses specialized feature detection systems responsive to innate and conditioned stimuli (Kobatake and Tanaka, 1994). One function of the amygdala is to serve in the initial categorization of sensory inputs according to their motivational characteristics. The rostral outputs of the amygdala involve the basal forebrain nuclei, especially the n. accumbens, septal nuclei, and the anterior cingulate gyrus. These structures then provide scaffolding on which are built interactions with the prefrontal cortex that take the form of frontal-limbic circuits. These circuits participate in the formulation of behavioral strategies (Winkielman and Berridge, 2004). It is during these frontal-limbic interactions that emotional reactions are formed in relation to current events. Disruption of these connections due to injury (Bechara et al., 1999; Damasio, 1994) or chemical imbalance (Drevets et al., 1997) leads to inappropriate motivational behaviors and altered affect.

In summary, the formation of emotions results from a process of cognitive evaluation of ongoing events. Under this formulation, the stress response may be considered a result of negative affective states involving fight-or-flight behavioral requirements. The systems the brain has evolved to form emotional responses are the same one that determine which events are experienced as psychological stressors that result in physiological stress reactions. We will incorporate the idea of motivated behavior, emotions, and stress reactions into a consideration of the sources of the individual differences in between people that may determine differences in stress reactivity.

4. Individual differences in stress reactivity

In considering how persons might differ from each other in the size, frequency, or duration of their cardiovascular responses to stress, I have chosen to use the Cannon-Bard preparation as a point of departure, using the dividing line between the hypothalamus and the cerebral hemispheres (telencephalon) as a natural point of demarcation in the anatomy and function of the central nervous system (Bard, 1928; Swanson, 2000). Accordingly, at the top level in our system of organization, we will consider individual differences in the functioning of the cerebral hemispheres above the hypothalamus. The second level in this three-way breakdown is the hypothalamus and brainstem. These again form a natural anatomical and functional unit. Larry Swanson (2000) has pointed out that the hypothalamus and brainstem are properly considered motor output controllers that supervise three families of behavior: somatomotor

functions, autonomic visceromotor outputs, and endocrine secretomotor functions. The third level of organization involves the peripheral organs and tissues. Evidence suggests that structural and functional differences in the cardiovascular and endocrine systems can themselves account for reactivity differences between persons. Such tissue-based effects can reflect preexisting pathology or inborn predispositions toward disease. The remainder of this tutorial consists of a discussion of my thoughts about how each of these systems as diagrammed in Fig. 2 might contribute to reactivity to stress and individual differences in reactivity.

4.1. The frontal-limbic system and the generation of emotions

Our discussion of the organization and function of the frontal-limbic system provides a first level of organization in thinking about stress reactivity. The activities of the limbic system in relation to elaborate processing of information in consciousness forms a basis for understanding not only affective coloration of the products of consciousness but also for thinking about why some persons may characteristically react in an emotionally biased way to social interactions. Referring to Fig. 3, we can see a system of interconnections among the primary structures of the limbic system. Sensory inputs arrive through multiple modalities and become increasingly elaborated as they are processed through higher-order association areas. Ultimately, these inputs converge on the parahippocampal gyrus, where they become accessible to the hippocampus and amygdala. The amygdala and hippocampus both shape our long-term reactions to events through their role as memory structures. The hippocampus is well known as the essential structure for the formation of declarative memories (memories of places, events, and facts). First reported by Scoville and Milner, patients with a loss of the hippocampus and overlying cortex become entirely unable to form new declarative memories, although earlier memories remain intact (Scoville and Milner, 1957). Recognition of people, places and things upon future encounters is an essential element in forming appropriately adaptive responses to successive encounters. The shaping of experience by

developing a repertoire of such memories is clearly an important basis for how persons come to differ in their reactions to situations they encounter.

However, hippocampally based memories would not be sufficient in themselves to forge significant emotional reactions to relevant events. For reactions calling for motivational responses, the amygdala proves to be the essential structure. Early in life, the amygdala participates in initiating emotional reactions to innate stimuli that have significant survival value or threaten the individual. The prototypical innate reaction is the inborn fear of snakes seen in primates. Young monkeys presented for the first time with a rubber toy snake will scream and retreat in fear even though a snake had never been seen before. Such reactions are abolished by prior destruction of the amygdala (Hitchcock and Davis, 1986). This innate, but limited, store of amygdala-conditioned reactions constitutes the core of what we might call the *emotional memory system* (Cahill, 2000; Davis, 2000; McGaugh et al., 2000). Future elaborations of this repertoire of emotional memories grow through Pavlovian conditioning (Rolls, 1992). Animals with bilateral destruction of the amygdala are unable to form classically conditioned reactions to novel pairings of conditioned and unconditioned stimuli, although prior responses are retained (Davis, 1992). This essential role of the amygdala in Pavlovian conditioning parallels that of the hippocampus in declarative memory formation (Scoville and Milner, 1957). As the animal's range of experience grows, initially innate reactions and unconditioned reflexes become elaborated through association with increasingly complex sets of conditioned stimuli, forming the store of emotional memories and becoming an individualized basis for individual differences in motivationally based responses.

Although such conditioning processes are often seen as reflexive in nature, they also serve to provide emotional coloration to the experience of current events. In this sense, the hippocampus and amygdala work in tandem to allow for events to be recognized and for the motivation of adaptive responses to be summoned forth. Pathways from these temporal lobe memory structures extend toward subcortical nuclei located along the midline rostral to the anterior commissure. Fig. 3 shows these relationships, in which the amygdala is shown projecting to one set of these subcortical nuclei, the bed nuclei of the stria terminalis (BNST), often referred to as extended amygdala (Cassell et al., 1999; Sun and Cassell, 1993). The BNST is in close contact with the n. accumbens, a structure associated with shaping hedonic responses to sensory inputs (Hasue and Shammah-Lagnado, 2002). Both nuclei are extensively interconnected with the anterior cingulate gyrus and several areas of the prefrontal cortex (Middleton and Strick, 2001). Collectively these interactions allow for events to be examined to a greater or lesser degree in consciousness, and through the affective coloration provided by frontal-limbic interactions the person can make motivationally based responses to these events (Bechara et al., 1999; Damasio, 1994).

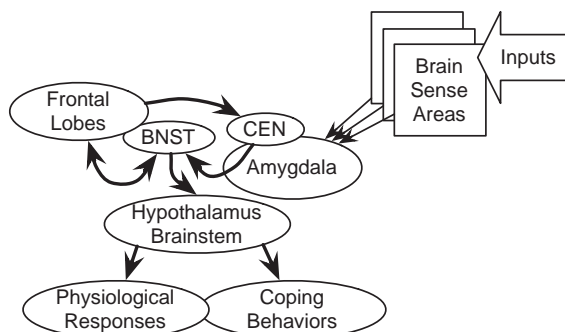


Fig. 3. Flow diagram of primary brain structures involved in physiological responses during states of psychological stress.

It is fundamental to our discussion of individual differences in stress reactivity that these frontal–limbic interactions form the underpinnings for psychologically based responses to events. This system provides a neurophysiological mechanism to support Lazarus's primary and secondary appraisal system. As inputs call forth memories of prior experience, along with emotional associations to those experiences, the person has the basis for forming primary appraisals of the event. These appraisals may be relatively reflexive and automatic in nature or more elaborately processed and thoughtfully considered. The extensive connections to the prefrontal cortex permit this highly conscious processing when needed. The classification of events thus involves interplay of frontal–limbic processes to begin the shaping of an adaptive response. This same system of frontal–limbic interactions would appear to underlie the process of secondary appraisals called for in Lazarus's model. The selection from a range of response alternatives, again more or less involving thoughtful conscious decision-making, completes the higher classification and response selection the person engages in as responses are developed to significant encounters with the environment.

The complexity of the systems involved at this stage of processing clearly permits a number of alternatives for the development and elaboration of individual differences in stress reactivity. These may include differences in the events encountered during life and in the emotional concomitants of those experiences. Along with these event-related processes, persons may have differences in neurochemical processes that shape not only the responses to first encounters with such events but in the evolving response repertoire that accompanies them.

4.2. Hypothalamus and brainstem

In order for psychologically based reactions to events to be properly configured as outputs to the body, they must engage with the regulatory centers contained in the hypothalamus and brainstem. As we noted in discussing the studies of Philip Bard (1928), the hypothalamus and brainstem form a functional unit that is capable not only of sustaining visceral functions but also of organizing complex skeletal motor behavioral, including locomotion and attack displays. Swanson has delineated the hypothalamus according to three midline-to-lateral layers supporting skeletal motor pattern controllers, secretomotor pattern controllers, and visceromotor pattern controllers (Swanson, 2000). Each set of controllers has its own set of output pathways via the: (1) skeletal motor brainstem pathways, (2) regulation of autonomic nuclei in the brainstem, (3) modulation of descending autonomic pathways in the brainstem and spinal cord, and (4) endocrine outflow via the pituitary. Through the activation of a series of highly specific programs, the hypothalamus and brainstem are able to provide descending patterns of behavioral, autonomic, and endocrine activity

appropriate to a wide range of emotional states and their associated behaviors.

In the case of stress reactions, we emphasize one specific set of hypothalamic patterns, those underlying the fight-or-flight reaction. This is a constellation of responses involving cardiovascular preparation for muscular exertion (increased cardiac output and stable or reduced vascular resistance) and endocrine adjustments to support vigorous efforts in the service of survival, including increased epinephrine secretion from the adrenal medulla and increased cortisol secretion from the adrenal cortex. This pattern is apparently initiated by activation of two sets of hypothalamic corticotropin releasing factor (CRF) neurons associated with the paraventricular nucleus (Petruzz and Merchenthaler, 1992). One set projects to the median eminence, where it is responsible for secretion of corticotropin releasing factor to the anterior pituitary, evoking the release of adrenocorticotropin into the systemic circulation and causing the release of cortisol by the adrenal medulla. The other set of corticotropin releasing factor neurons projects to the brainstem, including the nucleus paragigantocellularis, the locus coeruleus, and the nucleus of the tractus solitarius. Together these brainstem targets are responsible for the joint activation of descending sympathetic activation, inhibition of parasympathetic tone, and support of fight-or-flight behaviors, and activation of the rest of the central nervous system via noradrenergic fibers originating in the locus coeruleus.

In considering the potential contribution of the hypothalamus and brainstem to individual differences in reactivity, we will present evidence below that persons may differ characteristically in what we will call hypothalamic gain factors. These are neurochemically based differences between persons, perhaps genetic in origin, perhaps experientially shaped, that cause larger or smaller descending signals to the brainstem, and hence to the periphery.

4.3. Peripheral organs and tissues

For any given pattern and intensity of stress-related outputs arising from the central nervous system, their final expression in the body depends on the way these are transduced and into responses by the autonomically innervated organs and tissues and the recipients of endocrine stimulation. Tissues that differ in their response characteristics because of inborn differences could well produce larger or different responses to normal patterns of outflow from the hypothalamus and brainstem. An example of such an inborn disposition is the difference between individuals in the density of alpha and beta adrenoreceptors in the peripheral tissues. Differences in adrenergic receptor density may contribute to larger or smaller responses to stress, even though emotional reactions to the challenge and the hypothalamic outflow patterns may be the same as in persons with differing receptor densities. In addition, tissues that have been altered by the presence of disease, even in its

early, preclinical stages, could well alter the pattern of reactivity to stress.

4.3.1. Summary

This brief description of the three primary levels of the system that may determine individual differences in responses to stress forms the basis for examples of research presented below. These examples are intended to illustrate how it is possible to consider differing sources of reactivity differences given the design and interpretation of stress studies. We will follow each example with thoughts on how the engagement of each level in the system may well tell us different things about disease causation and risk.

4.4. Level I: cognitive-affective disposition and reactivity: hostility and CV reactions

The first example we will consider stems from a study done by Susan Everson to examine stress responses in persons high in hostility and the manipulation of these reactions by social provocation. This work was done in response to evidence that in studies of heart disease morbidity and mortality, the best predictor of risk in the psychosocial realm was the degree of hostility shown by the person (Dembroski et al., 1989; Rosenman et al., 1975). Persons manifesting overtly hostile reactions to the interviewer during the standard interview for the Type A behavior pattern had higher risk of heart disease and all other forms of death (Dembroski et al., 1989). Similarly, a self-report instrument to measure hostility, the Cook-Medley Hostility (Ho) Scale, was predictive of heart disease risk in the Western Collaborative Group Study (Barefoot et al., 1983).

Studies of hostile individuals in the laboratory had shown that neutral tasks did not provoke differential cardiovascular responses in individuals high vs. low in cynical hostility as measured by the Ho scale (Suarez and Williams, 1989). On the other hand, social provocation by a rude experimenter did elicit greater cardiovascular reactions in these cynically hostile subjects suggesting that the responses depended on a specific form of challenge.

In a follow up to these studies, Everson compared persons high and low in potential for hostility as initially defined by Dembroski (Dembroski et al., 1989). Volunteers were given the standard interview for the Type A behavior pattern, and these were rated for sarcastic statements and specific vocal characteristics. High- and low-hostile subjects then were invited back to the lab for an ostensibly different study on cardiovascular responses caused by cognitively difficult tasks. When the men returned the same staff member greeted them, and they were outfitted for cardiovascular measurements. After a suitable baseline, they were asked to perform a mental arithmetic task monitored by intercom with corrections for errors. They were then told to rest and to read magazines and that the task would be repeated later. A control group of both high- and low-hostile

men did indeed repeat the task under the original neutral instructions. The remainder of the subjects was greeted at the end of the rest period by a new female experimenter who adopted a brusque, rude attitude, telling the subject that the first experimenter had abandoned him, having forgotten an earlier appointment, and that she had asked the new experimenter to finish up the test session. She then answered a telephone outside the testing room and had a social conversation that the subject overheard while waiting with nothing to do. Terminating the call with, "I'll call you back later. I have to finish up with this guy in here," the experimenter started the second task, interrupting at three specified times with brusque requests to work faster and even correcting a right answer.

The results showed that the high- and low-hostile men experienced similar distress, tenseness, and irritation before and during the neutral task, but the high-hostiles were higher in these self-rated states during the second task following harassment. These self-reports are consistent with the interpretation that the high-hostile subjects were subject to the hostility manipulation and interpreted the situation in a very different light than did their low-hostile counterparts. Debriefing revealed that the high-hostiles took the harassment personally, stating that they felt mistreated. The low-hostiles were more likely to report thinking that the rude experimenter was "having a bad day." One high-hostile asked to discontinue the second task, stating that if we were going to treat people like that, he was not going to cooperate further. He was fully debriefed, but his reaction typifies the notion that the cognitive interpretation of this social challenge led to hostile reactions and negative mood states among this group.

The cardiovascular data presented in Fig. 4, the subjects in the neutral control condition, whether hostile or non-hostile, had smaller reactions to the second mental arithmetic task than to the first, consistent with an adaptation to the repetition of an innocuous task. For the subjects in the harassment condition, the high- and low-

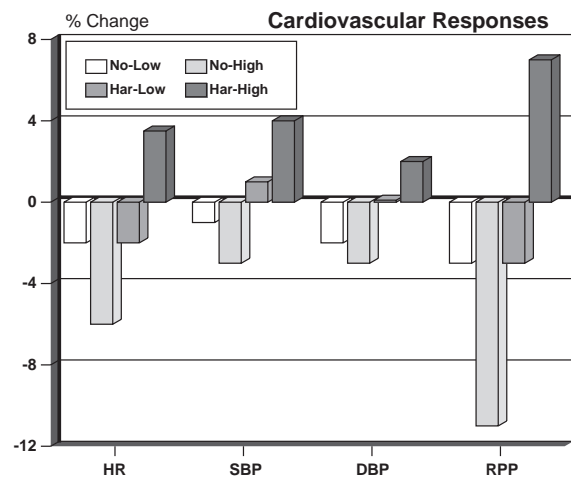


Fig. 4. Cardiovascular responses during mental arithmetic tasks given under neutral and harassing conditions to men rated high or low in trait hostility.

hostile subjects were equally reactive to the initial mental arithmetic task, the one given under neutral instructions. In contrast, after the harassment the groups showed different reactions to the second mental arithmetic task. In this case, the high-hostile men had larger cardiovascular reactions than the low-hostile men and larger reactions than they showed to the first task. In particular, the combined increases in heart rate and blood pressure caused the highly hostile men to have the largest increase in rate-pressure product (heart rate \times systolic blood pressure), a measure of myocardial work and oxygen demand.

The results indicate a particularly helpful use of self-report data in conjunction with physiological responses to the social situation created for the subject. The self-reports indicated that the high-hostile men did not differ from the low-hostiles when task conditions were not interpersonally challenging to their presumed hostile schema. The differences between groups, both psychologically and physiologically, emerged only in the context of a hostility-arousing social manipulation. For this reason, we attribute the findings to processes and brain structures depicted at Level I of our model of reactivity (Fig. 2). These incorporate interactions between limbic and prefrontal cortexes that we believe add emotional coloration to ongoing processes, especially processes that are being interpreted in consciousness. The emotional colorations appear to then engage output systems involving hypothalamic integrations of autonomic outflow and also brainstem autonomic control centers.

In considering the degree to which conscious and nonconscious processes may have determined these reactivity differences we will speculate that both may have been involved. In the case of the social manipulation, the high- and low-hostile men had different explanations for the behavior of the experimenter and for their reactions to the situation. Comments during the debriefing suggested that the high-hostile men in particular may have had an added element of nonconscious input to their emerging response to the situation. Compared to low-hostile men they were less likely to be suspicious that the experiment was an artificial set-up to make them react in a particular way. Because prospective subjects are often skeptical of the motives of the experimenter in a psychological study, we were concerned that the scenario may have been too artificial to be believable. In fact, the high-hostile subjects were unlikely to express suspicious thoughts during the debriefing, leading us to speculate that the hostile reactions of this group were highly overlearned and originated as a stereotyped reaction to the provocation, which then was elaborated in consciousness as the person became overtly irritated.

The purpose of this lengthy recounting of previously published data is to suggest that the use of self report data in conjunction with appropriate baseline and control manipulations can allow us to begin to separate out reasons behind exaggerated physiological responses to environmental chal-

lenges. As such, these manipulations allow us to begin to isolate levels in the central nervous system that are contributing to the exaggerated reactivity. Similarly, the data from this study allow us to say what processes were not primarily involved in the exaggerated reactivity. In this case, the highly hostile persons were not indiscriminately responsive to any form of challenge; they did not react differentially to the neutral task. So at the level of the hypothalamus and brainstem, descending activation due to purposeful engagement in an effortful task did not automatically result in larger responses than those seen in the low-hostile group. Examples below will however indicate that such interpretations may be tenable given different patterns of self-report and physiological data.

4.5. Level II: hypothalamic and brainstem sources of reactivity

Studies we have carried out on persons at high risk for hypertension suggest that reactions to potential sources of threat are not a result of specific cognitions or emotional cognitive reactions but may be due to a nonspecific reactivity to many sources of descending activation. Two sets of studies lead us to this conclusion. The first was a relatively large blood pressure screening of medical students at high and low risk for hypertension (al'Absi et al., 1995; Everson et al., 1992). The second was a study of cortisol reactivity of borderline hypertensive men to exposure to a novel laboratory situation (al'Absi and Lovallo, 1993). In the course of this work we adopted a published rule for documenting risk for hypertension (Paffenbarger et al., 1968; Thomas and Duszynski, 1982). Earlier studies found that a positive parental history of hypertension and a modestly elevated systolic blood pressure (>125 mmHg) together were strong predictors of future hypertension, with an odds ratio of increased risk of 12 over persons lacking both risk factors, based on 22 years of follow up (Thomas and Duszynski, 1982).

The blood pressure screening study was intended to document cardiovascular reactivity in persons at risk for hypertension and to identify the most discriminative risk factors for hypertension. We therefore brought male medical students to the laboratory and conducted blood pressure screening that mimicked a doctor's office visit and to meet criteria set forth by the American Heart Association. Students arrived at the appointment and were told to have a seat while the experimenter made preparations to test them. Exactly 5 min later the white-coated experimenter returned, put a blood pressure cuff on the subject's left arm and explained that an automated device would take the blood pressure, but that the device had to be checked for accuracy against a stethoscope. Three readings were taken over 5 min while the experimenter held a stethoscope to the brachial artery, ostensibly listening to Korotkoff sounds. This procedure matches the social interactions normally occurring when a patient is seen in a clinic. The experi-

menter announced that the machine was working perfectly and that a few more readings were to be taken to get an average. The subject was left alone for 10 min more while relaxing and reading magazines. After that, the subject was given a mental arithmetic test lasting 5 min.

We found three things of interest. First, high-risk persons who met both risk criteria had pressures substantially higher than the low-risk men; 127/72 mm Hg vs. 118/65 during the 10 min after the simulated manual pressure readings. Second, the high-risk subjects reacted more to mental arithmetic (+23/16 mm Hg vs. +14/12 mm Hg). Finally, the pressures seen in the high risk group recovered more from the simulated “White Coat” manipulation to the end of the 10 min rest, suggesting that they were indeed reacting to the presence of a stranger (Bernardy et al., 1995). These findings differ from those in the study on hostile men. First, the social interaction during the “White Coat” readings, and the subsequent mental arithmetic task were benign and emotionally neutral. The high responses to the mental arithmetic, and the greater recovery of pressures from the White Coat period to the end of the rest period, suggest a nonspecific reactivity to a variety of challenges, including social interaction with a stranger and effort on a cognitive task. However, these conclusions have to be tempered with the fact that we did not obtain self-report data in this study, and therefore we do not have any explicit evidence of the high-risk subjects’ perceptions and interpretations of the situation. We only know that the laboratory experiences were intended to be emotionally neutral and not threatening.

Stronger evidence comes from a related study we conducted on young men at high risk for hypertension. The study’s primary purpose was to test these men in response to stress combined with caffeine exposure, however, the resting data provided interesting insights into sources of reactivity in these persons. In this case the risk for hypertension was documented by what we then classified as a borderline hypertensive pressure at screening (135–154/84–95 mm Hg, now considered Stage 1 hypertension; Committee, 2003) compared to low risk persons as defined above. Subjects then visited the laboratory on four more occasions. We will focus on their reactions to entering the laboratory each day. The borderline hypertensive men had elevated cortisol readings on the first two mornings in the laboratory, relative to the consistently low levels seen in the control subjects (Fig. 5) (al’Absi and Lovallo, 1993).

We had previously shown that cortisol responses to nonmetabolic stimuli are indicative of a state of fight-or-flight associated with high levels of activation accompanied by negative affect and a sense of threat (Lovallo et al., 1990). Considering that these subjects had already visited the lab for two screening sessions, their spontaneously high levels of cortisol seemed unusual. Because the levels had normalized on the third and fourth days, we knew that they were not simply higher in cortisol production at all times. We interpreted these findings as indicating a higher level of response to exposure to a novel laboratory setting. In this

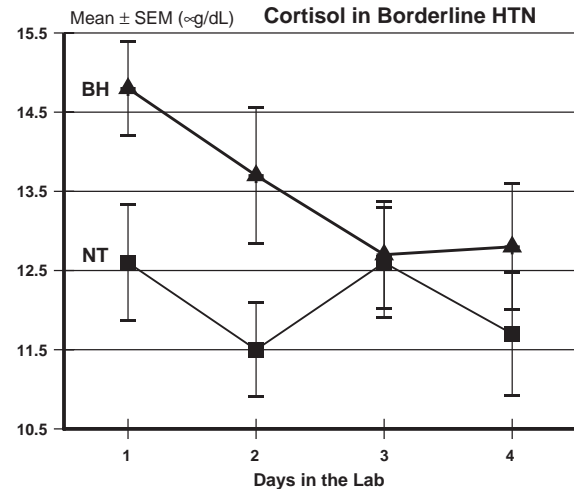


Fig. 5. Cortisol responses to a novel laboratory environment in men with borderline hypertension vs. low-risk normotensives.

study, although the subjects were preadapted to the laboratory, on test days they were instrumented for cardiovascular measurements and had a catheter placed in a forearm vein to permit blood draws. Apparently the hypertensives were capable of much greater activation of this core element of the stress response to these circumstances. Were these subjects consciously interpreting the situation as more threatening than the controls? To the extent that we assessed their subjective states, they did not reveal feeling more distressed than the controls, although on Day 1 there was a nonsignificant elevation of self reported nonspecific arousal.

We argued that the hypertensives therefore did not consciously perceive the situation as more threatening than the controls. Instead, it appeared that the hypertensives had “a relative hyperactivation of the hypothalamic-pituitary-adrenocortical axis...accompanied by a normal perception and cognitive interpretation of the experimental environment” (al’Absi and Lovallo, 1993). We considered this instead to be due to a greater hypothalamic gain factor. That is, the hypertensives appeared to be likely to generate a greater descending output signal at the level of the hypothalamus for a given level of descending activation. At the time there was no known mechanism to support this contention, but recent work suggests that of hypertension is accompanied by more CRF neurons in the central nervous system; spontaneously hypertensive rats show more such neurons than their control strain, and brains of humans who died with complications of hypertension also have more CRF neurons (Goncharuk et al., 2002). Because the CRF neuron is responsible for integrating the fight-or-flight response across the central nervous system and because the population of CRF neurons in the hypothalamic paraventricular nucleus is responsible for regulating the diurnal and stress-related secretion of cortisol, the findings of Buijs and colleagues may provide a mechanism for enhanced reactivity seen in hypertensives. As these authors noted, “Increased activity of

CRH-producing neurons in the PVN of hypertensive patients is proposed not only to entail hyperactivity of the hypothalamic-pituitary-adrenal axis, but also of the sympathetic nervous system and, thus, to be involved in the pathogenesis of hypertension” (Goncharuk et al., 2002).

This mechanism would exhibit three interesting features: (1) It is unlikely to be derived from cognitive and psychological causes. (2) It is potentially nonspecifically reactive. (3) Greater activation of the HPAC would be accompanied by greater cardiovascular responses. It is noteworthy that although hypertensives have long been known to have greater nonspecific responses to a variety of stressors (Brod, 1963), no single framework for a hypertensive personality type or a hypertensive psychological structure has been developed. This would be consistent with a reactivity that is based in structures of the central nervous system that are below the level of conscious awareness but that are able to respond to activation associated with cognitive challenges, psychomotor stimulation, and the like.

4.6. Level III: peripheral tissues

Although alterations in stress reactivity may originate as emotional reactions under control of frontal-limbic mechanisms, or as exaggerated hypothalamic and brainstem activity, the peripheral tissues may also play a role in how reactive an individual is. Tissues may have different response characteristics from birth or they may be altered as a function of existing disease pathology (Folkow, 1990). As a result, they will behave differently under the influence of descending activational signals than they would behave in a healthy person or someone at low risk.

4.6.1. Cardiovascular activity in men at high risk

Two examples of the influence of altered peripheral tissues on reactions to stress come from the work of Paul Mills (Mills et al., 1990), and studies by our lab (Lovallo and al’Absi, 1998; Marrero et al., 1997). In the first example, Mills et al. have pointed to the importance of peripheral adrenergic receptor densities in contributing to physiological response to mental stressors. Density of beta adrenergic receptors accounted for more of the response variance than traditional response measures, such as catecholamine activation, and these traditional measures in conjunction with receptor densities accounted for a considerable amount of the response variance. Cluster analysis of results from a large group of individuals indicated that peripheral receptor compliments may be a dominant factor in determining reactions to mental stress (Mills et al., 1994). An implication of these findings is that descending influences reflecting activation at the level of the frontal-limbic system or at the hypothalamus and brainstem will nonetheless have greater influences on persons with greater numbers of peripheral adrenergic receptors. Effectively, the receptor compliment can be a peripheral amplifier of descending signals.

The second example of peripheral tissue differences in relation to cardiovascular disease risk comes from a study of young men at high risk for hypertension (FH+ and SBP >125 mm Hg) compared to those at low risk (FH- and SBP <125 mm Hg). Both groups visited the laboratory on 2 days when they were asked either to perform mental arithmetic and a psychomotor task or, on the other day, to simply rest for the same 3-h period while watching videos or reading magazines (Lovallo and al’Absi, 1998). Subjects were instrumented for cardiovascular measurements and were asked to give self-reports on their state of activation and distress. The high-risk men did not differ from the low risk controls in these report measures at any point on either day. As expected, they had higher blood pressures at all times. A particularly revealing difference became apparent during the rest day. As the period of rest progressed, the high-risk men showed a progressive rise in vascular resistance, but no marked changes were noted in blood pressure or cardiac output over that time (Fig. 6).

These data were collected at rest, and as such they indicate that there are group differences in physiological functioning that appear when the subjects are at rest, and not under stress. Such differences point to peripheral changes that are probably not associated with autonomic or endocrine outflow but which are consistent with models of hypertension that argue for the existence of elevated peripheral resistance following from increased vascular wall thickness. Folkow (1990) has argued persuasively that this leads to a decrease in the diameter of resistance vessels that is both a preclinical indicator of hypertension and a causative factor. The data presented here therefore indicate that there can be purely peripheral indicators of a preclinical state that are apparent at rest, and which could contribute to differential stress reactions under appropriate test conditions. It is likely that these differences reflect peripheral physiological processes that are not in themselves due to

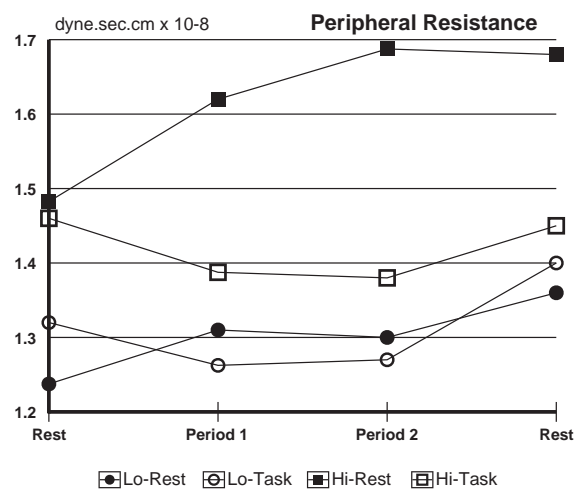


Fig. 6. Cardiovascular responses during rest and work on mental stressors in men with and without family histories of hypertension.

central nervous system differences or altered emotional reactivity.

5. Speculations—disease

The three levels at which differential reactivity to stress may relate to disease are presently a matter of speculation, but I believe these examples provide some reasonable guides for how each source of reactivity differences is related to alterations in the system and how each relates to cardiovascular disease.

Our example from higher levels of the central nervous system, reflecting frontal–limbic interactions (Fig. 2, Level I), shows that emotional factors may indeed contribute to disease risk. Although it is not likely that these factors alone can be a cause of cardiovascular disorders, they are likely to be able worsen disease processes that are already present. As such, intense emotional reactions, like the ones discussed above in relation to harassment, would result in high levels of descending activation that engage hypothalamic and brainstem output pathways. These frequent and potentially large activational processes could be expected to have more devastating consequences for individuals who already possess a range of other risk factors or in whom a disease process is in the preclinical stages. The potential for such increased activity to potentiate a pathophysiological process such as atherosclerotic plaque or vascular wall thickening seems reasonable, and there is no lack of particular mechanisms to be brought to bear on the question.

In contrast, the next source of reactivity, exaggerated hypothalamic gain factors or enhanced brainstem activation (Fig. 2, Level II), may occur in the absence of differential emotional reactions and in the absence of specific emotional triggers. Such differences between persons may be seen therefore in response to everyday demands and in the absence of negative affective states. Nonetheless, such causes may increase the magnitude of the resulting physiological response in the absence of any specific demand. If such changes have the opportunity to increase lipid mobilization, platelet aggregation, or blood pressure rises, then they have ample means to act on a disease prone system to increase risk. It is possible, even likely that there are individuals who are more reactive at both Levels I and II. In this case specific emotional triggers would produce exaggerated emotional reactions that would also receive a greater degree of amplification in shaping peripheral responses.

Reactivity differences at Level III (Fig. 2), in the periphery, may well not be causes of disease, but are likely to point to underlying disease predispositions due to gene- or environment-induced changes in tissue function or even to point to existing preclinical disease states. Once again, greater or more frequent reactions due to actions at Levels I or II would have a disproportionate impact on a system already altered in these ways, potentially accelerating pathogenic or pathologic processes.

6. Recommendations for research

The foregoing discussion suggests some guidelines for research in the area of cardiovascular reactivity.

Self-report data are perhaps a critical adjunct to physiological data for learning about the potential existence of cognitive-psychological inputs to elevated physiological reactions. Because most persons working in the area of reactivity are psychologists, and because psychologists have a healthy skepticism about self-report data, many studies in this area are conducted without obtaining self-reports of affective state. Although asking people to tell about how they feel is fraught with pitfalls, it would also seem that such data could provide a perspective on the physiological reactions of the person that goes beyond seeing the physiology as emerging from a black box. That said, such data are best taken in context. Since most studies of reactivity include a rigorous experimental protocol and careful conditions of testing, the context is well prepared for making interpretable and reliable measurements. There is presently no agreement on precisely what subjective states should be measured and how to take the measurements in studies of reactivity. The current lack of a consensus on what types of measures should be taken and whether there should be a set of preferred instruments for taking self-reports during acute stress suggests that this potentially important information is left to the perhaps arbitrary choices of individual experimenters. Some agreed upon methods and standardization would help. One caveat is that not all researchers would agree with my fundamental position that a person knows if he or she is experiencing an emotion (Winkelman and Berridge, 2004).

Cortisol is a useful indicator of hypothalamic reactions to stress. Our knowledge of the central nervous system origins of a cortisol response to psychological stress provides an interpretively useful way of identifying one level in the system that is clearly a player in generating such reactions (Lovallo, 2005). As I have tried to illustrate with the model shown in Fig. 3, if a bodily response originates as an experience and interpretation of an external event, the perception and interpretation must be caused by central nervous system sensory systems in contact with limbic areas. In addition, there is increasing agreement that the interpretive side of this transaction involves interactions between limbic structures and prefrontal ones, what we call frontal–limbic interactions. So a cortisol response to a psychological stressor engages the hypothalamus with this higher-level frontal–limbic interaction. Given appropriate experimental controls on time of day of testing and adequate attention to the state of the subject it is reasonable to make such interpretations of cortisol rises in response to acute stressors. It is particularly useful to include a nonstress resting control day of measurements if at all possible (Buchanan et al., 1999; Lovallo et al., 2000). Because cortisol appears to be especially responsive to negatively affective events (al'Absi et al., 1997; Buchanan et al., 1999;

Lovallo et al., 2000), the combination of cortisol measurements and self-reports may prove especially useful in particularizing the sources of exaggerated reactivity in certain groups and under given conditions of measurement.

As noted above, peripheral physiological measures can be used for interpretations that go beyond the simple documentation of the effect of a stressor. When considered in conjunction with self reports, they can be used to indicate clinical or preclinical changes in function. As such they may be helpful in knowing about altered organic function and existing disease and thus contributing to a more complete picture of how reactivity differences may be related to disease risk.

7. Reactivity—study designs

The foregoing considerations of interpretation in turn suggest aspects of study design that should be considered in the planning of studies comparing between-subject variations in reactivity to stress. Some of these are quite standard and some are less so. Studies of cardiovascular reactivity and disease risk should include some or all of the following elements.

7.1. Resting measures with no threat of stress

These measures form the classical baseline period that usually comes prior to administering a given challenge to the subject. The most common method of comparing groups on stress responses is therefore the comparison of change measures from baseline to stress. Less often used is measures of level of function after recovery when the stressor is now passed and no longer impending (Schwartz et al., 2003). The least often used, and most costly and labor intensive, is to have the subject visit the lab on a nonstress rest day during the same time period as on the stress day. Although this may seem overly burdensome, the data can be extremely useful because the true baseline can be gauged at each time point. This is most useful in studies of cortisol activation because cortisol does not present a steady-state level of baseline activity. Taking cortisol at several time points on this reference day to match data collection on a stress day provides an extra means of documenting stress effects making between group comparisons more reliable, and informative.

7.2. Self reports

As discussed above, these measures can be helpful, if not definitive, in disentangling the sources of group differences in response to stress.

7.3. Psychological stressors

Stressors that challenge appraisal and coping resources of the person of necessity engage frontal limbic processes. To

the extent that groups differ in reactivity to such a stressor, the response differences may be a result of differences in activity at that level, informed in particular by self report data and lack of baseline effects.

7.4. Physical stressors

Stressors that directly challenge homeostatic regulation and which necessarily engage hypothalamic or peripheral reactivity in the absence of psychological engagement may also be helpful when trying to interpret between subjects sources of difference. An excellent and simple task for such comparative purposes is the orthostatic challenge task. Simply having the subject rise to a standing position and measuring cardiovascular function for 3–5 min after a steady state of compensation has been achieved can provide a significant adaptational challenge to the cardiovascular system that is not accompanied by psychological and affectively driven influences. As a result, group differences that may emerge are most likely to reflect physiological causes. By the same token, lack of differences in response between groups can provide additional means for interpreting group differences where they do occur, to a psychological stressor, for example.

8. Conclusions

The examination of stress reactivity as a means of studying risk for disease has become an increasingly fruitful area of investigation. Although linkages between individual differences in stress reactivity and disease risk may be explored at a purely correlational level, use of appropriate study designs and data collection procedures can also yield useful insights into which components of the response are engaged in particular subgroups. The model presented here is a first attempt to parse the complexity of the individual and how the person engages with specific challenges in the environment. Attention to the ways in which the central nervous system and peripheral response patterns are activated by given types of stressors can aid in identifying specific sources of reactivity and hence in specifying sources of disease risk.

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