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Are Large Physiological Reactions to Acute Psychological Stress Always Bad for Health?

Running title: Reactivity and Health

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Abstract

How we react physiologically to stress has long been considered to have implications for our health. There is now persuasive evidence that individuals who show large cardiovascular reactions to stress are at increased risk of developing cardiovascular disease, particularly hypertension. By implication, low reactivity is protective or benign. However, there is recent evidence that low reactivity may predict elevated risk for a range of adverse health outcomes, such as depression, obesity, poor self-reported health, and compromised immunity. In addition, low cortisol and cardiovascular reactivity may be a characteristic of individuals with addictions to tobacco and alcohol, as well as those at risk of addiction and those who relapse from abstinence. Our ideas about reactivity may have to be revised in the light of such findings.

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Introduction

How the body reacts to emotions and psychological distress and the consequences of this for health have fascinated us for centuries (Mesulam & Perry, 1972). The extent and implications of such stress reactions came to be conceptualised as the 'reactivity hypothesis', which has been a subject of substantial scientific interest over the last 30 years. As originally conceived, it proposed that large magnitude cardiovascular reactions to acute psychological stress exposures increased the risk of developing high blood pressure or hypertension (Obrist, 1981). It has been expanded subsequently to link high reactivity with other related cardiovascular disease outcomes. An obvious upshot is that low reactivity will necessarily be protective. However, the generality of this latter assumption is something we believe is being challenged by a variety of recent findings.

Evidence linking reactivity to cardiovascular pathology

The evidence linking large magnitude cardiovascular reactions to stress and cardiovascular pathology has been reviewed many times over the years (Lovallo & Wilson, 1992; Schwartz et al., 2003; Treiber et al., 2003; Turner, 1994) and, given that there is reasonable consensus, our treatment can be brief. Indicative evidence comes from case-control studies that compare the magnitude of cardiovascular reactions to stress of individuals at risk and not at risk of developing hypertension. The risk markers most commonly tested have been parental hypertension and relatively high but sub-hypertensive blood pressure levels. Offspring of parents with hypertension (Carroll, Hewitt, Last, Turner, & Sims, 1985; Ditto, 1986; Miller & Ditto, 1991) and individuals with elevated, but sub-hypertensive, resting blood pressure exhibited larger cardiovascular reactions to acute stress than control participants (Carroll, Harris, & Cross, 1991; Drummond, 1983; Fredrikson & Matthews, 1990; Sims & Carroll, 1990).

Undoubtedly the most compelling evidence emerges from prospective studies, where cardiovascular reactions to acute stress were assessed at entry to the study and blood pressure status measured at some future time point. A number of large scale studies in a range of

populations attest to a reliable positive association between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure status (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Everson, Kaplan, Goldberg, & Salonen, 1996; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999; Treiber, Turner, Davis, & Strong, 1997). These associations are particularly impressive given that they were still manifest following statistical adjustment for a range of possible confounders in addition to resting cardiovascular levels. In addition, there is now preliminary evidence that high reactivity is positively associated with other cardiovascular outcomes. Four prospective studies in three independent samples have now examined the relationship between reactivity and indices of atherosclerosis in the carotid artery; all report positive associations (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998). Supportive evidence comes from experimental studies of stress manipulations in cynomolgus monkeys maintained on high fat diets. Briefly, animals that exhibited high heart rate reactions to the stress of the provocative presentation of the glove used for capturing them showed greater coronary atherosclerosis than low heart rate reactors (Manuck, Kaplan, Adams, & Clarkson, 1988; Manuck, Kaplan, & Clarkson, 1983). Finally, three studies have found a positive association between left ventricular mass and/or hypertrophy of the heart, strong predictors of cardiovascular disease morbidity and mortality, and high reactivity (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Murdison et al., 1998). In sum, there is now persuasive evidence that large magnitude cardiovascular reactions to acute psychological stress increase the risk of developing high blood pressure. There are also indications that high reactivity is positively associated with related outcomes such as atherosclerosis and left ventricular mass.

Stress exposures and acute cardiovascular events: the triggering hypothesis

The associations described above have emerged from the study of originally healthy individuals and thus implicate high reactivity in the aetiology of cardiovascular disease. There may be another role for acute stress and how we react to it in cardiovascular disease. The notion that

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psychological stress may trigger acute cardiovascular events, such as heart attacks and stroke has become increasingly popular. Survivors of acute cardiovascular events frequently report mental stress as a trigger of their event (Smith & Little, 1992; Tofler et al., 1990). More critically, a number of epidemiological studies indicate that environmental stressors such as earthquakes, terror attacks and even the stress associated with watching key soccer matches are associated with increased hospital admissions for and mortality from acute cardiovascular events (Carroll, Ebrahim, Tilling, Macleod, & Smith, 2002; Kario & Matsuo, 1995; Kario, McEwen, & Pickering, 2003; Leor & Kloner, 1996; Meisel et al., 1991; Trichopoulos, Katsouyanni, Zavitsanos, Tzonou, & Dalla-Vorgia, 1983; Witte, Bots, Hoes, & Grobbee, 2000). Despite this growing evidence of a link between psychological stress and acute cardiovascular events, the physiological mechanisms that may account for this link are poorly understood.

Evidence indicates that individuals with high resting levels of haematocrit and blood viscosity are at increased risk of mortality from acute cardiovascular events such as myocardial infarction and stroke, including possibly stress-induced events (Gagnon, Zhang, Brand, & Kannel, 1994; Lowe, Lee, Rumley, Price, & Fowkes, 1997). Haematocrit is the percentage volume of blood that is occupied by red blood cells and is positively related to blood viscosity, which is defined as the blood's resistance to flow. Elevated levels of haematocrit and blood viscosity would increase the shear stress on vulnerable atherosclerotic plaques, thereby increasing the likelihood of rupture; acute cardiovascular events, particularly heart attacks, are often the result of plaque rupture and coagulation. Thus, if psychological stress increases haematocrit and/or blood viscosity, such increases would provide a plausible physiological pathway linking stress to acute cardiovascular events. Increases in haematocrit or decreases in its converse, plasma volume, have frequently been found with acute psychological stress exposure (Allen & Patterson, 1995; Bachen, Muldoon, Matthews, & Manuck, 2002; de Boer, Ring, & Carroll, 2006; Mischler et al., 2005; Patterson, Krantz, & Jochum, 1995; Patterson, Marsland, Manuck, Kameneva, & Muldoon, 1998; Zgraggen et al., 2005). More recently, we observed a parallel increase in blood viscosity and a shortening of the time it took for blood to coagulate during psychological stress (de Boer et al., 2007). Add to this the haemodynamic effects of stress and the observation that pro-inflammatory cytokines, such as interleukin-6, are elevated following acute stress exposure (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004; Edwards, Burns, Ring, & Carroll, 2006),

and we have accumulating indications that acute psychological stress provokes what might be regarded as a 'prothromobotic' state. Such a state would increase the risk of a clot forming in vulnerable individuals precipitating a heart attack or stroke. What is missing is concerted evidence that those who show higher magnitude reactions in these prothrombotic markers are at particular risk of suffering a cardiovascular event. However, it has been reported that cardiac patients with relatively high blood pressure reactions to stress were at increased risk of future cardiac events (Krantz et al., 1999). Thus, there are indications that greater reactivity may constitute a risk for both the development and aggravation of inflammatory disease. Clearly there is considerable scope for further, particularly prospective, research in this context.

The association between acute stress exposure, reactivity and other health outcomes

We have seen that there is good support for the idea that persons with very large cardiovascular responses to mental stress are more likely to suffer negative cardiovascular outcomes over time. However, in recent years, the scope of the reactivity hypothesis has been expanded to embrace the notion that excessive reactivity may be implicated in non-cardiovascular health outcomes. It is from research examining aspects of this expanded role for reactivity that a number of seemingly paradoxical findings are emerging. A review of some of these areas may point the way for an expanded view of altered stress reactivity and its role in predicting health outcomes.

Depression, obesity, and self-reported health

Depression has been linked prospectively to mortality in general and death from cardiovascular disease in particular (Hemingway & Marmot, 1999; Wulsin, Vaillant, & Wells, 1999), although the mechanisms underlying this association have yet to be established. However, depression has been related to a variety of physiological adaptations that suggest altered autonomic function. For example, enhancement of cardiac sympathetic activity relative to vagal tone has been reported in those with depression and subclinical depressive symptoms (Carney et al., 1988; Light, Kothandapani, & Allen, 1998). Thus, the speculation that such autonomic dysregulation in depression may also be manifest as exaggerated cardiovascular reactions to stress is intuitively

appealing. A meta-analysis of 11 relevant studies found small to moderate effect sizes indicative of a positive association between depressive symptomatology and cardiovascular reactions to acute psychological stress (Kibler & Ma, 2004). Unfortunately, none of aggregate effects were statistically significant. The studies included in the meta-analysis generally tested small samples and few of them adjusted for potential confounding variables such as demographic factors and medication status. Since then two substantial studies have been published, one in a large community sample of over 1600 participants (Carroll, Phillips, Hunt, & Der, 2007) and the other in a coronary artery disease patient sample of over a 100 (York et al., 2007). In the first of these depression was measured using the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), and the data analysed both as continuous symptom scores and as a binary variable, using scores ≥ 8 to signify possible pathology. The stress task was a time-pressured mental arithmetic task. In the second, symptoms of depression were measured using the Beck Depression Inventory (Beck, Ward, Mendelsohn, Mock, Erbaugh, 1961), and the stress task was public speaking. In both studies, higher depressive symptom scores were associated with lower, not higher, reactivity. What is especially compelling about these negative associations is that they were still evident following adjustment for a relatively comprehensive range of covariates. Thus, it would appear that as putative risk factors for cardiovascular pathology, high levels of depressive symptomatology and exaggerated cardiovascular reactions to stress may operate independently of one another. They also beg the question, answerable only by prospective designs, of whether low reactivity could be a risk marker for depression. Given that depression is a heterogeneous condition, another issue requiring resolution is just which aspects of depression relate to low reactivity. The pattern of changes elicited suggests that the stress tasks used in these two studies provoked beta-adrenergic activation; these tasks have also been shown elicit cortisol activation, see e.g., (A.C. Phillips, Carroll, Burns, & Drayson, 2005). For example, in a recent study using a public speaking task we found marked increases in both cardiovascular and cortisol activity; indeed, the magnitude of the stress-induced changes in pre-ejection period, a marker of beta-adrenergic activation, strongly predicted the size of the subsequent cortisol response (Bosch et al., under review).

In the population study cited above, the associations among reactivity and adiposity and obesity were also examined (Carroll, Phillips, & Der, 2008). Both cross-sectional and

prospective analyses were possible in this case. Contrary to expectations based on the indicative rather than definitive outcomes of the few previous small scale studies, low cardiac reactivity was associated with a greater body mass index, more abdominal adiposity and greater likelihood of being obese. When the sample was trichotomised into lean (body mass index < 25 kg/m^2), overweight (> 25 but < 30 kg/m^2), and obese (> 30 kg/m^2), there was an orderly but negative dose-response relationship with cardiac reactivity. In addition, in prospective analyses low cardiac reactivity was associated with an increased risk of becoming obese in the subsequent five years. Again, these outcomes withstood adjustment for a range of socio-demographic factors and medication status. There is some other evidence that whereas the obese have elevated sympathetic tone in the resting state (Tentolouris, Liatis, & Katsilambros, 2006), their sympathetic nervous system may be less responsive to stimulation. For example, after ingestion of a meal, there is a postprandial sympathetic nervous system response as reflected by higher plasma norepinephrine concentrations and an increased low- to high-frequency ratio in the heart rate variability spectrum (Tentolouris et al., 2003; Welle, Lilavivat, & Campbell, 1981). However, this effect has been observed to be much smaller in obese as opposed to lean individuals (Tentolouris et al., 2003). Further, changes in heart rate and muscle sympathetic nerve stimulation after the infusion of antihypertensive and antihypotensive drugs were found to be significantly smaller in the obese than the non-obese (Grassi et al., 1995). In sum, the finding that it is low cardiac reactivity that characterises obesity would appear to be credible. Indeed, low reactivity, possibly by reflecting generally blunted sympathetic nervous system response to acute challenge, may even be a risk marker for developing obesity.

If reactivity has wider implications for health than originally envisaged, it is perhaps surprising that no study that we know of has examined whether it is associated with self-reported health. Intuitively, self-reported health is an interesting candidate in this context. The results of numerous large-scale prospective epidemiological studies testify that self-reported health predicts various health outcomes including mortality in a dose-response fashion, independently of traditional risk factors and medical status; those reporting poor health have a mortality risk two to seven times greater than those reporting excellent health (Idler & Benyamini, 1997). If self-reported health is affected by cardiovascular morbidity and its precursory processes, it might be expected to be related to reactivity. Again, we were able to examine this issue both cross-

sectionally and prospectively in the large community sample (A. C. Phillips, Der, & Carroll, in press). In cross-sectional analyses, those with excellent/good self-reported health exhibited larger cardiovascular reactions than those with fair/poor subjective health. In prospective analyses, participants who had larger cardiovascular reactions to stress were more likely to report excellent/good health five years later, taking into account their reported health status at the earlier assessment. As before, these associations withstood adjustment for a range of possible confounders, including body mass index and depressive symptomatology. Thus, as with depression and obesity, it was low reactivity that was associated with the poorer health outcomes.

Immunity

Self-reported health is likely to be a function of numerous factors and to depend on the integrity of multiple biological systems; it would certainly not appear to be determined simply by the subjective impact of occult or manifest cardiovascular disease. One system that would appear to be critical in this context is the immune system. Indeed, it has been proposed that what we experience as illness, sickness, and pain is, at least in part, determined by feedback from the immune system to the central nervous system (Maier & Watkins, 1998). Further, what is called the acute stress-induced immuno-enhancement hypothesis proposes that acute stress up-regulates various aspects of immunity and that this has functional implications for host defence (Dhabhar, 2002; Edwards et al., 2007). For example, secretory immunoglobulin A is regarded as the major antibody in immune defence at mucosal surfaces; whereas chronic stress is associated with its down-regulation (A. C. Phillips et al., 2006), acute stress has been repeatedly shown to elicit increases in secretion rate (Bosch & Carroll, 2007). Further, acute stress is also associated with increases in the number of circulating lymphocytes, most notably those, such as natural killer cells and particular subtypes of cytotoxic T-cell, which are better at killing pathogens (Bosch, Berntson, Cacioppo, Dhabhar, & Marucha, 2003; Bosch, Berntson, Cacioppo, & Marucha, 2005). These and other changes suggest that exposure to acute stress, and by implication large magnitude stress reactions, might actually enhance the immune system's ability to respond to a contemporary antigen challenge.

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More direct functional evidence that this is the case comes from vaccination studies. In rodents, several acute stress exposures, such as foot shock and restraint, have been shown to enhance the immune response to non-medical vaccination challenges (Dhabhar, 2003; Millan et al., 1996; Silberman, Wald, & Genaro, 2003). A recent human study from the Birmingham group exposed participants to a mental arithmetic stress task immediately prior to vaccination. As expected, the stress task induced significant heart rate increases. However, women exposed to the acute stress had higher peak antibody responses to the A/Panama influenza strain than women in a no stress control condition (Edwards, Burns, Reynolds et al., 2006). In addition, acute stress exposure prior to vaccination was also associated with an enhanced antibody response to meningococcal A in men (Edwards et al., 2008). However, what about individual differences in reactivity to acute stress? The acute stress-induced immunoenhancement hypothesis would imply that it would be the most reactive that would reap the greatest immunological dividend. We now have provisional evidence that this might be the case. Those who showed the greatest cortisol reactions to an acute stress task were more likely to mount a better antibody response to the A/Panama strain of the influenza vaccination (A.C. Phillips et al., 2005). Finally, greater blood pressure reactions toward the end of an acute stress task were characteristic of individuals who mounted a better antibody response to the A/Panama and B/Shangdong influenza strains (A. C. Phillips, Carroll, Burns, & Drayson, in press). In sum, it would appear that whereas high reactivity contributes to and exacerbates inflammatory cardiovascular disease, low reactivity may compromise immunity and our ability to fight infectious disease, and as such be the maladaptive response.

Stress reactivity and addiction

Does stress reactivity have any relevance for thinking about risk for addiction? While it may seem intuitive that physiological reactions to psychological stress might have relevance for the onset or progression of cardiovascular disease, it is perhaps less obvious that stress reactivity may similarly be a signal of risk for behavioural disorders, including addictions (Lovallo, 2006, 2007). A useful starting point for considering this possibility is to restate the observation that behavioural and psychological tendencies are also physiological response characteristics. That

is, at the level of the brain, thoughts and action tendencies that are the basis of all behaviour are always part of the physiology of the brain and this in turn become part of our peripheral physiological reactivity and our external behaviour (Lovallo, 2005c). Therefore, we consider that emotional reactions to the environment, their impact on physiological reactivity, and their health consequences are part of the expanded sense of reactivity and health under discussion here.

Events in our lives shape our emotional reactions through appraisal processes and coping resources (Lazarus & Folkman, 1984). As we encounter challenges in daily life, we automatically assess their threat value and form adaptive responses to these, either avoiding what is threatening or harmful or seeking to obtain things that are beneficial. In this endless balancing of approach and avoidance we experience states of emotion ranging from mild to extreme in intensity and from pleasure to fear in valence (Cuthbert, Bradley, & Lang, 1996). Along with these emotions that serve as our motivations, are patterns of brain activity that produce physiological outputs and bodily states that support the needed behaviours. Emotions are therefore seen as action dispositions with four components: affect or subjective feeling states; thoughts; visceral states; and overt behaviours. Under this formulation, either excessive or highly diminished states of physiological reactivity might be seen as signals that non-optimal emotion regulation is taking place, and that in turn might result in maladaptive behavioural tendencies.

We have elsewhere argued that our characteristic physiological response tendencies may have origins at three levels in our system (Lovallo, 2005a). At the highest level of the central nervous system our cognitions and emotions, and their corresponding patterns of brain activity, may result in either excessively large or small physiological output responses depending on some combination of genetic make up and prior experience. At a lower level we include the hypothalamus and brainstem; the brain's output systems that form the physiological and behavioural responses to the higher centres that underpin our thoughts and emotions. Finally, at the peripheral level are the body's motor responses that result in endocrine reactions, cardiovascular responses, and also overt behaviours. We have previously laid out evidence that reactivity differences between persons can occur at each of these levels, and so we will simply state without further proof that the idea of physiological reactivity is quite naturally of a piece

with the idea of emotional and behavioural reactivity, although this may not be perfectly obvious on the surface (Lovallo, 2005a).

We will comment here only on the highest level of the system because of its special relevance for emotions and behaviours. The brain structures in question, their anatomical interconnections, and their patterns of response to motivating circumstances are currently the subject of much research, and these have been described in some detail (Damasio et al., 2000). To review quite briefly, these structures involve the amygdala, the prefrontal cortex, and feedback from the body to these areas. The amygdala is now understood to be the core structure in forming emotional responses to danger as well as things we may wish to obtain (Rolls, 2000). Persons in whom the amygdala has been damaged or lost through disease are emotionally unresponsive and have a tendency to fail to avoid danger (Adolphs et al., 2005; Buchanan, Etzel, Adolphs, & Tranel, 2006). Similarly, persons who have intact amygdalas but who have lost their connections to the prefrontal cortex are similarly unable to form normal behavioural and physiological responses to appetitive or aversive circumstances (Bechara, Damasio, & Damasio, 2003). Still other evidence implicates two prefrontal areas as being critically involved in this process of appraising events and the forming responses to coping with these events; these are the dorsolateral prefrontal cortex, an area shown to be critical for the operation of working memory (Ungerleider, 1995), and the anterior cingulate gyrus and related sections of the cortex that bring together information concerning the approach-avoidance value of events with formulations of response strategies (Barch et al., 2001; Blair et al., 2006). The other crucial piece of the apparatus is the anterior portion of the insular cortex, the part of the brain that receives feedback from our internal organs and literally helps us to know how we feel about what is going on and allows us to make decisions based on those feelings (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Damasio, 1994). Persons with existing damage to the insula similarly have difficulty making decisions, and patients with recently acquired insular damage may show sudden changes in habits and preferences, including abruptly quitting smoking (Naqvi, Rudrauf, Damasio, & Bechara, 2007). In short, these structures and their patterns of interaction will affect not only our physiology, but also our feelings and behaviours. If we are willing to accept this perspective, then it becomes highly plausible that physiological reactivity might not only signal risk for physical diseases but also may serve as a window into less obvious conditions, such as the

addictions.

Although we strongly suspect that brain areas associated with differences between individuals in physiological reactivity to stress are the same ones involved in a range of other disorders, the addictions among them, this contention needs strong confirmation through the use of neuroimaging. This work is beginning to emerge as researchers study physiological response tendencies in light of resting patterns and reactivity-related activity of the limbic system and prefrontal cortex (Gianaros, May, Siegle, & Jennings, 2005; Gianaros et al., 2008). In similar fashion, this same kind of work needs to be done in comparing resting and reactive patterns of brain activity in persons at risk for addiction (Acheson, Robinson, Glahn, Lovallo, & Fox, 2008; Glahn, Lovallo, & Fox, 2007). This limited work suggests that activity in the limbic system, prefrontal cortex, and insular cortex are associated with cardiovascular reactivity and addiction-related activity differences.

There is emerging evidence that low or blunted cortisol and cardiovascular reactivity is characteristic of those with substance dependencies and may indeed be a general marker for risk of addiction (Lovallo, 2006). Let us consider smoking; the act of smoking *per se* is associated with increases in cardiovascular activity and cortisol (Kirschbaum, Wust, & Strasburger, 1992; Pomerleau, Fertig, Seyler, & Jaffe, 1983). However, habitual smokers have been found to show diminished salivary and plasma cortisol (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Kirschbaum, Scherer, & Strasburger, 1994; Kirschbaum, Strasburger, & Langkrar, 1993; Rohleder & Kirschbaum, 2006) and cardiovascular (Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; A. C. Phillips, Der, Hunt, & Carroll, under review; Roy, Steptoe, & Kirschbaum, 1994) (Sheffield, Smith, Carroll, Shipley, & Marmot, 1997; Straneva, Hinderliter, Wells, Lenahan, & Girdler, 2000) reactions to acute psychological stress. It is unlikely that these effects reflect temporary abstinence during stress testing and its effects on stress task engagement (Roy et al., 1994). Blunted cardiovascular reactivity has been observed in female smokers regardless of whether they were wearing a nicotine replacement patch or not (Girdler et al., 1997). In addition, cardiovascular reactivity has been compared among non-smokers, smokers who abstained from smoking, and smokers who continued to smoke at their usual rate; smokers, irrespective of their assigned condition, showed blunted cardiovascular and cortisol reactions to acute stress (al'Absi et al., 2003). Given that cardiovascular and cortisol stress reactivity are

strongly correlated (Cacioppo, 1994; Lovallo, Pincomb, Brackett, & Wilson, 1990), it is perhaps unsurprising that attenuated reactivity in one system is paralleled by the diminished reactions of the other. In addition, this cardiovascular and cortisol hypo-responsiveness has been found to predict relapse among smokers who have recently quit smoking (al'Absi, 2006; al'Absi, Hatsukami, & Davis, 2005). Thus, low reactivity not only characterizes those addicted to smoking; it may also be a risk marker of some prognostic significance (Lovallo, 2006; Lovallo, 2007).

Those addicted to alcohol have also been found to exhibit blunted cardiovascular and cortisol stress reactivity (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002). In addition, relatively low reactivity would appear to be a characteristic of non-alcoholics with a family history of alcoholism. In the Oklahoma Family Health Patterns project, young adults with a positive family history, particularly those with low sociability scores, showed lower cortisol and cardiac reactions to psychological stress than those with a negative family history of alcoholism and high sociability scores (Sorocco, Lovallo, Vincent, & Collins, 2006). Other studies of the offspring of parents addicted to alcohol or drugs provide further evidence; in a prospective study, boys with a positive family history who showed a blunted cortisol response to stress were more likely to experiment with cigarettes and marijuana (Moss, Vanyukov, Yao, & Kirillova, 1999). The data suggest that blunted reactivity may not only be a characteristic of those with a dependency, it may actually pre-date the addiction and signal risk of future addiction. Accordingly, in low reactivity we may have a marker of motivational dysregulation linked to inherited risk of a wide range of addictions (Lovallo, 2006). Thus, it is not only high physiological reactivity that can be a risk marker for poor health outcomes; low reactivity would also seem to be implicated.

Physiological stress reactivity, behavioural dispositions, risk for addictions, and health

The present review has discussed standard models of elevated stress reactivity and risk for cardiovascular health and disease. We have also commented on recent findings indicating how low levels of reactivity might be involved in maladaptive physiological tendencies and in behavioural dysregulation in the form of addiction proneness. Linking physiological response

tendencies to behavioural characteristics gives an interesting perspective to how the central nervous system engages with the external world with regard to adaptive behaviours. Such a perspective suggests that the brain's response characteristics may be fundamental and observable at several levels of brain organisation (Lovallo, 2005a, 2005b; W. R. Lovallo & W. Gerin, 2003; W.R. Lovallo & W. Gerin, 2003). The prefrontal cortex and its engagement with the limbic system is critical for organising our adaptive responses to the demands of the environment. These frontal-limbic interactions determine how supportive physiological responses accompany these adaptive behaviours. Under normal circumstances, responses are behaviourally and physiologically adaptive and within some theoretically normal limits. However, we have attempted to argue that when either or both of these depart from normal in the direction of exaggerated or diminished reactivity, then potential health consequences may ensue. This raises a question of what may determine the reaction tendencies of the frontal-limbic systems of the brain? One answer concerns genetic and epigenetic mechanisms and their individual differences. Although it is beyond the scope of this paper to have an exhaustive listing of all candidate genes and their supporting evidence, some brief examples may suffice to indicate how genetic and epigenetic factors may cause exaggerated and diminished stress reactivity and may relate to and health.

Polymorphisms of the serotonin transporter gene (5HTTLPR), which plays a key role in determining the magnitude and duration of both the central and peripheral actions of serotonin, would appear to be implicated in emotional regulation and physiological reactivity. Activity of the 5HTTLPR long allele is almost twice that of the short allele. Men who are homozygous for long allele have been found to score lower on measures of anxiety and depression (Lesch et al., 1996). Those with long alleles have also been found to exhibit higher blood pressure and heart rate reactions to a laboratory stress task (Williams et al., 2001; Williams et al., 2008). Interestingly, in the present context, college students with two short alleles who experienced multiple negative events in the previous year reported more frequent and heavier drinking, stronger intentions to drink, and greater non-prescribed drug use; no such effect was evident for those with two long alleles.

Another example of a single gene that can affect both behavioural and physiological reactivity, and one that is plausibly related to addiction risk, is a polymorphisms of the gene for

catechol-o-methyltransferase (COMT), a substance that breaks down neurotransmitters in the central nervous system (Goldman, Oroszi, & Ducci, 2005). COMT acts at points of interaction between the limbic system and the prefrontal cortex. A common polymorphism of the COMT gene is labelled (*val*^{158}*met)* where the amino acid valine (*val*) replaces the usual methionine (*met*) (Ishiguro, Haruo Shibuya, Toru, Saito, & Arinami, 1999). One COMT gene is inherited from each parent and persons with two copies of the *val* variant (*val/val*s) have a highly a stable COMT molecule that is highly effective at removing both dopamine and norepinephrine from synapses. Such persons are high in central opioid activity because of the nature of interactions between dopamine, norepinephrine, and the opioid neurons that regulate both mood and pain perception. In contrast, persons with two *met* copies are low in impulsivity and are behaviourally restrained. Persons with *val/val* genotypes are low in anxiety, stress-proneness, and are behaviourally unrestrained and impulsive (Lipsky et al., 2005; Smolka et al., 2005). During a study of prolonged pain induction, *val/val*s required the greatest amount of pain stimulus to reach a pain threshold, and they experienced the least negative affect during the procedure (Zubieta et al., 2003). Simultaneous neuroimaging if central opioid function showed that the *val/val* group the highest opioid levels in the nucleus accumbens and the amygdala, consistent with our frontal-limbic convergence zone. In Goldman's shorthand, the *val/val* group may be considered stress-resistant "Warriors" and the *met/met* group, stress-prone "Worriers" (Goldman et al., 2005). In addition to lower physiological and affective responsivity (Smolka et al., 2005), persons who are warriors are antisocial and more behaviourally impulsive, and both characteristics are associated with proneness to addictions (Enoch, Waheed, Harris, Albaugh, & Goldman, 2006; Vandenbergh, Rodriguez, Miller, Uhl, & Lachman, 1997).

A third example of a single genetic polymorphism that can have profound behavioural effects was investigated by Caspi and colleagues, who studied persons with polymorphisms of the gene for monoamine oxidase A (MAOA), a molecule that also breaks down neurotransmitter in central nervous system neurons (Caspi et al., 2002). In this case, young adults who had a low-activity variant of MAOA, and who had suffered significant early life stress, were violence prone and likely to have been imprisoned for violent crime. In contrast, persons with the most highly active form of MAOA were least likely to have a history of antisocial behaviour, and indeed were highly resistant to the damaging effects of early stress exposure. This study not only

illustrates the effects of specific genetic variations on behavioural dispositions, it also is an ideal example of the interaction of genes and environment in determining such outcomes. Other studies of this MAOA polymorphism also have found it to be associated with impulsivity and aggressiveness (Manuck, Flory, Ferrell, Mann, & Muldoon, 2000; Manuck, Flory, Muldoon, & Ferrell, 2002), and this set of characteristics is linked to central serotonin function, associated with long-term mood regulation. Persons with high central serotonin reactivity tend to have high aggression scores on self-report instruments (Manuck et al., 2002). In contrast, low serotonin reactivity using the same measure is associated with greater rates of metabolic syndrome (Muldoon et al., 2004).

A final example of the effects of person-environment interactions concerns the epigenetic effects of early rearing in rat pups. Epigenetic effects of environmental input affect how genes are expressed without altering the genes themselves. Researchers interested in how early experience might affect later development studied the effects of maternal nurturing and neglect in rat pups. Behavioural manipulations or endogenous behavioural traits that caused rat mothers to spend extra time licking and grooming their young offspring produced adult rats that were seen as "stress resistant" because they were behaviourally docile, lacking in anxiety, and low in cortisol reactivity (Caldji, Diorio, & Meaney, 2000; Liu, Caldji, Sharma, Plotsky, & Meaney, 2000; Plotsky & Meaney, 1993). In contrast, neglectful mothers produced offspring with high levels of central nervous system activation and high cortisol reactivity (Meaney & Aitken, 1985; Meaney et al., 1985). Examination of brain function in these developing rat pups showed that the highly nurtured ones had high levels of central serotonin activity that in turn affected the transcription of glucocorticoid receptors in the central nervous system, an effected that persisted into adulthood (Anisman, Zaharia, Meaney, & Merali, 1998; Plotsky & Meaney, 1993). Although the standard stress reactivity model might view such placid, stress resistant animals in a desirable light, others have explored the immune system outcomes in relation to early deprivation and glucocorticoid reactivity. Piglets exposed to early maternal deprivation and who had reduced glucocorticoid reactivity also had reduced immune response to immunological challenge, indicating that reduced stress reactivity may not be universally beneficial but instead can have potentially adverse health effects (Kanitz, Tuchscherer, Puppe, Tuchscherer, & Stabenow, 2004; Tuchscherer, Kanitz, Puppe, Tuchscherer, & Stabenow, 2004). Although we

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should not extrapolate directly from rats or pigs to humans, this work indicates that early experience can have permanent effects on stress reactivity and that reduced reactivity is not always beneficial for health.

Conclusions

The prevailing evidence testifies that large magnitude cardiovascular reactions to acute psychological stress place individuals at risk for the upward drift of resting blood pressure and hypertension. There are also indications that high reactivity might pose a risk for other manifestations of cardiovascular disease, such as atherosclerosis and increased left ventricular mass. In addition, although there have been no direct tests to date, the pattern of cardiovascular, rheological, and inflammatory changes with psychological stress exposure suggests that they may constitute a prothrombotic state, increasing the likelihood of acute cardiovascular events, such as heart attacks and stroke. However, from tests of the association between reactivity and other health outcomes a very different picture is starting to emerge. It is low, not high, reactivity that appears to be associated with depression, predicts the development of obesity, and is implicated in poor self-reported health. Further, acute stress exposure, although an issue for inflammatory disease, would appear to enhance other aspects of immunity in a way that may benefit our ability to ward off infection. There is preliminary evidence that those who respond best to a vaccination challenge are also those who show greater cardiovascular and cortisol reactions to stress. Finally, an increasing body of research indicates that low cardiovascular and cortisol reactivity is characteristic of individuals with an alcohol or tobacco dependence and, indeed, may predict risk of addiction, as well as signalling the likelihood of relapse following abstinence. It would appear that depending on the outcomes in question departures from the norm in either direction may pose problems, suggesting that in both instances the system is operating in a biased state, whether at the level of the higher CNS, at the level of the hypothalamus and brainstem, or at the level of the periphery. One of the challenges is to understand the neural substrates of both hypo- and hyper-reactivity to acute stress.

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We have discussed the results so far in terms of an inverted-U model where high and low reactivity are bad for health depending on the health outcome in question. However, a model which perceives of continuous positive associations between reactivity and some health outcomes and continuous negative associations between reactivity and other health outcomes can also fit the current data. We depict these two models in Figure 1. Time will tell which best serves any revision of the reactivity hypothesis. It should be conceded that this review has focussed on the magnitude of physiological of reactivity. Clearly both magnitude and duration are important for allostatic load. However, considerations of duration and recovery are beyond the scope of the current review.

Although we strongly suspect that brain areas associated with physiological reactivity differences between individuals are the same ones involved in a range of other disorders including addictions, this contention needs strong confirmation through the use of neuroimaging and prospective studies. Work in this area is beginning to emerge as researchers study physiological response tendencies in the context of resting and reactivity related activity of the limbic system and prefrontal cortex. In similar fashion, this same kind of work needs to be done in comparing resting and reactive patterns of brain activity in persons at risk for addiction, obesity and other health outcomes. This new perspective on reactivity may allow us to expand our conceptual model of how departures from normal physiological response patterns can predict risk for poorer health outcomes. Low, as well as high, reactivity may be bad for our health.

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Figure 1: Alternative models linking reactivity to health outcomes