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# **The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes.**

## **Introductory Paper**

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### Highlights

- Blunted reactions to acute laboratory stress relate to poor health outcomes.
- Blunting may reflect reduced effort, stress perceptions, or physiological capacity.
- Blunted responses may be a marker of central motivational dysregulation.
- Blunted reactivity is neurally based and independent of stress task effort.

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## **Abstract**

A cornerstone for research into the link between stress and health has been the reactivity hypothesis; cardiovascular reactivity to psychological stressors, if prolonged or exaggerated, can promote the development of cardiovascular disease. However, it has recently been argued that low or blunted reactivity is also associated with negative health outcomes. As such, in this special issue we present further evidence implicating that cardiovascular and stress hormone responses to acute stress at the other end of the response spectrum can also be considered a pathway to ill health. In this introductory article, we explore and review the origins of and potential mechanisms underlying blunted responses to acute stress. In so doing, we aim to highlight: what is currently known regarding this new conceptualization of the reactivity hypothesis; the potential explanations for blunted reactivity; the pathways underlying associations with health outcomes; and where this field is headed in terms of developing our understanding of the link between reactivity and health.

**Keywords:** blunted reactivity; cardiovascular reactivity; health outcomes; stress responses;

## 1.1 Introduction

A key focus of research into the link between stress and health for several decades has been the reactivity hypothesis, which proposes that cardiovascular reactivity to psychological stressors, if prolonged or exaggerated, can promote the development of cardiovascular disease (Obrist, 1981). Heightened cardiovascular reactivity is posited to result in changes to the structure and functioning of the heart that potentially promote a number of adverse disease outcomes, including sustained hypertension (Obrist, 1981) cardiac and vascular hypertrophy (Lovallo and Gerin, 2003), oxidation of low-density lipoproteins (Raitakari et al., 1997), and increased serum concentrations of both pro-inflammatory cytokines (Georgiades, 2007) and blood insulin (Nazzaro et al., 2002). Theoretical considerations of how negative health results from reactivity-related adaptations of the cardiovascular system have been corroborated by an extensive empirical literature linking heightened reactivity to objective outcomes, including hypertension (Carroll et al., 2003; Carroll et al., 1995; Carroll et al., 2001; Everson et al., 1996; Markovitz et al., 1998; Matthews et al., 1993; Newman et al., 1999; Treiber et al., 1997), atherosclerosis (Barnett et al., 1997; Everson et al., 1997; Lynch et al., 1998; Matthews et al., 1998), increased left ventricular mass and/or hypertrophy of the heart (Georgiades et al., 1997; Kapuku et al., 1999; Murdison et al., 1998), and cardiovascular disease mortality (Carroll et al., 2012b). Both qualitative reviews and meta-analyses of this evidence confirm the contention that exaggerated stress reactions signal poor future cardiovascular health (Chida and Steptoe, 2010; Gerin et al., 2000) (Schwartz et al., 2003; Taylor et al., 2003) (Treiber et al., 2003).

Given the emphasis placed on associations between exaggerated reactivity and disease pathogenesis, low or blunted reactivity to acute stress has, by implication, been assumed to be

benign or even protective. However, recent evidence suggests that low cardiovascular reactivity to stress, as well as low cortisol reactivity, may actually have serious adverse consequences for health and behaviour. For example, comparatively low cardiovascular and cortisol reactions to acute psychological stress have been found to characterize smokers (al'Absi, 2006; al'Absi et al., 2005; Girdler et al., 1997; Phillips et al., 2009b; Roy et al., 1994; Sheffield et al., 1997) and those with alcohol and other substance addictions (Brenner and Beauchaine, 2011; Lovallo, 2005; Lovallo et al., 2000; Panknin et al., 2002), as well as being associated with obesity (Carroll et al., 2008), depression (Brinkmann et al., 2009; Carroll et al., 2007; de Rooij et al., 2010; Phillips et al., 2011; Rottenberg et al., 2007; Salomon et al., 2009a; Schwerdtfeger and Rosenkaimer, 2011; York et al., 2007), poor self-reported health (De Rooij and Roseboom, 2010; Phillips et al., 2009a), exercise addiction (Heaney et al., 2011a), eating disorders (Ginty et al., 2012a), and poorer cognitive function (Ginty et al., 2011a; Ginty et al., 2011b; Ginty et al., 2012b). Comparatively reduced cardiovascular stress responses have also been associated with personality traits also indicative of future disease, such as Type D personality (Howard et al., 2011) and neuroticism (Hughes et al., 2011), and other studies have found low reactivity among people taking medications known to increase heart disease risk, such as oral contraceptives (Schallmayer and Hughes). In light of accumulating evidence supporting an association between blunted stress reactivity and addiction, and the emerging evidence relating blunted reactivity to other unhealthy behaviours and negative health outcomes, it would appear that both extremes, exaggerated and diminished reactivity are maladaptive responses to stress. This suggests that the most optimally healthy response to stress is a moderate reaction (Lovallo, 2011). This paper will examine the concept of blunted responses to stress, their possible origins and underlying mechanisms as an introduction to this special issue on blunted reactivity to acute stress.

## 2.1. What are the bases of 'blunted' reactivity?

We take the term 'blunted cardiovascular reactivity' to refer to an empirically demonstrable cardiovascular response pattern which is comparatively lower than that seen during typical states of homeostatic function during stress. As yet, the precise mechanism that determines the occurrence of blunting is unclear, and an important distinction needs to be made between reactivity that is blunted (which implies sub-normality) and reactivity that is simply low (which may be biologically normal within a given context). There are several possible bases of blunted reactivity, which we outline below. Overall, it can be noted that while there are a number of possibilities, several remain to be tested empirically.

### 2.1.1 Lower effort

One possibility is that lower reactions to acute stress tasks may reflect *lower effort* on the part of a participant; in other words, that blunted responses are primarily the result of behavioral factors rather than of cognitive or biological factors. Perceptions of how stressful a psychological stress task is might impact upon an individual's willingness to engage with the task, with reduced effort or motivation then underlying a negative health impact. It could be argued that symptoms of conditions such as depression, which are associated with blunted responses, might also relate to lower motivation levels. Certainly, depression is characterized by a reduced degree of motivation, and both depression and low motivation appear to be related to the same gene polymorphisms, such as the met variant of the Val158Met COMT gene (Aberg et al., 2011), which results in different levels of extracellular dopamine within key brain reward system areas. Yet, in neuropsychological tests requiring cognitive effort, depressed participants have not consistently performed worse (Hammar et al., 2011). Further, not all of the behaviours or conditions associated with blunted responses to stress relate to lower motivation or effort; indeed

some such as exercise dependence (Heaney et al., 2011b) require considerable motivation and effort. Finally, in studies produced by the Birmingham group, we have always found blunted responses to be independent of ratings of task stressfulness and engagement, as well as objective performance scores which are a proxy for task engagement (see e.g. (Ginty et al., 2012a; Heaney et al., 2011a)). Taken together, this evidence suggests that individuals characterised by blunted responses are not necessarily demonstrating lower task performance or perceptions of motivation. However, as performance is merely a proxy for effort, and not the same construct, it remains unclear whether or not the tendency to invest less effort accounts for trait-like patterns of blunted responses.

#### 2.1.2 Reduced awareness or perception of stress

An alternative theory of blunted reactivity is that it might reflect a *reduced awareness or perception of stress*; in other words, that blunted responses is primarily the result of cognitive factors rather than of behavioural or biological factors. An inability to detect stressors in the environment, or a tendency to view dangerous stimuli as innocuous, would logically serve to dampen physiological stress responses. It has long been established (a) that perceptual factors are important in determining whether an individual exhibits a physiological stress response (Speisman et al., 1964) and (b) that individuals differ in the extent to which they habitually regard otherwise innocuous stimuli as negatively valenced (Bishop, 2008). It has also been established that training participants to bias their attention away from negative stimuli serves to dampen their cardiovascular responses to subsequent stressors (Higgins and Hughes, 2012), implying that such perceptions are causally responsible for cardiovascular response profiles rather than the other way around. Moreover, such effects are most pronounced among persons with high levels of trait neuroticism (Connor-Smith and Flachsbart, 2007), a group also

characterised by blunted responses to stress (Phillips et al., 2005a). As such, blunted cardiovascular responses may reflect diminutions in stress vigilance and/or detection, although this remains to be tested directly.

### 2.1.3 The impact of task difficulty

One possibility underlying blunted reactivity is that of the impact of task difficulty. In stress tasks which employ active coping, it has been shown that the extent of reactivity is related to the difficulty or challenge levels of the task, such that both easy and over-challenging tasks can result in weaker cardiovascular responses (Richter and Gendolla, 2006). When task difficulty is manipulated, as it increases, so too do the magnitude of cardiovascular responses until difficulty levels where success is impossible (Carroll et al., 1986; Richter et al., 2008), although this has not been shown in all studies (Willemsen et al., 2000). This is considered to be due to effects on motivational intensity in active coping situations (Wright, 1996). Task difficulty is also thought to interact with mood resulting in different levels of perceived subjective demand, which in turn determine the amplitude of cardiovascular reactivity (Gendolla and Krusken, 2001). Indeed these situational manipulations of perceived task demand have been replicated multiple times to show the impact of effort on cardiovascular responses to stress. However, other studies have revealed that in situations of matched task difficulty (Phillips, 2011), and across different types of tasks (de Rooij, 2013 in press) in this special issue), there appear to be a sub-group of individuals who consistently show trait-like blunted responses to acute stress, independent of perceptions of tasks difficulty, see e.g., (Ginty et al., 2012a; Heaney et al., 2011a). This brings us to the next potential explanation for blunting.

### 2.1.4 Reduced physiological capacity to respond



A fourth explanation for blunted reactivity is that the blunted responses may reflect a reduced physiological capacity to respond to stress or a disengagement of the biological systems, rather than of behavioural or cognitive factors. For example, there is reasonably consistent evidence that the sympathetic nervous systems of individuals who have become obese, although characterized by high basal sympathetic nervous system activity (Carroll et al., 2008; Tentolouris et al., 2006), and higher basal cortisol levels (Bjorntorp, 1993; Bjorntorp and Rosmond, 2000), are less responsive to stimulation (Carroll et al., 2008; Tentolouris et al., 2006). There is evidence of a postprandial sympathetic nervous system response, as indicated by higher plasma norepinephrine concentrations and an increased low to high frequency ratio in the HR variability spectrum after ingestion of a meal (Tentolouris et al., 2003; Welle et al., 1981). Similarly, this is smaller among obese individuals than the non-obese (Tentolouris et al., 2003). In addition, the changes in HR and muscle sympathetic nerve stimulation following infusion of anti-hypertensive and anti-hypotensive drugs are significantly smaller in the obese than the non-obese (Grassi et al., 1995), consistent with the view that such blunted responses result from biologically-based attenuation. A further example is that of depression; where basal sympathetic nervous system activity, as indexed by a shift enhanced cardiac sympathetic activity relative to vagal tone (Carney et al., 1988), increased plasma noradrenaline concentrations (Rudorfer et al., 1985), and increased 24-hour urinary noradrenaline excretion (Hughes et al., 2004) has been shown to be higher in individuals with depression or depressive symptomatology compared to controls. This perhaps also makes depressed individuals less responsive to stimulation as shown in reactivity studies (Brinkmann and Gendolla, 2008; Carroll et al., 2007; de Rooij et al., 2010; Phillips et al., 2011; Salomon et al., 2009b; York et al., 2007), potentially via decreased  $\beta$ -adrenergic receptor responsiveness (Mazzola-Pomietto et al., 1994; Yu et al., 2008).

### 2.1.5 Motivational dysregulation within the brain

In line with this argument of a reduced physiological capacity to respond to stress, it has previously been proposed that blunted physiological stress reactivity may be a marker of central motivational dysregulation (Carroll et al., 2009, 2011), a suboptimal functioning of the physiological systems in the brain that support motivation and motivated behavior (e.g. a disengagement in the motivational areas of the brain when faced with an acute challenge). Support comes from the evidence that blunted physiological responses to acute stress are associated with addictions (al'Absi, 2006) (Girdler et al., 1997; Lovallo, 2005) and with a non-substance abuse addiction and disorder, bulimia (Ginty et al., 2012a; Koo-Loeb et al., 1998), related to hypo-functioning of the brain in response to reward (Bohon and Stice). Additionally, individuals with obesity have been observed to show reduced responses to food within the striatum (Stice et al., 2008). Persons with depression are characterised by reduced activation of the striatum to positive stimuli (Epstein et al., 2006) and reduced responsiveness to reward behaviourally through weaker emotional responses, neurologically in the frontostriatal systems, and neurochemically through dysregulated function in brain areas under the control of monoamines (Eshel and Roiser, 2010). Additional support comes from evidence that blunted reactions are associated with poorer cognitive ability in earlier life (Ginty et al., 2011a) and both cross-sectionally (Ginty et al., 2012b) and prospectively (Ginty et al., 2011b); cognitive performance requires the integrity of neural motivational systems (Busato et al., 2000; Dweck, 1986; McClelland et al., 1953; Pintrich and Schunk, 1986). Perhaps the most compelling evidence of motivational dysregulation comes from a recent study showing a hypo-activation during stress in blunted reactors compared to exaggerated reactors. This hypo-activation was concentrated in the anterior mid-cingulate cortex: an area of the brain associated with motivation,

high cognitive functioning, engagement, and emotional control. This study also demonstrated a deactivation during stress compared to rest in the amygdala and frontal cortex: areas of the brain associated with motivation and emotion and blunted reactors reported similar levels of stress task engagement, difficulty, and stressfulness (Ginty et al., 2013) . Thus it is plausible that blunted responses to acute stress situations might reflect unconscious reduced effort (i.e., where a person believes they are trying as hard as everyone else), as is suggested by our previously observed post-task ratings of effort and engagement as well as individuals' stress task performance scores which indicate effort (Ginty et al., 2012a). Indeed, we have recently shown that individuals with inadvertent reduced motivation, measured through forced expiratory volume, are also characterised by blunted stress reactions (Carroll et al., 2012a).

#### 2.1.6 Stifling or titration of the blood pressure response

A final scenario to account for blunting is where the individual detects and recognises stressors, is adequately motivated to respond, and duly initiates a orthodox physiological stress response that is then *stifled or dampened by (or titrated into) the activity of some other physiological response system*. For example, a cardiovascular stress response may be immediately interrupted and attenuated by a competing demand that serves to reduce blood pressure and heart rate. In relation to psychological stress, it is possible that cardiovascular and cortisol responses to stress are sometimes counterbalanced by competing physiological demands arising from emotional (e.g., fear, threat) or bodily (fatigue, hunger) determinants. For example, chronic sleep loss is associated with disruption to blood pressure (e.g., (Kotani et al., 2008)), and so will interfere with measures of cardiovascular stress responses. This in turn creates a likely complication in studies of cardiovascular function in populations whose characteristics are themselves associated with sleep disruption, such as depression (Benca and Peterson, 2008) and obesity (Vgontzas et

al., 2009), both of which have been implicated in cardiovascular blunting. Even within the cardiovascular response system alone, such competing demands play out in the central dynamic homeostatic relationship that exists between cardiac and vascular variables (James et al.). Changes in cardiac output (CO) can often be compensated for by corresponding inverse changes in total peripheral resistance (TPR), without elevating systolic or diastolic blood pressure. Accordingly, even when it appears as though a stress stimulus is eliciting a 'blunted' blood pressure response, the cardiovascular system overall may well be experiencing significant disruption in terms of shifts in CO and TPR. Transitioning from a myocardial (i.e., CO-driven) to a vascular (i.e., TPR-driven) response profile, while maintaining homeostasis in terms of blood pressure stability, is nonetheless indicative of disease risk (Palatini and Julius, 2009). A number of studies have suggested that persons who exhibit low (or blunted) systolic blood pressure reactivity tend to exhibit maladaptive haemodynamic profiles, such as shifting towards vascular-driven responses when experiencing archetypically myocardial stressors (e.g., (Hughes et al., 2011). Such possibilities highlight the importance of multivariate and multi-system analyses of physiological stress responses, both in general and with reference to blunting in particular.

Given these different potential reasons for blunted reactivity, and the uncertainty as to which might be the most likely explanation or set of explanations, the present special issue attempts to bring about an awareness of this issue by focusing on blunted responses to acute stress and their correlates in order to facilitate progress in developing an integrative explanation for these findings across studies from a variety of sources and populations.

### **3.1 Where does blunted reactivity come from?**

### 3.1.1 Prior events

The question of how people come to exhibit blunted reactivity can be considered with regard to both proximal and distal explanations. In the case of individual lifespan development, it may be that blunted cardiovascular responsivity emerges as the result of *prior psychological or physiological events*. It was originally thought that high biological reactivity to stressors might develop from highly stressful childhood social environments (Boyce and Ellis, 2005). For example, children raised in homes with low levels of organization and consistency show an elevated cortisol response to social stress (Ellenbogen and Hodgins, 2009). Further, in a study of children exposed to highly stressful environments in early childhood, sympathetic and adrenocortical reactivity was higher in comparison to children from moderately stressful environments (Ellis et al., 2005) although children in very supportive low stress environments also displayed high autonomic reactivity also (Ellis et al., 2005). Relatedly, babies whose mothers smoked also displayed heightened blood pressure and heart rate responses to tilt stress (Cohen et al., 2008). The animal literature on early life stress (maternal separation) on reactivity also supports these findings (Sanders and Anticevic, 2007). However, more recently, it has been shown that adults who had experienced significant adverse life events in childhood display smaller heart rate and cortisol responses to mental arithmetic and public speaking stress (Lovallo et al., 2012). Similarly, children who had experienced the stress of maltreatment or bullying showed lower cortisol responses to public speaking stress (Ouellet-Morin et al., 2011). Additionally, young adults with a history of negative family relationships who display hostile verbal behaviours during a role play task are characterised by attenuated HR responses to the task (Luecken and Roubinov, 2012). Finally, in older adults, those who had experienced more past stressful life events in childhood showed lower cortisol responses to the Trier Social Stress

Test (Armbruster et al., 2011). This is also in line with studies which have shown that prior stressful life events and increased perceptions of stressfulness of those life events is related to attenuated cardiovascular reactivity to acute psychological stress (Carroll et al., 2005; Phillips et al., 2005b). It is possible that the differences between studies in terms of early life stress predicting high or low reactivity depends on the age of the individuals undergoing reactivity testing, as many of the studies showing blunting are in adults or elders, which may suggest some type of adaptation of an initially large response in childhood to a blunted response in later life. This brings us on to our next possibility for where blunting comes from.

### 3.1.2 Adaptation

Consistent with some of the longest standing theories in biological psychology (e.g., the flight-or-fight response theory (Cannon, 1932), the cardiovascular stress response can be presumed to be a mechanism that has been naturally selected on the basis of adaptive pressures. As with other developed psychological mechanisms (such as pain detection, anxiety, or depression), one implication of this is that function of mid-range intensity is likely to be the most adaptive, with function at the extremes likely to be less so. As such, within a standard evolutionary framework, it is unsurprising that blunted cardiovascular stress responding (as well as exaggerated responding) is found to be associated with adverse outcomes for the individual organism. Of course, the observed range of cardiovascular reactivity to stress will be influenced by the balancing of adaptive and maladaptive features. Although blunted cardiovascular responses might well have adverse health consequences, they may also confer some ephemeral benefits that result in their being retained in the gene pool. Some initial studies have suggested that limited emotional response states, such as alexithymia, may in fact assist individuals in short-term coping, stress avoidance, and concentration, as well as having some beneficial socially

communicative effects (Nesse and Ellsworth, 2009). In this way, blunted cardiovascular and cortisol reactivity may comprise highly nuanced and developed elements of the physiological response to stress.

#### 4.1 Towards an understanding of blunting: Looking at the other side of the coin

Many psychological, social, and behavioural factors, such as depression, social support, early life adversity, personality, and addictions, have been examined in relation to stress reactivity, and as indicated above, many are emerging as correlates of blunted reactivity. Indeed, it may be that physiological blunted responses are manifest in particular behaviours or personality traits. This Special Issue of the *International Journal of Psychophysiology* provides an opportunity to examine in further depth the range of behavioural and personality manifestations associated with blunted responding, and their underlying commonalities. Some of these personality and behavioural characteristics are also evident among some of the health-related correlates of blunted reactivity, such as bulimia (Ginty et al., 2012a), and exercise dependence (Heaney et al., 2011a).

Knowing what is already established about the negative health outcomes of exaggerated reactivity to stress, it would appear that depending on the outcomes in question, departures from the norm of physiological responding in either direction may pose problems. This suggests 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 (Carroll et al., 2009). This can be conceptualised as an inverted-U model where high and low reactivity are bad for health depending on the health outcome in question (Carroll et al., 2009) as displayed in Figure 1.

Given their reliance on biological, psychological, and social factors, reactivity paradigms are inherently complex and many issues remain unclear. In order to fully understand the associations between reactivity and health, many important pathways need to be considered in more detail, including the associations between personality effects on motivation and stress responses, cognition and reactivity, and neural correlates of both lowered reactivity and reduced motivation. Understanding these multifaceted links in more detail will enable us to develop greater insight into the routes to risky health behaviours and resultant poor health, and indeed provide the potential for early detection and intervention. For example, blunted stress reactions predict relapse in smokers who have quit (al'Absi et al., 2005) and are also evident in the adolescent offspring of alcoholic parents (Sorocco et al., 2006), suggesting that blunted stress reactivity may have substantial prognostic value.

## 5.1 This special issue

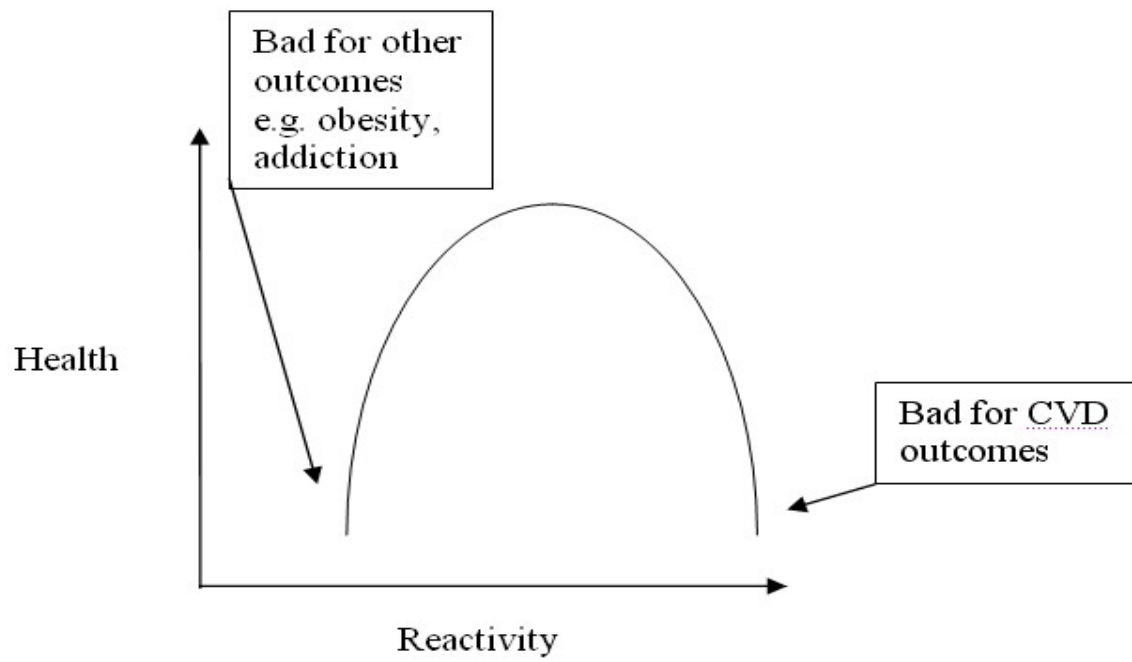
In this special issue, we explore the latest cutting edge research on the psychosocial and behavioural correlates of blunted reactivity and the potential biological and neural pathways by which these factors might have implications for health and disease. In so doing, we aim to highlight what is currently known regarding this new conceptualization of the reactivity hypothesis and the different theories of blunted reactivity, as outlined above, in order to facilitate understanding of what might be the most likely explanation for this phenomenon and where it emerges from. For example, the extent to which of a variety of negative and positive personality traits and mental health disorders or their symptoms are associated with blunted reactivity will be examined by Bibbey et al. (Bibbey et al., 2013 in press) Brindle et al. (Brindle et al., 2013, under



revision), O'Leary et al., (O'Leary et al., 2013 in press) Kupper et al. (Kupper, 2013 in press) Salomon et al. (Salomon et al., 2013 in press) and Schwerdtfeger and Gerteis (Schwerdtfeger and Gerteis). The role that perceptions of stress, behavioural approach/effort, and mood state play in the magnitude of stress reactivity will be examined by Brindle et al. (Brindle et al., 2013, under revision), Schwerdtfeger and Gerteis (Schwerdtfeger and Gerteis), and Salomon et al. (Salomon et al., 2013 in press) respectively. We will also examine the role of early life stress exposure and trauma on the development of blunted responses in papers by Lovallo et al., (Lovallo, 2013 in press) and D'Andrea (D'Andrea, under review), respectively. Further, psychosocial, cognitive, and health correlates of blunted responses and the mechanisms underlying these associations will be considered by Carroll et al. (Carroll et al., 2013 in press), O'Leary et al. (O'Leary et al., 2013 in press), de Rooij (de Rooij, 2013 in press), and Lovallo et al. (Lovallo, 2013 in press), including whether or not blunting can be experimentally induced (O'Leary et al., 2013 in press). Finally, we will address where this field is headed in terms of developing our understanding of the link between reactivity and health through a paper by Ginty (Ginty, 2013 under review) integrating blunted reactivity findings with theory regarding blunted responses to reward, and finally through the integrative commentary by Allen (Allen, 2013, in review). As such, this special issue seeks to expand upon current and previous reactivity literature, so that the contribution of the reactivity hypothesis to explaining the health consequences of key psychosocial and behavioural factors can reach its full potential.

Figure 1: A proposed model linking low and high reactivity to different health outcomes.

Adapted from (Carroll et al., 2009) with permission.



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