

Cardiovascular Stress Reactivity and Health: Recent Questions and Future Directions

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Abstract

Objective: High cardiovascular reactions to psychological stress are associated with the development of hypertension, systemic atherosclerosis, and cardiovascular disease.

However, it has become apparent that low biological stress reactivity also may have serious consequences for health, although less is known about the mechanisms of this. The objective of this narrative review and opinion paper is to summarise and consider where we are now in terms of the usefulness of the reactivity hypothesis and reactivity research, given that both ends of the reactivity spectrum appear to be associated with poor health, and to address some of the key criticisms and future challenges for the research area. **Methods:** This review is authored by the members of a panel discussion held at the American Psychosomatic Society meeting 2019 which included questions such as: How do we measure high and low reactivity? Can high reactivity ever indicate better health? Does low or blunted reactivity simply reflect less effort on task challenges? Where does low reactivity originate from, and what is a low reactor? **Results:** Cardiovascular (and cortisol) stress reactivity are used as a model to: demonstrate an increased understanding of the different individual pathways from stress responses to health/disease and show the challenges of how to understand and best use the reconstruction of a long-standing reactivity hypothesis given recent data. **Conclusions:** This discussion elucidates the gaps in knowledge and key research issues that still remain to be addressed in this field, and that systematic reviews and meta-analyses continue to be required.

Keywords: cardiovascular reactivity; cortisol; cardiovascular disease; stress;

List of abbreviations

BMI	Body Mass Index
BP	Blood Pressure
bpm	beats per minute
CO	Cardiac Output
COMT	Catechol-O-methyltransferase gene
CRH	Corticotrophin-Releasing Hormone
ELA	Early Life Adversity
HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
MHPG	3-methoxy-phenylglycol
mmHg	millimetres of mercury
SAM	Sympatho-Adrenal-Medullary
TPR	Total Peripheral Resistance

Stress reactivity is the body's physiological response to acute stress and is of interest due to its potential role in the pathophysiology of disease (1). In this non-systematic review and opinion paper we will first consider what stress reactivity is and how we might best measure it. Second, we will focus on the early research into exaggerated or high reactivity and adverse health outcomes. Third, we will then pose the question of how impaired recovery fits into the pattern of responses associated with ill health. Fourth, we will summarise the more recent concept of blunted or low reactivity and how this also relates to adverse health outcomes rather than simply reduced effort. Finally, we will address the issue of where low reactivity might originate from. before discussion of the future directions in this field arising from these considerations.

Before delving into these considerations, it is important to note the conceptual challenges related to the term 'stress' which can often be confused across the cause (stimulus) and effect (stress response to a stimulus). Throughout this paper, when we refer to 'stress', 'stressor', or 'stress task' we mean the source or stimulus, which in the case of cardiovascular reactivity is generally a laboratory task or naturalistically an acutely stressful event or hassle, such as losing one's keys. When such 'stress' or 'stressors' are experienced by an individual this is perceived as a lack of resources to cope (2). Stress responses are affective, behavioural and physiological, however, in the context of stress reactivity, the focus is generally physiological. The physiological correlates of the stress response include increases in heart rate, cardiac output, and blood pressure as a result of activation of the sympatho-adrenal-medullary (SAM) axis, which often go hand in hand with increases in peripherally-measured cortisol, the stress hormone output of the hypothalamic-adrenal-pituitary (HPA) axis (3). In this paper the main stress responses considered will be the biophysiological responses to acute stress, specifically heart rate, blood pressure and salivary cortisol, because these

measures are the most commonly used indicators of the stress response with regard to biophysiological stress reactivity.

The magnitude of reactivity to acute psychological stress appears to be a relatively stable and heritable trait or characteristic of an individual with high test-retest reliability (see e.g., (4–6). However, this does not mean that the magnitude of such a response generalises across different types of psychological stressors or to physical stressors such as exercise (see (5,7) for further discussion). In this paper we are considering psychological stressors, mainly active stressors, such as mental arithmetic or speech tasks, but also passive stressors where the participant has limited mental engagement such as immersing one’s hand in iced water (cold pressor task). Consequently, we are considering stress reactivity to be a relatively stable individual characteristic as far as it is elicited specifically to psychologically challenging stressors .

Methods

This review is authored by the members of a panel discussion held at the American Psychosomatic Society meeting 2019 based on questions generated by and split between the team to address during the session. These questions are derived from our own work and reading of the historical and contemporary literature as well as from common questions raised by undergraduate and graduate students, the media, and clinicians on encountering cardiovascular reactivity research. As such, this paper is not intended to be a systematic or exhaustive review of the field but a narrative review and opinion paper. We aim to briefly and non-exhaustively summarise a selection of the reactivity research literature which we believe best emphasise the key concepts and issues within this field, and address some of the contemporary questions that this research raises. Finally, we aim to provide a brief set of directions for future research arising from our considerations (see Table 1).

How do we measure and quantify reactivity?

Early research in the field of cardiovascular stress reactivity demonstrated that cardiovascular responses during acute psychological stress were metabolically excessive, meaning that the cardiovascular system was in excess of metabolic demand (1,8–12). Measurements of oxygen demand and cardiac output during psychological stressors were shown to produce greater blood flow than necessary for oxygen consumption when compared to metabolic demand during a graded exercise test. Cross-sectional evidence demonstrates that persons with metabolically excessive heart rate reactivity are prone to elevated blood pressure (10,13) including a relatively recent study where additional systolic blood pressure was related to greater intima-media thickness in adolescents (14). However, additional systolic blood pressure during stress did not predict above and beyond systolic blood pressure reactivity (i.e., reactivity not taking into account metabolic demand) (14). The concept of additional heart rate, or additional blood pressure, has not been widely supported in the literature and there have been no longitudinal studies of additional heart rate/blood pressure and cardiovascular outcomes. Most studies arising from the Reactivity Hypothesis (1) posit that exaggerated or high cardiovascular reactions to stress accumulating over time result in negative cardiovascular outcomes, specifically hypertension. Such exaggerated cardiovascular reactions have been proposed to exert shear tear or tensile stress on blood vessel walls over time and may accelerate atherosclerosis or influence future cardiovascular disease endpoints (1).

Ways of calculating reactivity

The majority of research examining cardiovascular reactivity to acute psychological stressors does not calculate additional heart rate. Typically, researchers measure cardiovascular activity at multiple points during a resting baseline and also during an acute psychological stressor task; cardiovascular reactivity is then calculated as change from the baseline values.

Research demonstrates that there are large individual differences in reactivity, e.g., (15–17) but shows that reactivity is relatively stable within individuals (4,6,18) over repeated exposures to the same stressor task during a span of weeks (4,19), months (20), and years (21–23). For example, in a recent study, participants completed a mental arithmetic task in the laboratory and cardiovascular activity was measured via electrocardiogram.

Approximately one year later, participants completed an interference task as part of a functional magnetic resonance imaging paradigm and cardiovascular activity was measured via pulse oximeter; individual differences in the magnitude of response were similar across the very different testing sessions (24). This approach to measuring individual response characteristics appears to be stable over time, across tasks, and using different measurement devices (25,26). Alternatively various researchers have opted to use residualised change scores rather than change scores as a way of calculating reactivity. This is calculated as the difference between the observed and predicted dependent variable score, with the dependent variable being the task/stress value regressed on (predicted from) the baseline value, and therefore residual scores are not linearly related to baseline. Others get over potential confounding of baseline being a major predictor of reactivity by controlling additionally for baseline in models predicting reactivity. On the whole, these different methods are considered to be reliable measures of reactivity but change scores may be more appropriate when assessing generalizability of reactivity across different types of task in future research (27).

Patterns of cardiovascular reactivity across cardiovascular variables

Early work in the field identified individual differences in hemodynamic patterning of responses. Specifically, some individuals were classified as having a more “vascular” response and others as a more “cardiac” response (19,28). However, the majority of research examining difference scores in reactivity and health outcomes tends to conduct separate

analyses of blood pressure reactivity and heart rate reactivity, thereby ignoring that these are interrelated physiologically. An interesting new approach is to examine cardiovascular reactivity patterns across multiple cardiovascular variables. This data driven approach uses statistical analyses to determine profiles of different types of stress responses. The rationale behind this approach is that focusing on a single cardiovascular reactivity variable may be limited in understanding disease risk. Research has demonstrated that variations in risk are associated with different patterns of end-organ responses (29). For example, research suggests a more vascular response and/or slower vascular recovery from stress is associated with adverse cardiovascular health outcomes (30–32). Indeed, blood pressure and heart rate are not independent of each other; increases in cardiac output increase blood pressure, likewise changes in blood pressure influence heart rate via baroreceptors (25). Brindle et al. (33) took this approach using data-driven multivariate cluster analyses. Results indicated four different clusters and that the cluster characterized by high blood pressure responses and modest heart rate responses was related to increased risk of development of hypertension over a 5-year period. A recent paper used a machine learning approach to demonstrate that different individuals exhibit different multivariate response patterns (using cardiac output, pre-ejection period, interbeat interval, and total peripheral resistance) to the same motivated performance task (34). Interestingly, although the two studies used different data driven approaches, both identified a group that consisted of minimal or blunted physiological responses to stress for all cardiovascular parameters (25, 26). Examining individual differences in patterns of cardiovascular reactivity across cardiovascular variables is a relatively untapped area that may better describe the pathways between cardiovascular stress reactivity and disease outcomes. It is also worth noting that different patterns of response may relate differently to specific health outcomes, so there is much yet to be explored. Pre-

existing datasets offer a unique opportunity to test the longitudinal associations between data driven cardiovascular reactivity patterns and future health outcomes.

What defines a high reactor or a low reactor?

The majority of analyses predicting health outcomes from reactivity rightly so treat cardiovascular reactivity as a continuous variable, which is generally normally distributed and linearly related to health outcomes, and only compare reactivity within the sample they are currently testing. Therefore, an exaggerated or high reactor is simply someone who has a higher cardiovascular reactivity compared to others in that sample, while a blunted or low reactor is someone who has lower cardiovascular reactivity compared to others in that sample. Given the normal distribution of reactivity and its positive and negative linear associations with different health outcomes in most reactivity research, it is likely unhelpful to attempt to define thresholds or cut-offs for high or low reactors, even with the intention of identifying sub-groups of the population at greater risk of disease, as there is currently no empirical foundation for such cut-offs. Importantly, such classification is not currently possible as there is no standardized protocol or even stress task for assessing reactivity; psychological stress tasks administered in the laboratory vary greatly and perturb the cardiovascular system differently. A meta-analysis found that the speech task is significantly more provocative than mental arithmetic and that different tasks perturb the sympathetic and parasympathetic systems differently, for example, there is greater parasympathetic withdrawal during Stroop compared to speech (15). Further, the number of observers during a socially evaluative stress task can influence the magnitude of responses (35). Commonly employed stress protocols are variations on the Trier Social Stress test which involves a socially-evaluated speech (e.g., 28) or mental arithmetic with or without social evaluation, time pressure and competition such as the Paced Auditory Serial Addition Task (PASAT)

(e.g., 26). These types of tasks tap in to the crucial elements of stress such as uncontrollability, social evaluation, and difficulty (without being impossible). Given the variability in individual stress perceptions, it is crucial to employ a stress task which is consistently rated as stressful (albeit with individual variability in the degree of perceived stressfulness) by all participants and to measure stress task perceptions (and ideally an objective measure of task engagement) in order to remove the possibility that variability in physiological response is only the result of how stressful or not the employed laboratory challenge is. It is worth noting at this point that psychological appraisals of stress tasks do not always map directly onto physiological responsiveness, and differences in stress reactivity can remain significant even taking into account differences in psychological stress perception. We discuss this issue later in the paper regarding whether low reactivity is just lower effort.

Another reason making it difficult to define high or low stress reactors is that cardiovascular variables measured in the laboratory, as mentioned above, differ from protocol to protocol; some may include more comprehensive measures such as cardiac output and total peripheral resistance, while others may include only heart rate and blood pressure. Further, a meta-analysis suggests the magnitude of different measures of reactivity vary with age (15) among other socio-demographic factors discussed above; this means that what is high and low reactivity alters across the lifespan and between different groups. Beyond these practicalities, we should be careful in our use of the terminology of ‘exaggerators’ and ‘blunters’ when referring to high and low reactors, as this may wrongly give the impression that these refer to valid labels with thresholds and diagnostic implications. However, several decades of research suggest that examining individual differences in cardiovascular reactivity within a given sample as a continuous variable is powerful enough to predict disease risk and other health outcomes.

High stress reactivity and health

Historically, 'exaggerated' or high cardiovascular reactions to acute mental stress have been implicated in the development and expression of cardiovascular disease (see e.g., (29,31,38–41). Together, studies indicate that large magnitude haemodynamic reactions to psychological stress, that were viewed as inappropriate for social stressors, confer a modest but fairly consistent risk for developing high blood pressure (41–48) This type of main effects risk model considers that larger than usual responses are damaging and a cause of cardiovascular disease (49). Much work including epidemiological and laboratory studies, has appeared in support of the hypothesis that exaggerated heart rate and blood pressure responses to acute stress represent a risk factor, and a possible causal influence on cardiovascular illness, including hypertension (e.g., (41,42,45,50–52)), atherosclerosis (53), increased left ventricular mass (54), cardiovascular disease mortality (55), and risk of cardiac events in people with advanced coronary artery disease (56,57). Meta-analyses and/or reviews confirm these findings (16,31,40). Further, in addition to cardiovascular reactivity, high cortisol responses to acute stress also predict hypertension (58), coronary artery calcification progression (59) and cardiac damage markers (60). The mechanism involving reactivity in the pathogenesis of cardiovascular disease is that small, persistent elevations in blood pressure in response to frequent stress exposure are considered to contribute to an extra load or strain on the heart and blood vessels. The exact mechanisms of how this might occur are not fully understood, but include that reactivity elicits an emotional reaction which is translated into autonomic and endocrine outputs, which if exaggerated could lead to exaggerated responses in the periphery (39). Such exaggerated responses may interact with individual differences, e.g. genetics, and the extent of existing disease, resulting in further increased vascular resistance, increased thickening and/or hardening of vessel walls, greater endothelial shear stress, or higher inflammatory reactions, which contribute to

the progression of diseases such as hypertension and atherosclerosis (39). Such mechanisms may also interact with a range of other regulatory processes at multiple levels of the central nervous system through to the periphery, all of which are also correlates of reactivity. These include but are not limited to: greater or altered beta-adrenergic receptor density or sensitivity; increased left ventricular mass/wall thickness; higher peripheral vascular resistance; hypothalamic-adrenal-pituitary (HPA) axis hyperactivity (indexed through increased numbers and activity of corticotrophin-releasing hormone (CRH) neurons, and greater cortisol production); and higher or altered neurophysiological activity e.g., greater amygdala and pre-frontal cortex activity in response to sensory input (61). As such, there are a variety of physiological pathways by which repeated high reactivity of the cardiovascular system in combination with frequent exposure to psychological stress can play an influential role in the development and certainly the worsening of cardiovascular disease; this topic is dealt with in detail elsewhere (see e.g., 56,57). We acknowledge that we cannot claim causality, given these potential mechanisms are correlates of reactivity and/or mediators of associations between high reactivity and cardiovascular disease in observational research. Exact causal mechanisms of how stress reactivity in terms of cardiovascular and neuroendocrine responses influence arterial wall biology or the structure of the heart and vasculature remain to be elucidated.

Patterns of reactivity across sub-groups of the population

Individual differences in the magnitude of cardiovascular reactivity have been identified between specific socio-demographic sub-groups of the population which may place them at greater risk of cardiovascular disease, e.g., hypertension. These may arise from many different physiological and/or psychological differences, for example, differences in: resting cardiovascular activity, the capacity/flexibility of the system to respond due to structural differences/changes, hormones and/or receptor sensitivity, and psychological appraisal and

task-specific perceptions of stress. For example, in the case of sex, men generally show greater SBP responses to stress than women (63,64) potentially due to difference in beta-adrenergic receptor responsiveness (65). In response to five behavioural stressors, among the males, Black men showed higher total peripheral resistance but white men had higher heart rate and cardiac output increases; in women, these racial group differences were similar but not evident for all tasks (63), underlining the impact of task perception in influencing group differences. Other ethnic group differences in reactivity have also been documented, for example, Asian Americans showed lower SBP reactivity to stress tasks than Caucasians (66) and American Indian adults have lower HR and cortisol reactivity to stress than Caucasians (67). Such racial group differences have been attributed to genetics determining differences in physiological function, but also important socio-cultural group differences (e.g., in task perceptions or psychological resources) (68). The importance of socio-cultural effects is underlined by evidence of socio-economic differences generally where those from manual occupational backgrounds showed higher BP reactivity than individuals from non-manual occupations (69). Further, age effects on reactivity have been demonstrated in the literature, for example, blood pressure reactivity appears to increase with age while heart rate reactivity declines (15,64) likely due to age-related decline in sympathetic nervous system responsiveness (15). Finally, different personality sub-types have been considered regularly with regard to reactivity, which cannot be considered in depth here but deserve mention as a sizeable area of reactivity research with regard to how personality might influence health and disease. Briefly, early work focused on Type A personality, e.g., (70) showing higher reactivity among those scoring highly on these behaviours. Similarly, Type D personality has received much attention in this context, particularly with regard to how the social evaluative threat element of Type D personality might have particular associations with reactivity to 'social' type stress tasks e.g., public speaking. Such research has generally shown that Type

D individuals show greater reactivity to stress than non-Type D individuals, and particularly to social stressors, e.g., (71). More recently, focus has tended towards elements of the Big Five personality characterization, showing negative associations between the more negative characteristics such as high neuroticism or low openness and reactivity, e.g., (72), and moderate (rather than exaggerated) reactivity among those scoring highly on positive traits such as optimism, e.g., (73). A discussion of these topics in depth or the exact mechanisms underlying these group differences are beyond the aims and scope of the current paper and warrant a review to themselves. However, these issues raise the importance of measuring and accounting for these variables in studies seeking to identify individual differences in reactivity related to e.g. psychological or behavioural characteristics which may also differ across some of these sub-groups.

Comorbidities as confounders

A related concept to that of covariates and sub-groups which should be considered when measuring reactivity is that health behaviours, and physiological and psychological comorbidities should be considered when examining associations between specific physiological/psychological characteristics and reactivity. As stated above, reactivity may predict disease when other factors are held equal, however, reactivity itself may be impacted by the presence of disease or conditions which correlate and are commonly comorbid with the health outcome of interest. For example, as described earlier, individuals with obesity may have autonomic dysfunction precluding an ability to physiologically respond to stress, thus BMI or similar measures should be considered in samples which may include obese individuals even where obesity is not the outcome or predictor of interest. Similarly, some eating disorders and exercise dependency often coexist and correlate with cardiovascular fitness, each influencing reactivity, albeit potentially by different mechanisms, thus these factors should not be examined in isolation. Although much of the research in reactivity and

that cited here is based on otherwise healthy individuals, in more representative samples this point is of particular importance. In research considering stress reactivity as a pathway to, or marker of, disease it will continue to be vital to consider comorbidities and their associated medications as potential confounders, and measure and adjust for these in the associations examined.

How does impaired recovery after stress fit into the pattern of associations with adverse health outcomes?

To understand how impaired recovery may fit alongside high cardiovascular reactivity in predicting disease, it may be useful to consider the concept of allostatic load. Allostatic load is the cumulative strain on physical, endocrine, metabolic, immune, and/or cardio-respiratory functions described originally by McEwen and others (see e.g., 65), which can result in disturbed stress regulation, and eventually clinical disease (75). Different patterns of allostatic load have been proposed including repeated physiological stress responses, lack of adaptation to repeated stress, prolonged responses and inadequate responses (76). The prolonged stress response has been described as the inability to shut off allostatic responses which include the catecholamine and glucocorticoid stress responses essential for adaptation, homeostasis and survival, once these responses are no longer required, i.e. when the stressor is removed or stressful situation is over (76,77). For example, an individual who has hypertensive parents but no hypertension evident yet themselves might show prolonged elevation of blood pressure following stress relative to the progeny of non-hypertensive parents. Again causal mechanisms cannot be identified in such observational research, but it illustrates how individual differences in magnitude and/or length of stress response are associated with the development of or worsening of disease. This is most readily recognised in the context of acute stress responses through patterns of impaired stress recovery. Much of the research on reduced recovery from stress has originated from the work of Steptoe and

colleagues. For example, impaired blood pressure and total peripheral resistance recovery after stress related to higher blood pressure at follow up (78) impaired clotting processes (79) atherosclerosis (80); and lower socio-economic status (81). Further, sometimes impaired recovery across cardiovascular measures is observed to relate to health outcomes also associated with low stress responses, for example, adiposity (82,83).

One question that has been raised is whether delayed recovery is a separate predictor of ill health or is strongly related to the magnitude of stress reactivity. For example, one study showed that individuals with a low cortisol response to acute stress were the same individuals who showed impaired cortisol recovery to stress (84), and diabetics who showed low cortisol and SBP reactivity to stress also showed impaired post-stress recovery in blood pressure and heart rate (85). However, from the same group, it was demonstrated that individuals with depressive symptoms showed higher diastolic blood pressure reactivity and 3-methoxy-phenylglycol (MHPG, the major metabolite of norepinephrine) reactivity to a negative mood inducing task and also higher levels of MHPG in recovery from the task (86).

Similarly, coronary artery disease patients high high trait hostility showed heightened blood pressure reactivity to mental stress and delayed SBP recovery (57). Other have also shown higher heart rate reactivity paired with slower blood pressure recovery among individuals with depressed mood (87). This suggests that slow recovery can be observed alongside no reactivity, or patterns of high or low reactivity among some individuals, and may be therefore an independent expression of dysregulation of the stress response, however, this suggestion warrants further investigation.

Is low stress reactivity also detrimental to health?

Although the focus on large stress reactions made intuitive sense (1), recent work has established that both very large and very small stress responses are likely to signal systems dysregulation (88,89), while response magnitudes in the midrange are likely to represent

normative responses, indicating healthy systems functioning (89,90). In either case, a poor calibration of responses to challenge indicate vulnerability to disease (89,90). As we have reviewed this elsewhere, here we will briefly focus on three examples. Much of the epidemiological research on individuals exhibiting low stress reactivity was based on the West of Scotland Twenty-07 study and the Dutch Famine Birth Cohort study. Detailed elsewhere, and in contrast with the prior literature, an association between lower cardiovascular responses to stress and the presence of depression or depressive symptoms corrected for a range of confounding variables was demonstrated in both studies (64,91,92) and by others in a range of samples (93–100).

Obesity is also commonly related to cardiovascular and metabolic disease (101,102) and consequently, it was thought that obesity and higher central adiposity would be correlated with high stress reactivity, which was demonstrated in some small scale studies with mixed findings depending on the cardiovascular indices measured (103–107). Other larger studies have on the whole found no association between reactivity and adiposity (82,83,108,109). In contrast, in the West of Scotland and Dutch Famine Birth Cohort large-scale studies we found that lower heart rate reactivity was associated with higher adiposity and increased risk of remaining or becoming obese years later (110,111). What we can conclude from this mixed literature is that the relationship between adiposity and reactivity is not straightforward, and that the direction of association found may reflect the cardiovascular measure used as well as the measure of adiposity. For example, a positive association is more likely to be found for diastolic blood pressure or vascular resistance measures and waist:hip ratio (82,104,105) whereas heart rate or cardiac measures either show no association with adiposity in some studies (82,105) or are negatively related (110,111). This suggests two things: 1) the association between reactivity and health is an inverted U-shaped curve rather than linear (112), albeit few studies have demonstrated a U-shaped association

between reactivity and adverse health outcomes in the same cohort, and, 2) health outcomes such as obesity may relate differently to cardiac and vascular stress reactivity. This latter conclusion is in line with recent findings which suggested that a combination of high blood pressure reactivity and moderate to low heart rate reactivity was most detrimental to health, in this instance, hypertension risk (33). This reiterates that multivariate approaches to stress psychophysiology may be a sensible way to advance this field.

Are lower responses just lower psychological effort/engagement?

The lower responses observed in the studies described above do not appear to reflect consciously reduced effort on stress tasks for several reasons. First, several studies relating low reactivity to negative health outcomes show no association between reactivity and task performance or self-reported ratings of stressfulness, effort or engagement (e.g. 83,100). Such subjective markers of effort may not be the most sensitive, given what is deemed stressful differs from person to person, this observed lack of association in some studies shows that individuals' physiological responses do not automatically link with their psychological appraisals of a task. Although psychological and physiological responses to stress tasks may not always correlate, it is important to assess (at least subjectively) individuals' appraisals of the stress task alongside some measure of task effort as: a) a manipulation check that the task is indeed consistently stressful across different individuals, and b) to examine the extent to which physiological responses are associated with psychological appraisals to a given stressor among different types of people. Second, where objective measures of performance or effort have been taken, e.g., number of unattempted questions in a task, no differences have been shown between high and low reactors to stress (7). Third, some low responding individuals, e.g. those with obesity, show autonomic dysfunction meaning they are unable to respond to pharmacological challenge, which is a challenge unrelated to effort (116). However, such dysfunction does not uniformly

characterize low responders and in some cases appears to be task specific; healthy individuals with low responses have shown cardiovascular responses to cold pressor and exercise stress but not active psychological stress tasks (7). Finally, some individuals may have altered capacity to physiologically respond to any challenges due to the medication associated with existing disease, for example, anti-hypertensives. Given this, much research may be conducted on healthy individuals in order to a) study reactivity in the process of developing disease and b) to avoid this confounder. However, this issue strongly underlines the need to adjust for physiological comorbidities as well as medication usage in samples with existing conditions such as hypertension or depression. It is worth noting that associations with low reactivity shown in the West-of-Scotland Twenty-07 and Dutch Famine Birth cohort studies outlined above withstood adjustment for such diagnoses and medications.

Another set of health outcomes and behaviours associated with lower rather than high stress responses, on the whole, has been that of impulsive or addictive behaviours, including: smoking (117–121), alcohol addiction (122,123), and other substance dependencies (124,125). Low reactivity in these instances is not due to the influence of toxic substances, such as alcohol or drugs, on the stress axis, as such low responses have been observed among non-substance addictions or dependencies such as exercise dependency (114). Further, finding low reactivity among the adolescent children of alcoholics implies that blunted stress reactivity may predate dependencies and, indeed, may be a marker of susceptibility (122). Where we were able to test this within the same large cohort studies, the associations between low stress reactivity and outcomes such as depression, obesity, and addictions appeared to be largely independent of one another. In fact, low reactivity may signal a constellation of behavioural risk factors and poor affect regulation that may shade off into one another.

The health outcomes and behaviours discussed above may at first appear to be quite diverse, however, all reflect motivational tendencies or poor behavioural control to some extent, a situation that has been termed ‘motivational dysregulation’ (112), suggesting impaired functioning of areas of the brain essential for motivation and behavioural regulation. Cognitive tasks require both motivation and aspects of behavioural control and, interestingly, low reactivity has also been associated with lower levels of (126–129) and decline in cognitive function (130,131). Thus, low cardiovascular and cortisol stress reactions appear to be peripheral markers of suboptimal functioning in key fronto-limbic brain systems when individuals are exposed to acute psychological stress (62,132). These are the same brain areas that are concerned with motivated behaviour and implicated in autonomic regulation (17,62,133).

Correlates and consequences of low reactivity

It is becoming apparent that the mechanisms by which low reactivity appears to be linked with a range of negative health outcomes/disease remain unclear, may vary between individuals, and appear substantially different from those by which high reactivity relates to disease, specifically cardiovascular disease, mentioned above. First, low reactivity does not appear to directly relate to cardiovascular disease or its antecedents, such as increasing blood pressure, but rather relates to a range of behavioural risk factors which may themselves relate to cardiovascular disease risk (e.g., obesity, smoking), thus providing an indirect effects pathway. Second, given the range of different correlates of low reactivity, although these have aspects in common as outlined above with regard to motivated behaviour, they do not necessarily overlap. Thus it is possible that low reactivity is indicating the existence of other non-cardiovascular comorbidities and disease processes, which are also associated with a range of differences in neurological activity. Finally, in the case of high reactivity and cardiovascular disease, changes in haemodynamics can have specific acute and chronic

effects on cardiovascular disease, e.g. changes in blood vessel wall structure (53), however, it is difficult to see a parallel for low reactivity. In other words, how might having lower heart rate of blood pressure responses to stress play an active role in the aetiology of the health outcomes it is associated with. For example, in the case of depression, there is no obvious mechanism by which low cardiovascular responses might alter brain hormone signalling or receptor sensitivity. Thus, as argued above, it is more likely that low reactivity is a peripheral marker of neurological alteration or dysfunction, which may of itself indicate the presence of existing disease or disorder.

It is important to note that it is not only negative psychological and behavioural characteristics that are related to blunted or lower stress responses, but also that several studies have shown positive psychological characteristics, such as self-esteem or affective wellbeing, are associated with reduced cortisol responses to stress. However, this may be reduced relative to individuals with 'exaggerated' responses, which would then place these results in the mid-range. For example, individuals with higher self-esteem when exposed to the stress of an online interpersonal rejection showed lower cortisol reactivity than individuals with low self-esteem (134). Similarly, manual workers with high work satisfaction and low presenteeism demonstrated lower SBP and HR reactivity (135). On the other hand, some chronic stressors, such as loneliness are related to greater cardiovascular and/or cortisol responses to acute stress (136,137) in certain sub-groups but lower cortisol reactivity in others (138). It is possible that the timing and severity of stressors is contributing to these differences in the direction of findings across the literature, of the relative range of reactivity in each sample, thus such elements need examination in future studies of stress and reactivity.

A growing literature of human neuroimaging studies suggest that individual differences in stressor-evoked neural activity in regions such as the anterior cingulate cortex, medial prefrontal cortex, insula, amygdala, and hippocampus are associated with individual differences in cardiovascular stress reactivity (for Reviews see: 58,131). For example, in a study comparing individuals with low reactivity to individuals with high reactivity, the low cardiovascular reactivity group displayed lower stressor-evoked activation in the anterior midcingulate cortex and insula (4). Recent work examining multivariate patterns of whole brain fMRI activity during stress has demonstrated that distinct patterns of brain activity encompassing the medial prefrontal cortex, anterior cingulate cortex, and insula are associated with individual differences in heart rate reactivity (140) and blood pressure reactivity (133). Interestingly, individuals with depression display lower levels of stressor-evoked neural activation in the anterior cingulate cortex (141). Further research of this type will provide insight into the neurological mechanisms underlying associations with reactivity.

Where do blunted or low responses originate from?

Our discussion is based on the recognition that both high and low stress reactivity represent clinically meaningful deviations from optimal or healthy regulation of the stress axis. By extension, these deviations represent different forms of systems dysfunction that may be relevant for health and disease. A productive line of inquiry is to ask how these deviations arise. Our discussion will be confined to individual differences in response psychological stressors and not to physiological stressors. As we have argued elsewhere, responses to challenges, such as the cold pressor, exercise, pharmacologic stimuli, and others mainly reflect peripheral physiology (39). Instead, our present thoughts are addressed to an understanding of altered reactivity to psychological stressors such as mental arithmetic or public speaking challenge. These sorts of tasks may be argued to exert their effects on physiological processes through top-down mechanisms (142). That is, they function as

stressors because of the person's interpretation of public speaking and mental arithmetic as social-evaluative threats with uncertain control over outcomes requiring expenditure of coping resources to meet the actual challenges of the tasks at hand. Therefore, it seems reasonable to argue that these tasks are primarily psychological stressors, as defined by Folkman and Lazarus (143,144). In addition, the outcome of this transactional evaluation is addressed to output systems that activate the periphery. These primarily recruit activity in the hypothalamus and brainstem (39). If one is interested in sources of altered reactivity to psychological stressors, it may be productive to start looking at how persons evaluate events, estimate their level of risk, and generate activational messages that descend to the body via the hypothalamus and brainstem.

In particular this leads us to the question, how do normal responses along these lines come to be suboptimal? Is this the result of inborn traits or with differences in exposure to the environment during development? Certainly the magnitude of reactivity is determined in part by genetics, as was originally shown in twin studies and now through genome analysis (e.g., 134). Regarding the impact of the environment, consider a couple of examples from recent research where persons exposed to nontraumatizing, mild to moderate, levels of social, psychological, and environmental adversity are likely to show blunted stress reactivity (36,146). The connection between early life adversity and low reactivity is strengthened by knowing that there is a dose-response relationship between the two (147). Most of the evidence comes from cortisol and heart rate responses to mental stress. Interestingly, in a simple comparison of reactivity tertiles in the Oklahoma Family Health Patterns Project, individuals exposed to ELA are significantly more likely to be low rather than medium or high reactors, and *vice versa*. Two elements in these data point to sources of the low or blunted reactivity: first, low and normative reactors report similar amounts of subjective activation and distress during the tasks, and second, they have equivalent resting levels of

physiological activity. These data suggest that the HPA and brainstem do not present inherently different levels of basal function. Also, the subjective reports indicate that low reactors have a similar appreciation of the situation as threatening and are expending similar levels of effort on solving problems and generating convincing speeches. How might early exposure result in such a response modification? We suspect that the remaining place to look for the origin of blunted reactivity is in the transactions between the prefrontal cortex and limbic system on the one hand and the hypothalamus and brainstem on the other hand. However, it should be noted that some of the literature regarding only peripheral cortisol responses to stress shows an elevated pattern of reactivity in individuals exposed to early life adversity who also demonstrate posttraumatic stress disorder and depression in adulthood, (148–150), and this pattern may be dependent on the trajectory of psychological distress in adulthood among individuals exposed to early adversity (151). How to reconcile this seeming contradiction in the literature? Potentially early adversity initially sensitises the stress response but chronic stress pervading into adulthood on top of this can result in allostatic load and a resulting reducing of the cortisol response in comparison to those with early life adversity but little or no adult distress, as observed by some (151). An alternative explanation might be that where higher responses are found, these are mainly in populations with already diagnosed psychopathology such as depression (148) whereas blunting seems to be observed among individuals whose trauma is less severe and without psychopathology (e.g., 135). Further research is needed on the interaction between childhood adversity and adult life stress. Specifically, it might be useful to examine the impact of severity of adversity, and/or the demarcation between early life trauma and early life stress or hardship, as well as the age of occurrence of trauma and age of measurement of reactivity.

We recognise that this emerging story must attend equally to the effects of the person's early environment and to the person's genotype and levels of gene expression. Compelling work

by Caspi and Moffitt (152) and Michael Meaney (153) have drawn our attention to gene by environment interactions on the one hand and on the impact of environmental stimulation on epigenetic effects on gene expression. In the Oklahoma Family Health Patterns Project, there is preliminary evidence that blunted stress reactivity, as a phenotype, reveals that persons with a family history of alcoholism are more vulnerable to ELA than are persons with no such history (154). In probing for genetic characteristics that may play a role in these processes, we found that persons with a specific polymorphism of the gene for catechol-O-methyltransferase (COMT) are differentially vulnerable to ELA, in showing blunted stress reactivity, and following ELA exposure, are more likely to begin drinking alcohol at an earlier age and to experiment with a wider range of recreational drugs (155); see also (156). This gene by environment interaction in relation to the ELA and COMT polymorphisms may plausibly modify the actions of dopamine and norepinephrine in the central nervous system. These provide useful places to look in future studies of blunted stress reactivity. The focus on central catecholamines also lends credence to the idea that persons displaying blunted stress reactivity display diminished motivation and responsivity to hedonically positive and negative events (17).

Conclusion and Future Directions

Taken together, the field has advanced considerably over the past 15 years to encompass the antecedents and potential consequences of both extremes of biological reactivity to acute stress. This review has defined what reactivity is and where it originates from (summarized in Figure 1); raised issues with how it is measured; presented examples of how stress responses at either end of the spectrum, as well as delayed recovery, can relate to ill health; and considered the utility of reactivity as a biomarker. On considering the recent literature in this area, we believe there are some important questions still to be answered in the field of

reactivity and health which are summarized in Table 1. Further, this review is selective and highlights that systematic reviews and meta-analyses continue to be required.

[Insert Table 1 about here]

First, combining data from more than one response measure may provide more stable assessments of associations with risk factors and disease outcomes; indeed different patterns across cardiovascular and cortisol measures may relate differently to specific disease outcomes. Second, studies of gene-by-environment interactions may provide us with a more rounded picture of why some individuals are at increased risk of ill health. Third, the neural mechanisms underlying individual differences in reactivity are still poorly understood, and examining patterns of neural response associated with stress and peripheral reactivity may be an important future direction (133). Fourth, where the literature is mixed, more detailed attention to the measures used e.g. different stress or adiposity measures may provide insight as to why findings from different studies are contradictory. Fifth, it should be remembered that the majority of reactivity research to date has been correlational in design with the exception of experimental blockade studies, yet to fully understand the mechanisms underlying why individuals may show different magnitudes of response, more experimental studies are needed. Sixth, although low responses to stress do not appear to reflect an inability to respond or lack of stress task engagement in most individuals, it is important to measure stress task effort and engagement when discussing individual differences in reactivity, and to bear in mind that individuals may not be aware of reduced motivation. Finally, although there are various issues in terms of using reactivity data as a biomarker, where reactivity data is available, it may give important insights as to which individuals in a cohort may need additional support in terms of perseverance and adherence to health and

behavioural interventions. In conclusion, it appears that there are still many things to be learned regarding the mechanisms and implications of both high and low stress reactions.

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Table 1: Directions for Future Research

Theme	Directions for future research
Calculating reactivity	As there are different ways of calculating reactivity thus your choice should be strongly justified and you should consider comparing whether results differ when using different calculations.
Patterns of reactivity	Multivariate approaches to stress psychophysiology may be a sensible way to advance the field. To what extent does the pattern of response across cardiac and vascular measures predict health outcomes including non-cardiovascular disease outcomes? Pre-existing datasets offer a unique opportunity to test the longitudinal associations between data driven cardiovascular reactivity patterns and future health outcomes.
Sub-groups and socio-demographics	Reactivity differs across specific sub-groups. Studies seeking to identify individual differences in psychological or behavioural characteristics and how these relate to reactivity related should measure and account for important socio-demographic factors. Also consider theoretical comorbidities as potential confounders, and measure and adjust for these in the associations examined.
Recovery	To what extent does delayed recovery relate to the magnitude of reactivity? Is it most commonly observed alongside high or low reactivity, or does it independently predict disease outcomes?
Direction of association	To what extent do the timing and severity of stressors contribute to differences in the direction of association with reactivity as well as the relative range of reactivity in each sample?
Neurological mechanisms of low reactivity	Mental health can be associated low or high cardiovascular responses across different studies. More detailed investigation of the brain activity associated with these conditions as well as with low stress responses will provide insight into the

neurological mechanisms underlying these associations. Multivariate patterns of association with reactivity should also be considered.

Reactivity and health - models	Research on low reactivity suggests the association between reactivity and health is an inverted U-shaped curve rather than linear. Can this be confirmed through seeking to demonstrate a U-shaped association between reactivity and adverse health outcomes in the same cohort?
Psychological appraisals of tasks	Although psychological and physiological responses to stress tasks may not always correlate, it is important to a) employ a stress task which is considered to be consistently stressful by participants; b) assess (at least subjectively) individuals' appraisals of the stress task alongside some measure of effort as a manipulation check that the task is indeed stressful and c) examine the extent to which physiological responses are related to psychological appraisals, d) control for task perception effects on physiological responses.
Adversity as a determinant of reactivity magnitude	Much work remains to be done to examine the impact of severity of adversity, and/or the demarcation between early life trauma and early life stress or hardship, as well as the age of occurrence of trauma and age of measurement of reactivity on the magnitude of stress response. The extent to which low reactivity is a product of exposure to early or adult adversity and their interaction currently remains to be answered.

Figure Captions

Figure 1: Pathways of biological and environmental exposure through reactivity to CV health outcomes

