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Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease

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Abstract

Psychologically stressful experiences evoke changes in cardiovascular physiology that may influence risk for cardiovascular disease (CVD). But what are the neural circuits and intermediate physiological pathways that link stressful experiences to cardiovascular changes that might in turn confer disease risk? This question is important because it has broader implications for our understanding of the neurophysiological pathways that link stressful and other psychological experiences to physical health. This review highlights selected findings from brain imaging studies of stressor-evoked cardiovascular reactivity and CVD risk. Converging evidence across these studies complements animal models and patient lesion studies to suggest that a network of cortical, limbic, and brainstem areas for central autonomic and physiological control are important for generating and regulating stressor-evoked cardiovascular reactivity via visceromotor and viscerosensory mechanisms. Emerging evidence further suggests that these brain areas may play a role in stress-related CVD risk, specifically by their involvement in mediating metabolically-dysregulated or extreme stressor-evoked cardiovascular reactions. Contextually, the research reviewed here offers an example of how brain imaging and health neuroscience methods can be integrated to address open and mechanistic questions about the neurophysiological pathways linking psychological stress and physical health.

Keywords

cardiovascular disease; central autonomic network; functional connectivity; stressor-evoked cardiovascular reactivity; visceral prediction errors

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1. Introduction

How do stress-related processes instantiated in the brain relate to an individual's risk for atherosclerotic cardiovascular disease (CVD) and related adverse cardiovascular outcomes that continue to be leading burdens to public health (Mozaffarian et al., 2016)? Addressing this open question is important: it has the potential to (*i*) advance our mechanistic understanding of the human neurophysiological substrates for psychological and behavioral influences on the development of CVD and (*ii*) inform novel and brain-based efforts to better predict and possibly reduce CVD risk. Historically, acute cardiovascular reactions (e.g., rapid and autonomically mediated rises in blood pressure [BP] and heart rate [HR]) to psychological stressors have been among the most heavily investigated stress-related parameters of CVD risk. Over the short-term, such stressor-evoked cardiovascular reactions may be adaptive, insofar as they provide hemodynamic and metabolic support for contextually appropriate behaviors that confer survival advantage (e.g., fight-or-flight behaviors). Over the long-term, however, stressor-evoked cardiovascular reactions that are exaggerated, prolonged, and repeatedly expressed may initiate or exacerbate pathophysiological changes in the heart and vasculature. More precisely, there is longstanding and cumulative epidemiological evidence that individuals who exhibit a phenotype characterized by the expression of large-magnitude or metabolically-exaggerated stressor-evoked cardiovascular reactions are at elevated risk for clinical and preclinical endpoints of CVD (for reviews, see Gerin et al., 2000; Chida & Steptoe, 2010; Taylor, Kamarck, Dianzumba, 2003; Krantz & Manuck, 1984; Scwartz et al., 2003; Treiber et al., 2003). These endpoints include an accelerated progression of atherosclerosis (e.g., Barnett et al., 1997; Jennings et al., 2004); the premature development of hypertension (e.g., Carroll et al., 2011; Carroll et al., 2012); increased ventricular mass (e.g., Allen, Matthews, & Sherman, 1997; Georgiades et al., 1996); concentric remodeling of the heart (e.g., al'Absi et al., 2006); future coronary events (e.g, myocardial infarctions) (Schwartz et al., 2003, Trieber et al., 2003); and cardiovascular disease mortality (Carroll et al., 2012).

The brain has long been implicated in the control of cardiovascular function, particularly in linking stressful experiences to cardiovascular changes associated with clinical events and disease pathophysiology (for reviews see Dampney, 2015; Lane et al., 2009a; 2009b; Palma & Benarroch, 2014; Taggart et al., 2016; Esler, 2017). For example, Cannon originally proposed that intense emotions, such as fright, were generated in the brain and triggered peripheral physiological responses that could end one's life in "voodoo death" (Cannon, 1928; 1942). It has also long been known that brain damage and neurological phenomena (e.g., epilepsy, stroke) can result in detrimental effects on circulatory control via the autonomic nervous system, including sudden cardiac death (Colivicchi et al., 2005; Oppenheimer, 2006; Abboud et al., 2006; Tomson, Nashef, & Ryvlin, 2008; Nagai, Hoshide, & Kario, 2010). It is in this historical and behavioral medicine context that a growing number of brain imaging studies have sought to explicate the neural circuits that are jointly (*i*) engaged by psychological stressors and (*ii*) involved in coordinating autonomic and neuroendocrine activity to proximally influence cardiovascular responding. From a health neuroscience perspective (Erickson et al., 2014), a guiding assumption of these brain-imaging studies is that a better understanding of these neural circuits will help define the

mechanistic pathways by which psychological stress may confer CVD risk and result in adverse clinical events. The goal of this brief review is to highlight key and convergent findings from these studies, as well as describe salient methodological issues, interpretive caveats, and future directions inherent to brain-imaging studies of cardiovascular reactivity and CVD risk.

2. Stressor-evoked cardiovascular reactivity and CVD

Psychological stressors can be defined as perceived threats to well-being that tax or exceed an individual's capacity to cope with such threats (Lazarus, 1966). Individuals differ appreciably, however, in the extent to which they ascribe threat-related and psychological meaning to events, contexts, and myriad other stimuli. They also differ in the extent to which they construe their available coping resources and options as adequate for managing potential sources of threat. These individual differences are thought to arise from psychological *appraisal processes* that usually operate outside of awareness and are instantiated in forebrain neural circuits that (*i*) process internal and external sources of information for their personal relevance and threat-related meaning and (*ii*) calibrate peripheral physiology with behavioral action to support stressor coping and responding (Cohen, Gianaros, & Manuck, 2016). From this perspective, individual differences in stressor-evoked cardiovascular reactions that are linked to CVD risk are believed to be accounted for in part by corresponding differences in the functionality of forebrain neural circuits that link stressor processing (psychological appraisals) with physiological regulation, especially autonomic and neuroendocrine regulation of the cardiovascular system (Gianaros & Wager, 2015). To elaborate, stressor-evoked cardiovascular reactions result from intermediate changes in sympathetic and parasympathetic nervous system and hypothalamic-pituitary-adrenal axis outflow to the heart and vasculature. These autonomic and neuroendocrine effector changes in turn influence parameters of cardiovascular physiology (e.g., cardiac output, peripheral vessel resistance) to redirect blood flow and perfuse tissues according to anticipated or ongoing behavioral needs. Accordingly, a major focus in human and nonhuman animal studies on the neurobiology of cardiovascular stress reactivity has focused on cortical and subcortical circuits that proximally influence autonomic and neuroendocrine function. An emerging conceptual perspective is that these circuits specifically generate anticipatory visceromotor commands to alter parameters of cardiovascular physiology that *prepare* individuals to behaviorally cope with appraised threats (psychological stressors) (Gianaros & Wager, 2015). Thus, these visceromotor commands can be conceptualized as 'visceral predictions', insofar as they are anticipatory to the metabolic and behavioral demands engendered by appraised stressors (cf., Clark et al., 2013; Chanes & Feldman Barrett, 2017). As noted above, some individuals who are vulnerable to CVD exhibit a phenotype that is typified by cardiovascular changes (e.g., increases in HR and BP) that are in excess of the metabolic and behavioral demands of a given stressor. An example would be an individual with a stable, trait-like phenotype to exhibit a rise in HR in excess of 30 beats per minute (bpm) and/or a rise in systolic blood pressure (SBP) in excess of 30 mmHg while anticipating the delivery of a public speech that requires minimal metabolic effort. In this example, such stressor-evoked changes in HR and BP reflect a metabolic *mis*-calibration between anticipatory cardiovascular function and

actual behavioral needs, a so-called ‘visceral prediction error’. Such exaggerated stressor-evoked cardiovascular reactions can be contrasted with coordinated changes in cardiovascular physiology that occur with physical activity and exercise for leisure or sport, where energy and metabolic needs are calibrated, presumably by central visceromotor commands that are updated and fine-tuned according to viscerosensory feedback (Fisher, Young, & Fadel, 2015; Shoemaker et al., 2015). Metabolically-exaggerated, cardiovascular reactions to psychological stressors can be readily assessed using laboratory paradigms that integrate psychological (mental) stress testing with conventional exercise physiology methods (e.g., Carroll, Phillips, & Balanos, 2009; Balanos et al., 2010). In these paradigms, ‘exaggerated reactors’ are those individuals who exhibit stressor-evoked cardiovascular changes that well exceed their stressor-evoked oxygen consumption change (i.e., their cardiovascular system is working in excess of their metabolic system; Turner & Carroll, 1985). For example, in a study assessing metabolic and cardiovascular activity in healthy young adults, an ‘exaggerated reactor’ had a heart rate of ~115 beats per minute (bpm) during psychological stress, when the metabolically appropriate response, predicted by oxygen consumption and determined by exercise performance testing, was only 85 bpm (i.e., heart rate was 30 bpm in excess of what was predicted as ‘metabolically appropriate’; Turner & Carroll, 1985). A longstanding view is that the repeated and cumulative expression of such metabolically-disproportionate, stressor-evoked cardiovascular reactions contribute to or exacerbate pathophysiological changes that are conducive to CVD and CVD events among vulnerable individuals (Carroll, Phillips, & Balanos, 2009; Balanos et al., 2010; Turner & Carroll, 1985; Sherwood, Allen, Obrist, & Langer, 1986; Obrist, 1981). Likewise, there has been a recent surge of research focusing on different kind of ‘visceral prediction error’, involving *failures* to mount appropriate cardiovascular reactions to psychological stressors. Hence, some individuals exhibit a tendency to show blunted or minimal changes in cardiovascular physiology across a range of motivated behavioral states, including those related to psychologically stressful experiences. Compared with their more reactive counterparts, individuals expressing a phenotype for blunted reactivity are more likely to engage in disadvantageous health behaviors that confer CVD risk through pathways that are independent from those of exaggerated reactors (e.g., Ginty et al., 2016; Wiggert et al., 2016) and they exhibit motivational and psychological characteristics (e.g. substance use problems, depressive symptoms, impulsivity) that may heighten CVD risk (e.g., Carroll et al., in press; de Rooij, 2013; Bennett et al., 2014). Advances in brain-imaging have recently provided the necessary tools to characterize the putative neural circuits that contribute to these individual differences in stressor-evoked cardiovascular reactivity, particularly via intermediate autonomic and neuroendocrine pathways. Specifically, brain-imaging studies have shown that individuals who exhibit larger rises in blood pressure and heart rate (i.e., greater cardiovascular reactivity) during stress often exhibit concurrently greater increases in activity in several regions for visceral control, including the anterior cingulate cortex, medial prefrontal cortex, insula, hippocampus, basal ganglia, periacqueductal gray (PAG), and pons. There is also some evidence to suggest that people who exhibit greater cardiovascular reactivity also display greater activation in the amygdala and extended amygdala, but this has not been a reliable finding (Gianaros et al. 2008, Wager et al., 2009). In this regard, the increasing integration of multivariate and whole-brain pattern analyses with brain-imaging studes of stress will provide greater specificity with respect to network-level quantitative

changes that predict individual differences in cardiovascular reactivity (Woo et al., 2017). For example, Eisenbarth et al., 2016 demonstrated that multivariate patterns of activity across the entire brain were reliably predictive of concurrent increases in heart rate and skin conductance during the anticipation of delivering a socially evaluated speech. Moreover, these multivariate patterns expressed some overlap within limbic areas, as well as some specificity (non-overlap) with respect to heart rate and skin conductance predictive associations (Eisenbarth et al., 2016). These findings suggest that a focus on particular brain regions or directional activity changes in particular brain regions during stress may ultimately have circumscribed utility in understanding the neural bases of stress physiology and that multivariate methods may better capture activity patterns across brain networks that are associated with different parameters of stress physiology. We next describe common paradigms and approaches used in these studies, and we highlight selected convergent findings on the neural correlates of stressor-evoked cardiovascular reactivity.

3. Brain-imaging studies of stressor-evoked cardiovascular reactivity

As detailed in recent meta-analyses and other reviews (e.g., Gianaros & Wager, 2015; Thayer et al., 2012; Myers 2016; Shoemaker & Goswami, 2015; Beissner et al. 2013, Muscatell & Eisenberger), functional divisions of the anterior cingulate cortex (ACC) and adjacent medial prefrontal cortex (mPFC), insula, hippocampus, and amygdala may be viewed as a core – albeit not exclusive – components of a broader network of forebrain systems involved in mediating stressor-evoked changes in cardiovascular activity. These forebrain systems are specifically viewed to play a role in stress appraisal processes, by ascribing personal and threat-related meaning to events, contexts, and other sources of information that are encoded and experienced (Gianaros & Wager, 2015). These forebrain systems are also viewed to play a dual role in peripheral physiological regulation via their functional interactions with subcortical circuits that proximally alter autonomic and neuroendocrine outflow to the periphery (e.g., heart and vasculature). Specifically, forebrain areas can functionally interact with one another as a network to modulate visceromotor and viscerosensory functions of cell groups within the thalamus, hypothalamus, PAG and medullary regions – which govern and monitor autonomic and neuroendocrine outflow to the heart and blood vessels in coordination with behavioral actions and motivated dispositions to act (Bandler, Keay, Floyd, & Price, 2000; Öngür & Price, 2000; Saper, 2002; Ulrich-Lai & Herman, 2009). Across several recent brain-imaging studies, stressor-evoked cardiovascular changes (e.g., in BP and HR) have been reliably associated with activity changes in these forebrain and subcortical regions, consistent with invasive animal work and patient lesion studies on central cardiovascular, autonomic, and neuroendocrine control (Critchely et al., 2003; Oppenheimer & Cechetto, 2016; Shoemaker et al., 2015; Shoemaker & Goswami, 2015). Conventionally, these forebrain and subcortical regions have been referred to as components or nodes of a central autonomic network (Bennarroch, 1993; Saper, 2002) or, more inclusively, a visceral control network.

A common methodological approach in brain-imaging studies that examine stressor-evoked cardiovascular and other physiological reactions to activity changes in visceral control regions is to employ behavioral task paradigms that involve processing conflicting stimuli, performing under time-pressure and negative social evaluation, and even anticipating electric

shocks (see Table 1 for extended examples). During these task paradigms, changes in peripheral physiology (e.g., HR and BP) are often measured concurrently with ongoing functional activity across the whole brain or in selected brain regions. By this methodological approach, researchers seek to identify patterns of neural activity that may correspond to psychological threat appraisal processes, as well as visceromotor commands (e.g., the basis of presumptive visceral prediction errors) or viscerosensory processes linked to the efferent generation and afferent representation of changes in peripheral physiology, respectively. As one example, Wager and colleagues (2009) demonstrated that ventromedial PFC (vmPFC) and rostral ACC activity during the anticipation of a socially-evaluated speech predicted individual differences in the magnitude of HR reactivity. Moreover, they demonstrated that vmPFC and ACC associations with HR reactivity were *mediated* (statistically accounted for) by concurrent changes in the PAG and thalamus, thus potentially defining a forebrain-to-subcortical pathway for stressor-evoked cardiovascular (HR) reactivity. These findings agree with neuroanatomical tracing work in primates and other nonhuman animal models demonstrating projections from the medial prefrontal cortex to the PAG and hypothalamus (Bandler et al., 2000; Dampney, 2015), as well as primate anatomical work on the coritical control of the adrenal medulla (Dum et al., 2016). As noted above, this particular line of work was also extended recently to define a *multivariate* pattern of neural activity encompassing the vmPFC and other networked limbic regions that reliably predicted individual differences in stressor-evoked HR and sympathetic nervous system reactivity (skin conductance) using multivariate methods (Eisenbarth, Chang, & Wager, 2016). In parallel work, Gianaros et al. (2008) demonstrated that individual differences in stressor-evoked BP reactivity related to concurrently greater activation in the amygdala, as well as more strongly correlated activity of the amygdala with the rostral ACC and brainstem (pons). In aggregate, these and related studies employing other stressor paradigms are thus helping to define the forebrain and subcortical neural circuits that couple presumptive psychological threat appraisals with the peripheral expression of cardiovascular reactions implicated in CVD risk.

It is important to note that efferent visceromotor and afferent viscerosensory processes that influence and represent stressor-evoked changes in peripheral (e.g., cardiovascular) physiology are thought to be represented by the functional interplay or network-level interactions among forebrain and subcortical neural circuits. In other words, it is implausible that any given brain area acts in isolation from networked areas to generate or control peripheral physiological stress reactions, including cardiovascular reactivity. Recent advances in brain-imaging analytical approaches have provided a basis for quantifying such network-level interactions and relating them to changes in peripheral physiology (e.g., Hermens et al., 2011; Quaedflieg et al., 2015). These approaches specifically provide for metrics of stressor-evoked changes in functional connectivity (i.e., cross-correlated activity between multiple areas of the brain), and have made use of three broad methodological techniques. Here, augmented stressor-evoked connectivity is represented by an overall increase in the positive correlations between two areas or within a given network as a whole. In contrast, weakened or inverse stressor-evoked connectivity would be represented by overall decreases or more negative correlations between two areas or within network as a whole. The first and most common approach in this line of work is to select a predetermined,

anatomical region-of-interest or 'seed' (e.g., the amygdala) and then compare the relationships (correlations) between activity in that seed and activity in other brain regions at rest, during a stressor task, or during stressor recovery (e.g., Fan et al., 2015; Sinha et al., 2016). Studies using these network-based approaches typically examine how groups of brain areas are altered by stressor tasks, but they have rarely measured how individual differences in peripheral physiological (e.g., HR, BP) responses relate to network-level or connectivity changes. For example, using a seed-based approach Sinha and colleagues (2016) demonstrated that viewing aversive pictures increased the functional connectivity (cross-correlation) between vmPFC activity and the left anterior PFC, dorsolateral PFC, and inferior parietal lobe. As another example, using a seed-based approach, Gianaros and colleagues (2012) demonstrated that functional connectivity of a canonical visceral control area, the anterior insula (Oppenheimer & Cechetto, 2016), was increased during a psychological stressor that increased BP and decreased cardiovagal baroreflex sensitivity. Specifically, stressor-evoked changes were observed between the anterior insula and ACC, amygdala, PAG, and pons. A second approach to quantifying network-level properties involves the application of multivariate time-series analyses, such as independent component analyses (ICA) (Beckmann et al., 2005; Bullmore & Sporns, 2009; Calhoun et al., 2001). This approach involves identifying distributed brain networks that exhibit coherent patterns of activity across time, and examining how connectivity across the identified networks changes either during or after stressor tasks. As an example, Hermans and colleagues (2011) applied ICA to neural activity assessed while subjects viewed aversive film clips and identified a canonical "ventral attention" or "salience network", primarily consisting of previously described forebrain and subcortical structures including the cingulate, insula, and amygdala. Across participants, connectivity within this network related to stressor-evoked cortisol and salivary alpha-amylase responses. A third and more recent approach first partitions the entire brain into multiple regions, and examines connectivity between every pair of regions across the whole brain, in turn treating the brain as a network in an unbiased manner. This approach is conceptually similar to seed-based analyses, with the distinction that it involves characterizing connectivity across every seed-to-seed pair rather than a few *a priori* selected pairs or regions. Recently, Maron-Katz and colleagues (2016) examined connectivity across 490 brain regions before and after a stress induction, and found that stress increased connectivity of the thalamus and cerebral cortex, and reduced connectivity between the parietal and temporal lobes. A more extended summary of this line of research bearing on stressor-evoked changes in network-level changes can be found in Tables 2 and 3.

Despite the growth of work in this area, however, what remains incompletely understood are some of the more precise functions and actions encoded within network-level properties of visceral control circuits and how they proximally influence stressor-evoked cardiovascular reactions. For example, are these actions representing visceral prediction errors and efferent commands, afferent processing, or both? And, over what time scale? In these regards, methodological advances in brain-imaging and concurrent physiological monitoring have not yet enabled researchers to readily differentiate the neural correlates of afferent and efferent processes in the context of stressor-evoked cardiovascular reactions, as has been done with other physiological adjustments (e.g., with exercise or baroreceptor unloading ; Shoemaker & Goswami, 2015; Shoemaker et al., 2015; Shoemaker, Wong, & Cechetto,

2012). Another major frontier for future work on stressor-evoked cardiovascular reactivity will be to integrate emerging image acquisition methods for more precise functional assessments of brainstem circuits, which relay both descending stressor-evoked visceromotor commands from forebrain areas and ascending viscerosensory information from the periphery to these forebrain areas (Beissner, 2015; Beissner et al., 2014; Bar et al., 2016).

In addition to the latter future directions, another need in this area of research is an interpretive framework for conceptualizing the neurophysiological correlates (e.g., network-level metrics of visceral control areas) of stressor-evoked changes in physiology, particularly cardiovascular physiology in the context of risk for CVD. Specifically, there is not a uniform conceptual framework for understanding the mechanisms and processes by which psychological stressors engage or alter coordinated activity among central visceral control regions to influence cardiovascular reactivity, particularly via visceromotor and viscerosensory processes. Nor are there quantitative metrics that reflect the bidirectional relationships between stressor-evoked cardiovascular reactions and neural activity patterns that generate and represent these reactions. An emerging perspective, described in the next section, however, is that forebrain regions that are engaged by psychological stressors and involved in threat appraisal processes influence cardiovascular responding by alternating the operational characteristics of homeostatic feedback loops for circulatory control (visceral control loops) (Gianaros & Wager, 2015).

4. Central visceral control mechanisms for stressor-evoked cardiovascular reactivity

As noted earlier, changes in BP and HR are reliably evoked by psychological stressors, and these stressor-evoked cardiovascular changes have long been linked to CVD risk. BP itself is a circulatory parameter that is under the control of the baroreflex. The baroreflex constrains beat-to-beat variation in BP by adjusting sympathetic and parasympathetic outflow to the heart and vasculature to alter heart rate and vessel tone, and hence cardiac output and peripheral resistance. Rises in BP distort stretch-sensitive baroreceptors with free nerve endings situated most densely in the bulb of the carotid artery and the aortic arch. This distortion caused by rises in BP increases the transmission of pressure-related information encoded by the baroreceptors along vagal and glossopharyngeal pathways to the nucleus of the solitary tract (NTS) in the brainstem, which issues mono- and multi-synaptic projections not only to pre-autonomic source nuclei in the brainstem (dorsal vagal nucleus, nucleus ambiguous, caudal and ventrolateral medulla), but also to forebrain regions that are presumably involved in psychological threat appraisals (e.g., vmPFC, ACC, insula, amygdala). NTS projections to pre-autonomic source nuclei serve to proximally alter vagal and sympathetic outflow to adjust BP toward a homeostatic set point (e.g., by modulating HR, cardiac output, and peripheral resistance). By contrast, NTS projections to forebrain regions enable the afferent representation of BP (Dampney, 1994; Berntson, Sarter, & Cacioppo, 1998; Critchely & Harrison, 2013). In addition to these ascending projections of the NTS that transmit viscerosensory information, forebrain regions project back to the NTS. These descending projections provide a basis for forebrain regions to modify the

normal operating characteristics of the baroreflex at the level of the brainstem across a range of behavioral states. Such modifications may well vary across behavioral states, individuals, and particular stages of lifespan development. They may also have differential implications for health and disease risk. In this regard, illustrative comparisons may be drawn between reflex modifications that that unfold during experiences of psychological stress and physical activity (e.g., exercise).

To elaborate, exercise increases both BP and heart rate as is the case for psychological stress. Yet despite some early suggestions to the contrary, the arterial baroreflex continues to function while its set-point is 'reset' to function around the prevailing BP (Lind et al., 1964; Raven, Fadel, & Ogoh, 2006; Potts, 2006; Fisher, Young, & Fadel, 2015). In fact it appears that by buffering increases in vasomotor tone, an appropriately functioning baroreflex is important in restraining the BP response to exercise (Joyner, 2006). In terms of carotid baroreflex control of heart rate, the maximum gain of the stimulus-response reflex function curve is preserved, however the operating point, which is located near the point of maximal gain at rest, is shifted away from the centering point and towards the threshold at a locus of reduced gain (i.e., sensitivity). As noted, psychological stress reliably reduces baroreflex sensitivity, specifically cardiovasgal sensitivity, is shown. However, the full stimulus-response relationship during experiences of stress has yet to be elucidated. The baroreflex alterations observed during exercise have been attributed to the interactive effects of visceromotor central neural commands and viscerosensory information arising from the exercise pressor reflex (for reviews see Raven et al., 2006; Potts, 2006; Fisher et al., 2015). In contrast to exercise, typical experiences of acute psychological stress are *not* accompanied by similar metabolic and mechanical viscerosensory changes, and thus no discernable exercise pressor reflex (Turner & Carroll, 1985). However, several areas of the brain associated with central command during exercise are also engaged by acute psychological stressors: ACC, insula, PAG (e.g., Green & Paterson, 2008; Green et al., 2007; Nowak et al., 2005; Thornton et al., 2001). Thus, forebrain regions involved in the appraisal of psychological stressors may evoke cardiovascular stress reactions (e.g., simultaneous rises in BP and HR) via visceral predictive processes described above that modify visceral or homeostatic control loops, such as the baroreflex. In extension, individuals with a phenotype for exaggerated cardiovascular reactivity may be at elevated risk for CVD because of the chronic expression of visceral prediction errors that repeatedly dampen the sensitivity of homeostatic control loops in ways that differ from behavioral states, such as exercise, and confer vulnerability for consequent pathology over time. What is more, to the extent that baroafferent traffic conveys viscerosensory information regarding the magnitude of BP changes to the NTS and forebrain regions for visceral control, it would appear that a phenotype for exaggerated stressor-evoked cardiovascular reactivity may reflect impairment in 'visceral learning'. In other words, among individuals with this phenotype visceral prediction errors do not appear to be 'corrected' over time - insofar as exaggerated cardiovascular reactivity is reliably and repeatedly expressed in the laboratory and daily life (Zanstra & Johnston, 2011). This perspective can be extended and applied to what is referred to as prolonged cardiovascular responding, or responding that does not recover to resting or baseline levels. Impaired or delayed BP recovery, failure to return back to resting cardiovascular activity levels, to psychological stressors, for example, has been associated

with hypertension (Steptoe & Marmot, 2005; Stewart, Janicki, & Kamarck, 2006). Here, it would appear that baroafferent traffic is failing to result in a homeostatic return of BP, possibly via input to brainstem baroreflex circuits by forebrain systems for stressor appraisal. In this interpretive framework, visceromotor and viscerosensory mechanisms appear to be key components of the brain-body pathways by which appraisal systems of the forebrain may link states of psychological stress and physiological responding to influence physical health (see Figure 1). However, the effect of psychological stress on baroreflex function is incompletely understood. The majority of the research examining baroreflex function during psychological stress has focused on cardiovagal sensitivity with limited consideration of baroreflex control of sympathetic nerve activity to the skeletal muscle vasculature. The scant research in the area suggests that there are individual differences in muscle sympathetic nerve activity responses to psychological stress and an attenuation of the sympathetic baroreflex at the onset of psychological stress (Carter & Ray, 2009; Durocher, Klein, & Carter, 2011). Similarly, the full-stimulus response characteristics of baroreflex control during psychological stress are not well understood. More work is needed to understand the regulation of baroreflex function during psychological stress and the implications for health and disease.

5. Conclusions

The neurophysiological or ‘brain-body’ pathways linking psychological stress and CVD risk still remain largely uncertain (Lovallo, 2005; Lane et al., 2009). Arguably, delineating these pathways may not only aid in developing brain-based strategies for augmenting CVD risk stratification and prediction in the emerging field of neurocardiology (Shivkumar et al., 2016; Silvani et al., 2016), but also in furthering a mechanistic understanding of stress-related processes contributing to CVD vulnerability. To illustrate, a recent seminal study demonstrated that higher levels of resting amygdalar activity predicted development of CVD over a 3.7 year period (Tawakol et al., 2017). Additionally, increased amygdalar activity was associated with alterations in immune activity, arterial inflammation, and perceived stress providing evidence of potential mechanistic pathways underpinning CVD development (Tawakol et al., 2017). Such work represents the next generation of research on neurobiology of stress and disease risk. In view of these possibilities, a growing corpus of brain-imaging research is helping to better define these pathways. Existing findings are converging to suggest that individual differences in stressor-evoked cardiovascular reactivity are associated with activity and connectivity in brain systems that are jointly involved in processing (appraising) stressors and regulating the cardiovascular system via autonomic and neuroendocrine pathways. These systems encompass a distributed network of cortical and subcortical brain areas involved in mobilizing hemodynamic and metabolic support for stress-related behavioral responding via visceromotor commands. These systems also represent dimensions of cardiovascular physiology via viscerosensory pathways. An emerging perspective is that brain areas for visceral control calibrate the magnitude of physiological (e.g., cardiovascular) reactions to self-relevant stressors to support contextually-adaptive behavioral coping processes. An individual’s propensity to exhibit ‘*mis*-calibrations’ reflected by network-level interactions between these regions may reflect a dimension of individual differences that underlies the expression of ‘exaggerated’

(metabolically-excessive or pathophysiological) cardiovascular reactions, including stressor-evoked BP and HR reactions that are linked to preclinical and clinical CVD endpoints. Such '*mis*-calibrations' may be conceptualized as visceral prediction errors, in that they reflect anticipatory visceromotor commands for putatively pathogenic changes in physiology that outstrip metabolic needs and arise from the suppression of homeostatic visceral control loops. What is needed are methods and metrics to better quantify network signaling (e.g., connectivity) characteristics among forebrain and brainstem visceral control areas to test hypotheses derived from this conceptual view and relate these network-level characteristics to markers of CVD pathology and vulnerability. Additionally, what is also needed is work determining the possible genetic and developmental origins of these individual differences in central circulatory control, as well as work on lifestyle and behavioral factors linked to stress and stress physiology (e.g., physical activity) that influence the neurobiology of CVD risk and are amenendable to intervention effort.

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Highlights

Cardiovascular reactions to stress may confer CVD risk.

Brain circuits for autonomic control generate and regulate cardiovascular stress reactions.

These circuits may be important for linking stress to CVD.

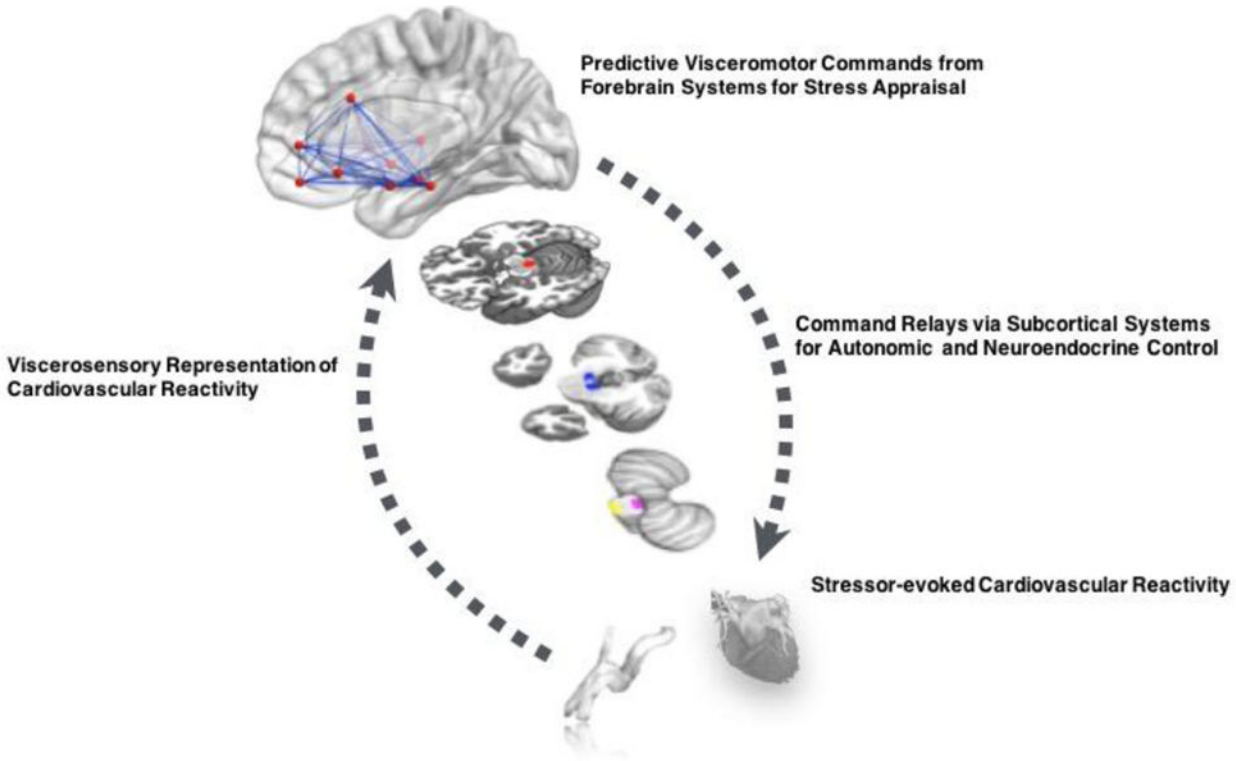

Figure 1.

Conceptual illustration of brain-body pathways linking psychological stress to stressor-evoked cardiovascular reactions linked to cardiovascular disease risk. A network of forebrain areas appraise psychological stimuli as threats that tax or exceed coping capacities. These appraisals lead to visceromotor commands or 'predictions' for anticipated metabolic support for motivated behaviors. These commands are relayed via subcortical and brainstem cell groups to influence autonomic and neuroendocrine outflow to the heart and vasculature. Chronically exaggerated or metabolically disproportionate stressor-evoked cardiovascular (e.g., BP) reactions may exert shear or tensile stress on blood vessel walls over time, and they may accelerate atherosclerosis or influence risk for later cardiovascular disease endpoints. Vagal and other viscerosensory channels relay feedback signals from visceral organs and systems in the periphery, enabling the afferent representation of peripheral stressor-evoked physiological reactions by forebrain areas. Afferent feedback may influence the magnitude, duration, or general patterning of stressor-evoked reactions and may also affect appraisal-related neural activity.

Table 1

Example studies of stressor-evoked neural, autonomic, neuroendocrine, and cardiovascular reactivity.

Citation	Stress task	Physiological measures
Critchley et al., 2000	Mental arithmetic, isometric exercise	Heart rate, blood pressure
Dalton et al., 2005	Electric shocks	Cardiac contractility
Dedovic et al., 2014	Montreal Imaging Stress Task	Salivary cortisol
Eisenberger et al., 2007	Cyberball (social exclusion)	Salivary cortisol
Gianaros et al., 2004	Verbal working memory task; spatial working memory task	Heart rate, High-frequency heart rate variability
Gianaros et al., 2007	Stroop interference task	Blood pressure
Gianaros et al., 2012	Multisource Interference Task	Blood pressure, heart rate, baroreflex sensitivity
Ginty et al., 2012	Multisource Interference Task	Heart rate
Holsen et al., 2012	Visual stimuli	High-frequency heart rate variability
Hermens et al. 2011	Aversive video clip	Salivary cortisol, heart rate
Wang et al., 2005	Mental arithmetic	Salivary cortisol, heart rate
Wager et al., 2009	Speech preparation	Heart rate

Table 2

Studies examining stressor-evoked functional connectivity changes.

Citation	Stress task	Analysis	Seed Region	Stressor-evoked changes
Admon et al. 2009	Backward masked photographs, prior to and following military service	Seed-based	Hippocampus	↑Psychological stress, ↓vmPFC connectivity
Akdeniz et al. 2014	Mental arithmetic and mental rotation	Seed-based	pgACC	↑Perceived discrimination, ↑ connectivity with dACC
Fan et al. 2015	Montreal Imaging Stress Task	Seed-based	Amygdala	↑Connectivity with mPFC, posterior cingulate cortex, anterior insula, putamen, caudate, thalamus
Gianaros et al. 2012	Multisource Interference Task	Seed-based	Insula	↑Connectivity with ACC, amygdala, pons, midbrain PAG
Liston et al. 2009	Attention-shifting task following 1 month of chronic psychosocial stress	Seed-based	Left and right dorsolateral prefrontal cortex	↓Connectivity with contralateral dorsolateral prefrontal cortex, ventral prefrontal cortex, putamen, anterior and posterior cingulate, premotor, posterior parietal, and fusiform cortex, and cerebellum; ↑Connectivity with middle temporal lobe
Maron-Katz et al. 2016	Serial subtraction task	Network-based	N/A (or many)	↑Thalamo-cortical connectivity, ↓parietal-temporal connectivity
McMenamin et al. 2014	Aversive shock	Network-based; graph theory	N/A (or many)	Initial ↑ in ventral-attention network efficiency, encompassing ACC, insula, followed by ↓connectivity in ventral-attention network
Sinha et al. 2016	Aversive pictures	Seed-based	vmPFC	↑Connectivity with left anterior prefrontal cortex, dorsolateral prefrontal cortex, and inferior parietal lobe
Van Marle et al. 2010	Immediately following aversive movie	Seed-based	Amygdala	↑Connectivity with dACC, anterior insula, dorso-rostral pontine
Veer et al. 2011	Immediately following Trier Social Stress Task	Seed-based	Amygdala	↑Connectivity with the posterior cingulate cortex, and vmPFC

Table 3

Studies examining stressor-evoked functional connectivity changes and physiological changes.

Citation	Stress task	Seed Region	Stressor-evoked changes and physiology
Gianaros et al. 2008	Stroop interference task	Amygdala	↑Mean arterial pressure reactivity associated with ↑amygdala functional connectivity with the pgACC, pons, orbitofrontal cortex, insula, hippocampus, caudate, middle temporal lobe, occipital cortex, and cerebellum
Hermens et al. 2011	Aversive pictures	Independent component analysis	↑Cortisol and alpha-amyalse responses associated with stronger 'salience network' interconnectivity
Quaedflieg et al. 2015	Imaging Maastricht Acute Stress Task	Amygdala	Cortisol responders had ↑amygdala connectivity with anterior hippocampal complex and parahippocampal gyrus
Wager et al. 2009	Speech preparation task		PFC/ACC activity related to ↑PAG and thalamus activity and heart rate reactivity