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PSYCHOLOGICAL ASPECTS OF CARDIOVASCULAR DISEASES (A STEPTOE, SECTION EDITOR)

Neural Mechanisms Linking Emotion with Cardiovascular Disease

Thomas E. Kraynak[1,2] · Anna L. Marsland[1] · Peter J. Gianaros[1,2]

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Abstract

Purpose of Review The present review discusses brain circuits that are engaged by negative emotions and possibly linked to cardiovascular disease risk. It describes recent human brain imaging studies that relate activity in these brain circuits to emotional processes, peripheral physiology, preclinical pathophysiology, as well as clinical outcomes.

Recent Findings Negative emotions and the regulation of negative emotions reliably engage several brain regions that cross-sectional and longitudinal brain imaging studies have associated with CVD risk markers and outcomes. These brain regions include the amygdala, anterior cingulate cortex, medial prefrontal cortex, and insula. Other studies have applied advanced statistical techniques to characterize multivariate patterns of brain activity and brain connectivity that associate with negative emotion and CVD-relevant peripheral physiology.

Summary Brain imaging studies on emotion and cardiovascular disease risk are expanding our understanding of the brain-body bases of psychosocial and behavioral risk for cardiovascular disease.

Keywords Amygdala · Brain imaging · Emotion · Emotion regulation · Medial prefrontal cortex · Stress

Introduction

Cardiovascular disease (CVD) is a leading contributor to morbidity and mortality in the developed world. A large body of epidemiological research suggests that negative emotions and mood states may play a significant role in the development and progression of CVD. Moreover, it is thought that negative emotions, moods, and related dispositional traits (e.g., anxiety, anger, and depressive phenotypes) may impact CVD risk and progression via peripheral physiological changes that are evoked by stressful or otherwise adverse experiences. However, the brain mechanisms that link the experience, expression, and regulation of negative affective states and traits with downstream physiological changes are not fully understood.

To better understand these mechanisms, parallel lines of research using animal models, as well as human brain imaging studies, have attempted to identify brain circuits that are implicated in processing and responding to negative emotional stimuli, as well as the regulation of autonomic, neuroendocrine, immune, and cardiovascular physiology. Emerging human brain imaging studies have, moreover, begun to link functioning in these brain circuits to preclinical and clinical CVD endpoints. Accordingly, the present review summarizes findings from these brain imaging studies, which together point to localized activity as well as patterned and network-level responses within a brain circuitry encompassing specific brainstem, subcortical, and cortical structures. After this summary, we identify open questions for further research in this field.

This article is part of the Topical Collection on *Psychological Aspects of Cardiovascular Diseases*

✉ Thomas E. Kraynak
tekraynak@pitt.edu

Anna L. Marsland
marsland@pitt.edu

Peter J. Gianaros
gianaros@pitt.edu

[1] Department of Psychology, University of Pittsburgh, 210 South Bouquet Street, Pittsburgh, PA 15260, USA

[2] Center for the Neural Basis of Cognition, Pittsburgh, PA, USA

Emotion, Stress, and Cardiovascular Disease

Although mortality due to cardiovascular disease (CVD) has declined in recent decades, it nonetheless remains a leading cause of death among adult men and women in developed

countries [1]. In addition to traditional CVD risk factors, psychosocial factors are thought to influence the development and progression of CVD across the lifespan [2, 3]. Key among these psychosocial factors are processes involving the generation and regulation of negative emotions [4]. Negative emotions may relate to CVD within at least two contexts. First, chronic or prolonged experiences of negative emotional or mood states, such as clinical depression, as well as the trait-like tendency to experience negative emotion, each associate with preclinical CVD disease markers, clinical CVD incidence, as well as treatment outcomes [5–7]. Along these lines, increased CVD risk has been demonstrated in relation to several other clinical disorders (e.g., anxiety, post-traumatic stress) and personality characteristics (e.g., hostility) that involve negative emotions [8–10]. Second, acute emotional responses to negative events may trigger cardiac events in at-risk individuals or individuals with ongoing CVD [11]. Importantly, reported associations between CVD and experiences of chronic or acute negative emotion are often independent of conventional CVD risk factors, such as lipid levels, blood pressure, and tobacco use [12]. Similarly, the statistical effect size of associations between negative emotionality and CVD is comparable to these and other CVD risk factors [13]. We note that, in addition to the literature on negative emotions, a parallel line of research suggests a possible protective role for *positive emotions* in CVD risk and incidence [14, 15]; however, to our knowledge, none of the brain imaging studies described below have yet examined neural correlates of positive emotions as they relate to CVD risk. Hence, taken together, chronic and acute negative emotional states represent a substantial and potentially modifiable source of risk for CVD and other chronic diseases of aging.

Despite cumulative epidemiological and clinical evidence linking negative emotions to CVD, physiological mechanisms underlying this link are not fully understood. A key component of negative emotional responses is the generation of peripheral physiological changes involving the autonomic, immune, and neuroendocrine systems. Some of the most frequently documented physiological changes that accompany negative emotions and are jointly implicated in CVD pathogenesis include a suppression of parasympathetic cardiac control, an increase in sympathetic nervous system activity, an increase in systemic inflammation, and activation of the hypothalamic-pituitary-adrenal axis [16–19]. The role of these different peripheral physiological changes in the context of emotion and CVD is beyond the scope of the present review; yet, we note that these peripheral physiological responses can vary substantially across different emotions, contexts, and individuals. Regarding the latter, observed inter-individual variability in peripheral physiological responses may correspond to specific phenotypes that forecast an individual's CVD risk or prognosis [20].

In a separate line of research, the peripheral physiological responses listed above (and others) are considered to comprise biological aspects of the canonical *stress response*: they are evoked when environmental demands tax or exceed an individuals' ability to cope in order to prepare or motivate the individual to respond to changing environmental contexts and life circumstances [21]. In the context of emotional responses, these stressor-evoked peripheral physiological adjustments are adaptive insofar as they provide the individual with energy and metabolic support to respond to changes in the environment. However, it is thought that prolonged or repeated experience of stress and negative emotions may induce pathological changes in the heart and vasculature via activation of these physiological pathways [22]. For example, there are appreciable individual differences in peripheral blood pressure responses to acute stressors; moreover, individuals with a tendency to show larger and perhaps more sustained (longer lasting) physiological stress responses have increased risk for future incident CVD [23]. Accordingly, these and other perspectives on psychological *stress* have the goal of identifying components of negative emotions that translate into peripheral physiological responses and hence CVD risk.

Importantly, however, for emotional or stressful stimuli to be translated into downstream physiological responses and hence CVD risk, they must first be processed by the brain [24]. Hence, the brain represents an integral yet relatively underappreciated component in the emotion-CVD link [25]. Drawing from preclinical animal models of stress and CVD, a growing line of research aims to delineate the brain circuits jointly involved in generating and regulating stress and negative emotions, as well as in generating and regulating subsequent peripheral physiological responses. These neurobiological accounts and their accompanying brain imaging studies, reviewed below, indicate that there are overlapping neural circuits for negative emotion and CVD risk, respectively.

Neural Substrates of Negative Emotion and Psychological Stress

There is not a complete agreement of how negative emotions and mood states are generated and regulated in the brain. Nonetheless, many leading neurobiological models attribute emotional and stress processing to a core brain circuit comprising brainstem and subcortical regions including the amygdala, hypothalamus, periaqueductal gray (PAG), as well as cortical regions including the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and insula (Fig. 1) [26]. Hence, it is not plausible that there is any single brain region for negative emotions in particular. Rather, emotional and stressful experiences engage circuit-level *patterns* in the brain, and these patterns likely vary across contexts and

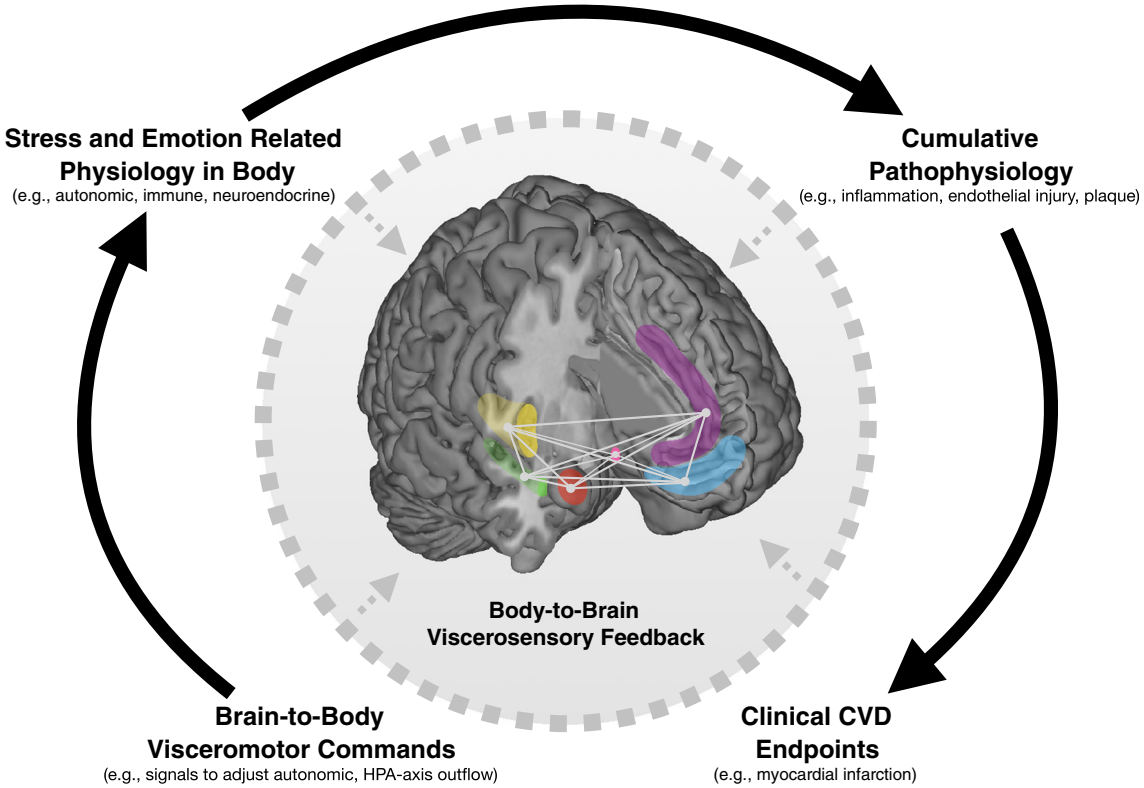

Fig. 1 Neuroanatomically connected limbic and cortical brain regions linking negative emotion, psychological stress, and regulation of peripheral physiology. Highlighted are limbic regions including the amygdala (*red*), hippocampus (*green*), and hypothalamus (*pink*) as well as cortical regions including the insula (*yellow*), anterior cingulate cortex (*purple*), and ventromedial prefrontal cortex (*blue*). Negative emotion and psychological stress engage these regions via changes in (1) local (within-region) activity, (2) distributed and patterned (across-region) activity, and (3) network-level interactions between regions over time. These responses issue brain-to-body visceromotor commands via specific brainstem nuclei to influence physiology in peripheral organs. Exaggerated or prolonged engagement of these responses promotes cumulative pathophysiology and future clinical CVD endpoints. Along this pathway, the effect of stress and negative emotion on the body affects the brain via body-to-brain viscerosensory feedback (*dotted arrows*), including baroreceptor firing, recruitment of circulating mediators of systemic inflammation into the brain, and brain structural damage/remodeling following myocardial infarction

individuals [27]. Moreover, these patterns of neural responses within and across the above brain regions may be most important for emotion and emotion-associated risk for CVD.

Notwithstanding, of particular relevance to understanding the affective neurobiology of CVD risk is the role of the amygdala. The amygdala (Fig. 1, red) is thought to be involved in assigning salience and relevance to environmental stimuli [28]. In particular, the amygdala is critical for pairing fearful stimuli and situations with appropriate responses [29]. Moreover, the amygdala issues neuroanatomical connections to the regions listed above, particularly the mPFC (Fig. 1, blue) [30–32]. Animal models suggest that lesions to the amygdala associate with impaired physiological and behavioral responses to emotional stimuli [33]; in contrast, electrical stimulation of the amygdala in humans and animals results in an array of subjective, behavioral, and downstream physiological responses including feelings of fear and anxiety, altered respiration, and increased heart rate and blood pressure [34]. Finally, many, but not all, human brain imaging studies show that negative emotional states reliably evoke activity within the amygdala [35–37], and alterations in amygdala responsivity are consistently observed in clinical depression and other affective disorders [38]. Collectively, the amygdala is a major focus in neuroscience research linking emotion to peripheral physiology.

Parallel to subcortical and brainstem structures are regions within the cortex, particularly the mPFC, ACC, and insula, that are involved in negative emotion. Moreover, substantial human brain imaging evidence indicates that these cortical regions represent and regulate downstream visceral physiological signals, especially those of the autonomic, vascular, neuroendocrine, and immune systems [39, 40].

Briefly, the mPFC and ACC (Fig. 1, blue and purple, respectively) are thought to be involved in processes including executive control, conflict monitoring, and the expression and regulation of negative emotion [41–44]. Regarding the latter process, the mPFC and ACC are critically implicated in the regulation of negative emotion, in particular cognitive reappraisal [45]. Cognitive reappraisal is a major clinical focus of behavioral interventions for depression and other affective disorders [46], and individual differences in the tendency to use cognitive regulation of emotion associates with preclinical

markers of CVD [47]; hence, the role of these cortical structures in emotion *regulation* and CVD risk is an emerging line of research. Separately, the mPFC and ACC issue 'brain-to-body' visceromotor commands in the form of autonomic and cardiovascular responses to environmental stimuli [48–50]. In particular, dorsal and ventral divisions of the ACC and mPFC may be involved in generating sympathetic and parasympathetic responses to stimuli, respectively [25]. Stimulation of the ventral mPFC (vmPFC) appears to reduce sympathetic tone and arterial pressure [51, 52]. Neurological patients with focal damage to areas in the dorsal ACC exhibit altered (i.e., "blunted") autonomic and cardiovascular responses to effortful cognitive tasks [53], perhaps indicating that more dorsal and midline cortical territories participate in generating sympathetic nervous system responding.

Another cortical brain region implicated in emotion and CVD risk is the insula (Fig. 1, yellow). In the context of emotion, the insula integrates 'body-to-brain' viscerosensory feedback into subjective emotional states [54, 55]. Specifically, viscerosensory feedback (e.g., autonomic, immune) conveying bodily states is sensed by the posterior insula and subsequently integrated and interpreted by the anterior insula. The process by which viscerosensory feedback is sensed and processed is known as interoception, and hence, the insula is considered to be an 'interoceptive cortex' [56, 57]. In the context of emotion, viscerosensory feedback shapes feeling states (e.g., fatigue), and biases motivations and drives to maintain optimal functioning [58]. Separately, the insula is involved in regulating cardiac function [59••]. Interestingly, several studies have found that stroke patients with infarctions localized to the insula, when compared to patients with infarctions in other brain regions, exhibit altered autonomic tone, elevated blood pressure, and more complex arrhythmias [60–62]. Moreover, stimulating the insula can induce cardiac arrhythmias as well as structural damage to cells of the heart (myocytolysis) [63]. Along these lines, it has been suggested that the insula may be involved in acute emotion-induced cardiac alterations, arrhythmias, and sudden death, including Takotsubo cardiomyopathy [64].

Taken together, brain substrates for emotion and CVD risk are not limited to evolutionarily 'old' subcortical and brainstem structures, but additionally implicate cortical and insular regions and networks involved in higher-order cognitive, emotional, and social behavioral processes [65].

Brain Imaging Studies of Emotion, Stress, and CVD

Drawing from the evidence linking emotional processes to CVD risk as described above, an emerging body of brain imaging research examines brain circuits jointly implicated in processing emotional and stressful experiences as well as regulating physiology that is involved in CVD [66, 67]. To this end, such brain imaging studies typically employ behavioral task paradigms in the scanner, requiring participants to view emotional or aversive pictures or film clips [68], complete difficult cognitive tasks under unpredictable time pressure and negative feedback [69], prepare a difficult speech before an unsupportive panel of judges [68], or respond to social exclusion during a computerized group interactions [70]. Further, these studies examine an array of peripheral physiological systems that are engaged by negative emotion and also relate to CVD pathophysiology, including heart rate [71], heart rate variability [72], cardiac contractility [73], baroreflex sensitivity [74], and blood pressure [75]. Broadly, these studies consistently report brain regions, particularly those described above, that relate to peripheral physiology during emotional and stressful experiences [74, 76, 77]. For example, a recent study observed an association between amygdala responses during the processing of threatening faces with circulating levels of C-reactive protein (CRP) [78], a marker of systemic inflammation known to predict incident CVD independently of traditional CVD risk factors [79]. In another study, negative emotion inductions engaged areas in the mPFC, insula, and PAG, and responses in these areas associated with changes in high-frequency heart rate variability [80], an indirect or surrogate index of cardiac parasympathetic autonomic nervous system function that is linked to CVD risk [81].

Other brain imaging studies examine associations of emotion processing with markers of preclinical CVD pathophysiology. In one study, amygdala responses during the processing of emotional faces associated with carotid intima-media thickness (cIMT), a preclinical marker of CVD risk [82]. In another study, activity in the dorsal subdivision of the ACC (dACC) during cognitive regulation of negative emotional stimuli associated with cIMT [83]. In the latter study, the observed association was statistically mediated by circulating levels of the pro-inflammatory cytokine interleukin(IL)-6. Several other regions in the mPFC, ACC, and insula associated with IL-6, but not with cIMT. Notably, however, this study failed to replicate the above association between amygdala activity during the processing of negative emotional stimuli and cIMT, indicating that single brain areas including the amygdala may not be uniformly associated with CVD risk across all contexts and subject populations.

While the above studies are promising insofar as they identify candidate brain regions linking emotion to CVD, nearly all are cross sectional, which limits generating causal interpretations. As mentioned previously, some of the candidate brain regions reviewed here are implicated in relaying and representing viscerosensory feedback to the brain; hence, it is plausible that preclinical changes in peripheral CVD risk factors (e.g., inflammatory or vascular state) could influence, in a body-to-brain manner, brain activity observed in response

to emotion [39]. Accordingly, to better interrogate the directionality of these brain-body pathways, what is needed are longitudinal brain imaging studies demonstrating that functional activity in brain circuits involved in negative emotion *precede* the development of CVD, or otherwise *predict* clinical outcomes in CVD patients.

The only study so far to take a longitudinal approach to these questions used a brain imaging method called positron emission tomography to examine resting metabolism of the amygdala in a sample of nearly 300 individuals [84••]. This study showed that higher resting activity in the amygdala at baseline was associated with a greater incidence of CVD events, defined as coronary death, myocardial infarction, coronary insufficiency, angina, cerebrovascular accidents, revascularization, peripheral artery disease, and heart failure, over a median follow-up period of 3.7 years. Importantly, the predictive utility of resting amygdala activity on these subsequent events remained following statistical adjustment for several traditional CVD risk factors at baseline. Finally, the relation between baseline amygdala activity and CVD event incidence was statistically mediated by bone marrow activity and arterial inflammation, and amygdala activity was positively associated with increased symptoms of perceived stress in a subset of participants. In summary, this study provided crucial longitudinal evidence in a clinical population linking neural substrates of negative emotion to objective CVD outcomes, and moreover identified physiological pathways that plausibly mediate this longitudinal risk.

Toward Brain Networks and Multivariate Patterns for Predicting CVD Risk

Thus far, the majority of brain imaging research on negative emotion, stress reactivity, and CVD has focused on mean levels of activity within discrete regions of the brain. Two emerging lines of research aim to expand current knowledge using novel conceptual and statistical approaches: formulating the brain into *networks* of *connections* between brain regions, as well as examining *patterns of activity* across distinct brain regions.

First, brain circuits involved in emotional responses and physiological control may be conceptualized as *networks*. These networks comprise brain regions that are structurally connected via white matter fibers (i.e., structural connectivity networks [85]) as well as brain regions whose observed activities correlate with each other over time (i.e., functional connectivity networks [86]). The reformulation of brain regions into networks and their resulting connections attracts substantial interest, as metrics of communication *between* brain regions might estimate underlying neuronal processes more accurately than activity levels *within* brain regions [87].

As mentioned above, candidate brain regions involved in emotion and CVD risk are richly interconnected. Hence, metrics of structural and functional connectivity between these brain regions may more accurately estimate biobehavioral risk in the context of negative emotions and stress. Indeed, psychological stress consistently alters functional connectivity between the amygdala, insula, ACC, and mPFC, and changes in these estimates of functional connectivity relate to downstream autonomic and cardiovascular reactivity (for review, see [66]). Several of these regions can be grouped into a *corticolimbic circuit* involving limbic (subcortical) regions such as the amygdala and hippocampus, as well as neuroanatomically connected cortical regions in the ACC and mPFC. This circuit is involved in emotion regulation, stress reactivity, and control over peripheral autonomic and cardiovascular physiology [88, 89]. Connections between these regions as well as the insula, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla have moreover been historically described as comprising a *central autonomic network* [90]. Several brain imaging studies have linked connectivity across this network with peripheral physiology and CVD. For example, during a cognitive stressor task, individuals with exaggerated blood pressure responses also exhibited increased functional connectivity (i.e., cross-correlation) between the amygdala and other regions including the mPFC, insula, hippocampus, and pons [91]. Similarly, during a task in which participants received negative social feedback, individuals with greater IL-6 responses to the task also exhibited greater functional connectivity between the amygdala and mPFC [92]. Collectively, these and other studies suggest that functional connectivity between subcortical (i.e., amygdala) and cortical (e.g., mPFC) regions may link negative emotional states to peripheral physiological pathways as well as preclinical markers for CVD.

Parallel to the above are advances in statistical approaches to characterizing *patterns of brain activity*. These statistical approaches contend that complex psychological phenomena, such as negative emotions, may be expressed in the brain by *distributed patterns*, or *signatures*, of activity across multiple regions. Due to the multivariate nature of these brain patterns, studies typically employ machine learning algorithms to examine the predictive utility on unseen, out-of-sample observations. Similar to the above argument for brain networks, it is thought that patterns of neural responses across the entire brain may be important to consider above-and-beyond those observed in individual regions [93].

Indeed, several 'brain signatures' have recently been generated in the context of emotion and CVD. In one study, a brain signature encompassing the amygdala, insula, ACC, mPFC, as well as other regions, predicted subjective response to viewing negative affective pictures [94]. In the context of peripheral physiology, a separate recent study identified a

brain signature comprising the dACC, ventral mPFC (vmPFC), and brainstem that predicted peripheral autonomic (i.e., heart rate, skin conductance) responses to a social stressor over time [95•]. Moving toward individual differences in physiological reactivity, a recent study identified a brain signature for interindividual variability in cardiovascular responses to stress, which comprised similar regions within the ACC and vmPFC, as well as the insula [96•]. Importantly, brain signatures identified in these studies were able to accurately predict emotional and physiological responses in participants who were not used to model and generate the brain signature, showing that these brain signatures are generalizable. Moreover, these multivariate patterns predicted responses better than individual regions. To our knowledge, no studies have yet leveraged these statistical techniques toward predicting future preclinical CVD factors or clinical incidence; hence, this is a promising avenue for future research.

Open Questions and Future Directions

So far, brain imaging studies reviewed above suggest that brain regions involved in negative emotion and stress, as well as their network-level interactions and distributed patterns of activity, may associate with concurrent and future CVD risk. However, several open questions remain regarding the precise nature of these observed relationships, their reliability and generalizability, their relation to downstream physiology and health behaviors, as well as their clinical utility.

First, while the present review focuses on brain circuits for immediate emotional responses and downstream peripheral physiology, there are nonetheless other indirect pathways that could plausibly link emotion to CVD risk that implicate entirely independent sets of brain regions and circuits. One clear example points to behavioral evidence linking emotion to *health behaviors* that are known to elevate CVD risk, in particular diet, physical activity, alcohol intake, and smoking habits [97]. These behaviors and lifestyles are influenced by emotions but engage somewhat distinct brain circuits from the set reviewed here. Specifically, a corticostriatal network, including components of the basal ganglia and neuroanatomically connected divisions of the mPFC, is implicated in reward valuation, craving, reinforcement learning, and motor planning [98]. Alterations in this corticostriatal circuitry have been extensively documented in mood and stress-related disorders [99] and could plausibly be implicated in biasing individuals toward adopting unhealthy behaviors following negative emotional states [100]. Neural activity in these brain areas has also been linked to systemic inflammation [101]. However, to our knowledge, no brain imaging studies have yet examined this specific link in the context of emotion and CVD.

Second, there is a lack of consensus on the generalizability and reliability of task paradigms that evoke stress and negative emotion in the above reviewed studies. For example, anger and hostility have long been proposed to confer CVD risk, but no studies have used anger provocation tasks during brain imaging in order to link brain activity to physiology and disease markers. It is unclear whether brain circuits engaged by anger would similarly associate with peripheral physiology and CVD risk markers. In contrast, a separate and emerging brain imaging method examines brain activity and functional connectivity networks *at rest* [102]. Connectivity across these networks at rest, also called *intrinsic connectivity networks*, has been linked to individual differences in emotion as well as peripheral markers of CVD risk (e.g., inflammation, heart rate variability) [103–105]. To this end, it is unclear whether individual differences in these brain circuits measured at rest, including the longitudinal study discussed above, are comparable or generalizable to individual differences evoked by emotions or stress in the context of CVD. Similarly, while the reliability of some of the above brain imaging tasks have been previously examined [106], there are open questions about whether other brain imaging studies of other emotion or emotion regulation tasks reliably reveal individual difference phenotypes that effectively stratify participants according to emotional responsivity and CVD risk.

Third, nearly all the extant brain imaging research on emotion and CVD focuses on risk factors and clinical occurrence, with little or no focus on functional or clinical prognosis for participants currently affected by chronic affective disorders or clinical CVD. Hence, future research is needed to characterize the role of these and other brain circuits in clinical samples. To this end, a recent study examined neural correlates of mental stress-induced myocardial ischemia (MI) in coronary heart disease patients [107•]. This study found that patients exhibiting mental stress-induced MI also demonstrated exaggerated responsivity to stress in prefrontal cortical regions including the ACC. Whether these differences in stress-induced brain responsivity in this clinical sample relate to clinical prognosis is an exciting question for future study. Separately, as the majority of the above brain imaging studies was conducted on psychiatrically healthy community samples, it is relatively unknown whether these findings extend to individuals diagnosed with chronic psychiatric disorders. Along these lines, acute CVD events confer elevated risk for poor mental health outcomes (e.g., posttraumatic stress disorder) which in turn is associated with risk for recurrent CVD events [108]; hence, future studies may examine whether brain changes or remodeling following CVD events prospectively predict mental and physical health outcomes.

Finally, future studies might examine surrogate or intermediate markers in psychosocial interventions designed to reduce negative emotion or improve emotion regulation (e.g., cognitive behavioral therapy, mindfulness meditation) prior to

later stage endpoints, particularly in patients with clinical depression or other affective disorders who are at elevated CVD risk [109].

Conclusions

The recent research presented in this review adds to a growing body of evidence indicating that activity within specific brain regions and circuits may link negative emotional and mood states and psychological stress to CVD risk. However, this evidence largely relies on cross-sectional studies on individuals without CVD and does not systematically examine potential mediating pathways or moderating influences. Future studies that adopt longitudinal designs, employ advanced statistical techniques, and consider potential mediating pathways across diverse healthy and clinical samples stand to greatly increase our understanding of the brain-body pathways linking emotion with CVD [25].

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Compliance with Ethical Standards

Conflict of Interest Thomas E. Kraynak, Anna L. Marsland, and Peter J. Gianaros declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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