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SPECIAL ARTICLE

Central nervous system involvement in the autonomic responses to psychological distress

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Abstract Psychological distress can trigger acute coronary syndromes and sudden cardiac death in vulnerable patients. The primary pathophysiological mechanism that plays a role in stress-induced cardiac events involves the autonomic nervous system, particularly disproportional sympathetic activation and parasympathetic withdrawal. This article describes the relation between psychological distress and autonomic nervous system function, with a focus on subsequent adverse cardiovascular outcomes. The role of the central nervous system in these associations is addressed, and a systematic review is presented of studies examining the association between stress-induced central nervous system responses measured by neuroimaging techniques and autonomic nervous system activation. Results of the systematic review indicate that the primary brain areas involved in the autonomic component of the brain-heart association are the insula, medial prefrontal cortex, and cerebellum (based on 121 participants across three studies that fitted the inclusion criteria). Other areas involved in stress-induced autonomic modulation are the (anterior) cingulate cortex, parietal cortex, somatomotor cortex/precentral gyrus, and temporal cortex. The interaction between central and autonomic nervous system responses may have implications for further investigations of the brain-heart associations and mechanisms by which acute and chronic psychological distress increase the risk of myocardial infarction, cardiac arrhythmias, and sudden cardiac death.

Keywords Autonomic nervous system · Mental stress · Central autonomic network · Heart rate variability · Functional brain imaging

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Introduction

Acute coronary syndromes and sudden cardiac death can be triggered by acute psychological distress, such as intense emotions, anger and mental stress [1, 2]. In addition to these acute psychological triggers, epidemiological evidence shows that episodes of depression and personality factors, such as hostility, are associated with increased risks of acute coronary syndromes and sudden cardiac death [3, 4]. These elevated risks associated with psychological factors may result from disproportional autonomic nervous system activity, particularly sympathetic nervous system activation and parasympathetic withdrawal [5, 6]. The adverse cardiovascular effects of stress-induced autonomic nervous system activity can result from the disproportional magnitude of the autonomic response to exogenous challenges and/or the vulnerability of individuals for adverse events based on underlying (sub)clinical coronary artery disease or myocardial tissue abnormalities. The connection between the central nervous system and the heart is supported by clinical observations in patients with various neurological conditions such as stroke, subarachnoid haemorrhage, epilepsy, and those with substantially elevated intracranial pressure, who demonstrate substantial ECG abnormalities and, in rare

cases, cardiac pathology. These cardiac abnormalities in acute neurological conditions are mediated by the autonomic nervous system [1]. The current article describes the relation between psychological distress and autonomic nervous system responses, with a focus on subsequent adverse cardiovascular outcomes. We address the role of the central nervous system and present a systematic review of studies examining the association between stress-induced central nervous system responses, measured by neuroimaging techniques, and autonomic nervous system function.

Acute mental stress can induce myocardial ischaemia in 30-70% of patients with coronary artery disease [5]. Mental stress-induced ischaemia is generally asymptomatic, occurs at low cardiac demand, involves reduced myocardial blood supply (via epicardial coronary constriction or impaired function of the cardiac microvasculature), and is associated with an unfavourable prognosis [5]. Moreover, mental stress can induce cardiac electrical instability, as assessed by T-wave alternans, even in the absence of myocardial ischaemia, and this cardiac electrical instability may lead to life-threatening arrhythmias [7].

Autonomic nervous system dysregulation (disproportional sympathetic activation and/or parasympathetic withdrawal) is among the primary pathophysiological mechanisms of mental stress-triggered cardiac events. Autonomic nervous system modulation can be measured using heart rate variability (HRV) [8]. High-frequency (HF) HRV is an index of parasympathetic cardiac activity [8, 9], and low-frequency (LF) HRV has been used as a measure of sympathetic activity, although this index also contains parasympathetic components [8–10]. Acute psychological distress and negative emotions (e.g., anger) result in altered autonomic nervous system activity, characterised by HRV indices of parasympathetic withdrawal and sympathetic activity, whereas positive emotions result in increased parasympathetic nervous system activity [11]. This autonomic nervous system response pattern is not consistently found, however, and individual response differences may be a consequence of psychological or physiological background factors or unintended divergent emotional responses induced by tasks that are designed to elicit a particular emotional state [12].

Autonomic dysregulation is a short-term and long-term risk factor for myocardial ischaemia and arrhythmias. Mental stress-induced myocardial ischaemia during daily life activities is preceded by a decrease in HF-HRV suggesting parasympathetic withdrawal [13]. In addition, HRV-based indices of autonomic dysregulation are associated with the long-term risk of various cardiovascular disorders, including myocardial infarction and arrhythmias [14, 15], although some negative studies have been reported as well (e.g., [16]). A reverse pathway is also well documented, such that myocardial ischaemia results in autonomic dysregulation [17].

The main central nervous system components associated with autonomic regulation constitute the Central Autonomic Network (CAN). The CAN is a functional network of cortical and subcortical central nervous system structures that receives information from humoural, visceral, and environmental sources, and integrates these inputs to generate autonomic, endocrine, and behavioural outputs [18, 19]. Table 1 displays the main components of the CAN (as established from animal studies). Bidirectional interconnections exist between CAN structures, enabling the integration of sensory inputs from the periphery with processed information from paralimbic brain areas. Hence, the CAN is capable of responding in an integrative manner to both internal and external stimuli. The main effectors of the CAN are the preganglionic sympathetic and parasympathetic neurons, which innervate the heart via the stellate ganglia and the vagus nerve. We hypothesise that the (human equivalent of the) CAN is an important system in the relationship between psychological factors such as depression and acute

Table 1 Main components of the Central Autonomic Network

Supratentorial components	Cerebral cortex	Anterior cingulate cortex
		Insular cortex
		Ventromedial prefrontal (orbitofrontal) cortex
	Amygdala	Central nucleus
	Basal forebrain	Bed nucleus of the stria terminalis
Brain stem components	Hypothalamus	Paraventricular nucleus and other nuclei
	Midbrain	Periaqueductal grey matter
	Pons	Parabrachial nucleus and A5 group
	Medulla	Nucleus of the solitary tract
		Nucleus ambiguus
		Dorsal motor nucleus of the vagus
		Ventrolateral medulla
		Ventromedial medulla
		Intermediate reticular zone

distress, and autonomic nervous system-related cardiovascular reactivity.

Systematic review

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT), now enable the study of specific cerebral regions involved in the brain-heart connection in humans in response to experimentally induced acute stress, including structures involved in the CAN. These responses can be investigated by correlating measures of regional cerebral blood flow (rCBF) or blood oxygen level-dependent (BOLD) signals in the brain with cardiovascular measures such as heart rate, blood pressure, or HRV. We performed a systematic review of the literature to reveal brain areas that are associated with HRV during mental stress-inducing tasks. This systematic literature review was conducted in accordance with the PRISMA guidelines [20], which are in line with other review strategies such as the Cochrane criteria [21]. Research articles reporting on studies examining HRV and functional brain imaging during mental stress-inducing tasks were included in this review. Inclusion criteria for studies were: 1) original research articles (i.e. abstracts, posters, review articles, and methodological papers were excluded); 2) published in a peer-reviewed journal; and 3) abstract available in English (no other language constraints). Papers were excluded if: 1) the study was based on a clinical or otherwise selected sample; 2) performance of a mental challenge task was not part of the study; 3) there was no simultaneous determination of HRV and functional brain imaging measures; and 4) no correlational analyses were reported between HRV indices and measures of functional brain imaging. No other restrictions were applied regarding study designs.

Articles published between 1 January 1990 and 15 September 2012 (the date when the literature search was completed) were searched using the Medline database (PubMed). The following a priori determined search terms were used: ((“heart rate variability”) OR (“heart period variability”)) AND (brain) AND ((functional imaging) OR (fMRI) OR (PET) OR (SPECT)). The search was limited to studies involving human participants. A total of 55 articles were found during this first selection. Titles and abstracts were screened first and potentially eligible articles were examined in full text. Of the initial selection of 55 papers, seven were excluded because they were review papers or methodological papers, 25 because they were based on clinical or otherwise selected samples, 15 because they did not include a mental challenge task, and five because they did not measure HRV indices and functional brain imaging simultaneously or they did not report correlational analyses between HRV indices and measures of functional brain imaging. The reference lists of selected journal articles were inspected for additional published articles that fulfilled the inclusion criteria. This reference list search did not yield any additional studies. Therefore, three papers were included in the final selection covering data on 121 participants. Data included in the article and any supplementary materials were extracted for patient characteristics, methods, and results. Table 2 shows a summary of the stress protocol, the imaging methodology, the HRV indices and the results of the studies that met the criteria for this review.

These studies revealed several brain areas involved in the association between the psychological stress response and autonomic nervous system modulation. The three areas that consistently correlated with HRV in all three studies were: 1) the insula, 2) the medial prefrontal cortex, and 3) the cerebellum. The insula, which is part of the CAN, functions as the primary viscerosensory cortex and as a higher-order somatosensory cortex. This paralimbic region has afferent and efferent connections with many other CAN areas and can thereby affect cardiovascular function [18]. The (ventro)medial prefrontal cortex is part of the CAN and is involved in high-level emotional and cognitive functions. This paralimbic region integrates exteroceptive and viscerosomatic information, via connections with the amygdala and other CAN regions [18]. The cerebellum is not part of the CAN, but may be involved in stress-induced autonomic activation by 1) modulation related to motor activity and balance and 2) inter-connections with CAN structures such as the hypothalamus [22]. In addition to the insula, medial prefrontal cortex, and cerebellum, two of the selected studies documented involvement of the (anterior) cingulate cortex, parietal cortex, somatomotor cortex/precentral gyrus, and temporal cortex.

These results are in agreement with other studies investigating HRV and functional brain imaging responses to various tasks that did not meet the criteria for this systematic review. For example, Matthews and colleagues correlated HRV and fMRI BOLD signal changes, which were measured during two separate task sessions. A positive correlation was found between peak HF-HRV and fMRI BOLD signal in the left ventral anterior cingulate cortex during a counting Stroop task [23]. No correlational analyses were reported for other brain areas. Napadow and colleagues used novel methodologies to study continuous HRV and cardiac-gated fMRI BOLD signals during a physical perturbation task (dynamic handgrip exercise). Changes in HF-HRV were positively related to fMRI BOLD signal in the right dorsomedial and dorsolateral prefrontal cortex, left amygdala, left hypothalamus and right anterior hippocampus, and negative associations were found between changes in HF-HRV and the left posterior insula, right cerebellum, right

Table 2 Overview of the methods and results of studies included in the systematic review of research on stress-induced brain responses and autonomic nervous system activity

Reference	Stressor tasks	Participants	Imaging method	HRV indices	Brain areas associated with HRV
Critchley et al. Brain 2003 [27]	N-back task and handgrip task (2 difficulty levels); results of tasks aggregated	*N*=6 2 females 4 males age: 33±2 year	fMRI, BOLD	HF-HRV LF-HRV *Continuous*	Positive associations: right dorsomedial prefrontal cortex/supplementary motor area (*t* score: 4.27), right cerebellar cortex (*t* score: 4.83), left cingulate, superior parietal lobule, left fusiform gyrus, left somatomotor cortex, right somatosensory cortex with HF-HRV; insula (*t* scores: L 5.62, R 4.38), anterior cingulate, left mediodorsal thalamus, right medial temporal pole, right somatosensory cortex, right inferior parietal lobule, left superior temporal gyrus with LF-HRV
Gianaros et al. Psychophysiology 2004 [28]	Verbal and spatial working-memory tasks (2 difficulty levels each) and control task	*N*=93 39 females 54 males age: 50–70 year	PET, rCBF	HF-HRV (ln)	Positive associations: left insula (*t* score: 4.72), right ventromedial prefrontal cortex (*t* score: 5.14), left amygdala-hippocampal complex; Negative associations: right cerebellum (*t* score: -4.61)
Nugent et al. International Journal of Psychophysiology 2011 [29]	N-back task and handgrip task (3 difficulty levels each) and fixation task	*N*=22 7 females 15 males age: 31±9 year	PET, rCBF	HF-HRV (ln) LF-HRV (ln) LF/HF ratio RMSSD	Positive associations: *N-back task*: precentral gyrus with LF/HF ratio; inferior parietal cortex, medial temporal gyrus, ventrolateral prefrontal cortex with RMSSD; *Handgrip task*: anterior insula (*Z* score: 4.31) with HF-HRV; dorsomedial prefrontal cortex (*Z* score: 4.09) with LF-HRV; medial cerebellum (*Z* score: 3.72) with LF/HF ratio; dorsal anterior cingulate, precentral gyrus with RMSSD; Negative associations: *N-back task*: cerebellar vermis (declive) (*Z* score: -4.33) with HF-HRV; *Handgrip task*: inferior parietal cortex with LF-HRV; medial temporal gyrus with LF/HF ratio

Initial selection revealed 55 studies of which three met the inclusion criteria (see text). The three studies that made the final selection included responses of 121 apparently healthy participants; *BOLD* Blood oxygen level-dependent; *fMRI* Functional magnetic resonance imaging; *HF* High frequency; *HRV* Heart rate variability; *L* Left; *LF* Low frequency; *ln* Natural logarithm; *N-back task* A challenging working-memory task; *PET* Positron emission tomography; *R* Right, *rCBF* Regional cerebral blood flow; *RMSSD* Root mean square of the standard deviation. t scores or Z scores are shown for the three areas that were consistently found to be associated with HRV in all three studies

mediodorsal thalamus, right parabrachial nucleus/locus ceruleus, left periaqueductal grey, right posterior hippocampus, left caudate nucleus, right septal nucleus, and right medial temporal gyrus [22]. Moreover, Lane and colleagues reported that during emotion induction tasks, HF-HRV correlates with emotion-specific rCBF in the left insula, the medial prefrontal cortex, caudate nucleus, and midbrain (including periaqueductal grey) [24].

The findings of the present systematic review and other studies on HRV and functional brain imaging are consistent with research on the brain areas implicated in stressor-evoked blood pressure reactivity [25]. Those studies indicated that the insula, cingulate cortex, and amygdala are the core components implicated in the blood pressure responses to stress. Blood pressure responses were also related to altered rCBF or BOLD signal changes in the medial, lateral, and dorsal prefrontal cortices, the parietal cortex, occipital cortex, somatosensory cortex, cuneus, lentiform area, caudate, thalamus, and cerebellum [25]. Interpretation and generalisation of the results of the present systematic review and other summary articles in this area are complicated by methodological differences, the potential of statistical type I error related to the analysis of multiple brain structures, and the relatively small number of studies that simultaneously assessed cardiovascular measures and brain responses to psychological distress.

Conclusions

The brain-heart connection plays an important role in the interaction between environmental psychological and physical challenges, and the individual autonomic responses to these challenges. Brain areas of particular importance in the

autonomic component of the brain-heart association are the insula, medial prefrontal cortex, and cerebellum. Other areas potentially involved in stress-induced autonomic modulation are the (anterior) cingulate cortex, parietal cortex, somatomotor cortex/precentral gyrus, and temporal cortex. These results are consistent with our hypothesis that CAN areas are important in the relationship between psychological factors and autonomic nervous system-related cardiovascular reactivity. In addition, the results point to areas that are not part of the CAN, such as the cerebellum and various cortical areas. These cortical areas could be important in the integration of psychological factors and the autonomic nervous system, possibly through connections with the CAN. The time trajectories of psychological and physical challenges on brain activation and autonomic responses need further investigation, requiring innovations in short-term assessments of autonomic tone that parallel the rapid cerebral responses documented by neuroimaging [26]. Furthermore, more information is needed regarding the nature of the emotional response and the role of cerebral lateralisation in the brain-heart connection [12, 23, 24]. The conclusions of this review are based on data from healthy individuals, and the results may be relevant in the setting of cardiovascular diseases (e.g., myocardial ischaemia and infarction and life-threatening arrhythmias) and neurological and psychiatric disorders. It is possible that the brain-heart connection becomes maladaptive in response to repeated exposure to uncontrollable psychological distress and that the autonomic dysregulation associated with these exposures increases the risk of myocardial ischaemia and cardiac arrhythmias in patients with underlying (sub)clinical anatomical or structural vulnerability. More information is needed about the relevance of these brain-heart associations for the patient's quality of life, particularly mood states, cognitive function, physical activity levels, and fatigue. Systematic experimental and clinical investigation of the brain-heart associations will further elucidate the autonomic and central nervous system mechanisms by which acute and chronic psychological distress increase the risk of myocardial infarction, cardiac arrhythmias, and sudden cardiac death.

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