ARTICLE

Forebrain Network Associated With Cardiovascular Control in Exercising Humans

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Key Points

- The successful adaptation to muscular exercise is marked by an immediate increase in heart rate caused, largely, by a rapid reduction in cardiovagal impact at the sinoatrial node. However, the mechanisms mediating this rapid neural response remain poorly understood.
- We have tested the hypothesis that a forebrain network modulates autonomic function during exercise in humans. Using functional neuroimaging methods with short-term handgrip exercise models and isolated muscle sensory nerve stimulation, we exposed neural activation patterns that correlate to heart rate patterns in the absence of sympathetic activation at the exercise onset.
- Key regions in this network are marked by reduced activity in the hippocampus, medial prefrontal cortex, dorsal insula cortex along with elevated activity in the anterior insula cortex. These patterns do not relate to muscle sensory representation. These novel data support the hypothesis of a cortical network that enables rapid cardiovascular adjustments at the exercise onset.

INTRODUCTION

Successful adaptation to muscular work requires cardiovascular adjustments that include elevated cardiac output and redirection of blood flow to active tissues. These adjustments are caused by targeted changes in autonomic nervous system outflow to various organs. Inappropriate autonomic adjustments to exercise can lead to inadequate hemodynamic responses, the failure to match the metabolic demands of working skeletal muscle with oxygen delivery, and impaired exercise tolerance.

A critical period of this adjustment phase is the first 10–30 s when heart rate (HR) increases rapidly, whereas sympathetic-mediated changes in vascular contractile state are delayed (1,2). Figure 1 provides an illustration of sympathetic nerve activity and cardiovascular adjustments to each of three 30-s bouts of isometric handgrip exercise in a representative young, healthy individual. The magnitude of the HR response during this onset period relates directly to the exercise intensity (1,3) and can be mitigated severely by vagal blockade but not sympathetic cardiac blockade (4,5). Therefore, this rapid HR response to exercise is mediated by a rapid reduction in cardiovagal dominance. This response also represents clinical interests. Specifically, the response is blunted severely in aging individuals (1) and in those with heart disease (6). As the cardiovascular adjustments during this period exert critical influence on oxygen usage in the active muscle (7), and slow oxygen uptake kinetics are associated with poor exercise intolerance (8), understanding the regulation of cardiac function at the exercise onset has important implications not only for general knowledge of neural control of the circulation but also of how this concept affects, or relates to, health and disease. This article illustrates our efforts to understand the cortical pathway(s) associated with this response.

Typically, changes in sympathetic-vagal balance early in exercise are thought to occur through brainstem neural pathways that engage the nucleus tractus solitarius, dorsal motor nucleus/nucleus ambiguous, caudal ventro-lateral medulla, and rostral ventro-lateral medulla that are involved in the negative feedback baroreflex (9) set point (10). However, the brainstem reflex model does not explain fully many observations such as the following: 1) the anticipatory rise in HR and respiration before the exercise onset, reported first by Krogh and Lindhard (11), who speculated the concept of "irradiating" neural control,
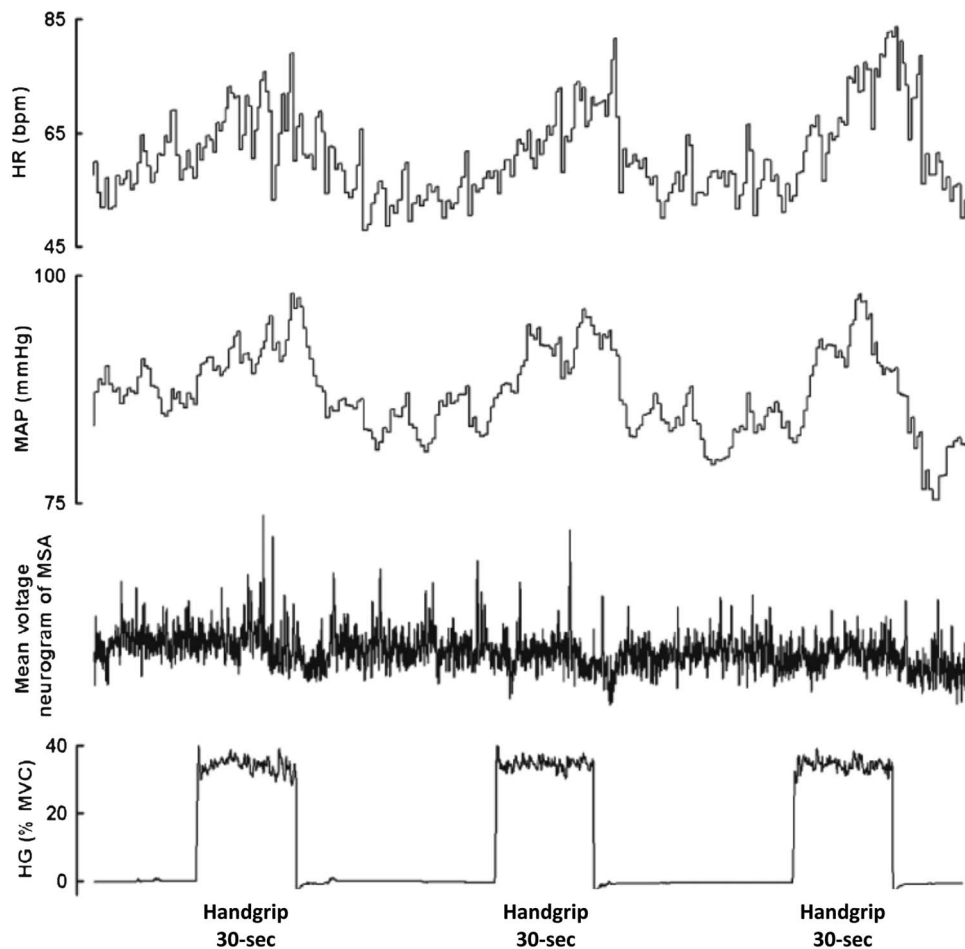
Figure 1. Time course of changes in heart rate (HR) and mean arterial pressure (MAP) during repeated 30-s bouts of handgrip exercise performed at 35% of maximal voluntary contraction (MVC) strength in a representative individual. Notice the reproducible changes in HR and MAP with minimal changes in efferent sympathetic nerve activity.

whereby region(s) of the cerebral cortex provided coordinated parallel and concurrent adjustments in respiratory and autonomic neural systems to support the volitional muscular activity; 2) the cardiovascular response during real, imagined, or inhibited muscular function (12–14); and 3) clinical observations of cardiac arrhythmias and sudden cardiac death in epilepsy, after stroke, or under severe emotional stress (see (15) for review). These observations provide strong rationale for studying the cerebral cortex as a modulator or determinant of cardiovascular control. This concept is supported by experimental data from decerebrate feline preparations (16) and a growing base of data from nonhuman experimental animal models performed in the last half of the 20th century (17–19) that indicate the presence of a cortical, or central, autonomic network (CAN) (20).

Although the specific regions within the CAN vary depending on the study model, each of the following have been implicated in this network: insula cortex (IC), medial prefrontal cortex (MPFC), amygdala, hippocampus (HC), anterior cingulate cortex (ACC), hypothalamic nuclei, periacqueductal gray, and the better known brainstem nuclei (see (15,21,22) for review). Based on these observations, we have tested the hypothesis that the rapid HR response to volitional exercise is supported by a forebrain neural network.

CORTICAL AUTONOMIC NETWORK AND EXERCISE

Functional Forebrain Neurocircuitry Associated With HR at the Exercise Onset

Our studies have used Blood Oxygenation Level-Dependent (BOLD) functional magnetic resonance imaging methods to observe regional changes in cortical activation patterns that can be correlated to a stimulus or a cardiovascular outcome such as HR.

Our first observations are provided in Figure 2 (3). This model explored the cortical activation patterns to repeated bouts of both 5% and 35% maximal voluntary contraction handgrip exercise. The 5% handgrip strength trial provided a minimal effort control to account for sensory and cognitive aspects of performing the handgrip exercise. This figure highlights four major sites of activation change that correlate with HR, namely, the left motor cortex (MC) (increased activity in accordance with right-handed exercise), the left IC, the ventral MPFC (vMPFC), and posterior cingulate cortex (PCC) (not shown are the right IC and thalamus). Two important observations can be made from these findings. First, some regions of the brain increase their state of activation, such as the MC and anterior IC. However, regions such as the MPFC and PCC are characterized by a reduction in activation relative to the prestimulus baseline period. Second, only the MPFC produced patterns of activation
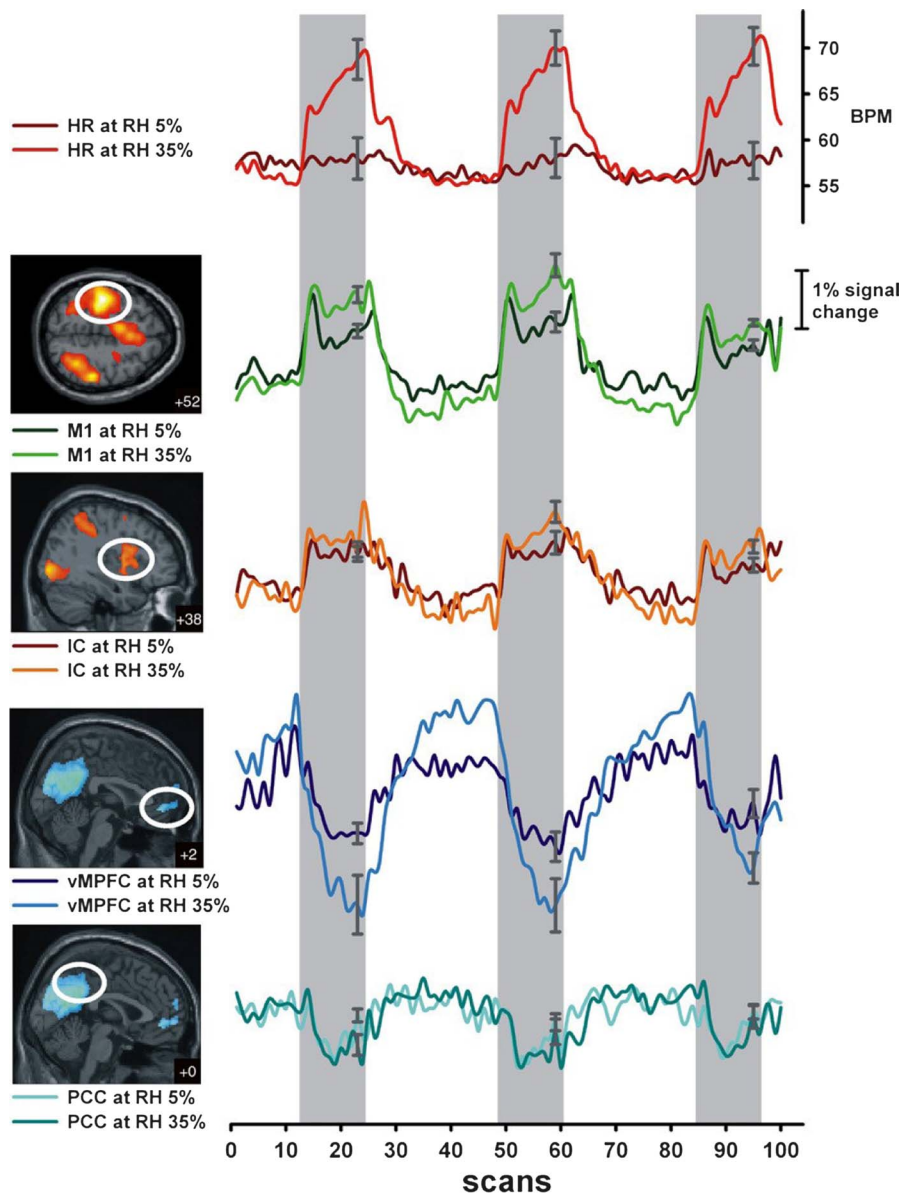
Figure 2. Averaged time course of the heart rate (HR) (top panel) and cortical responses during repeated 30-s trials of 5% and 35% exercise. The imaging panels show the averaged activity at the left motor cortex (M1), right insula (IC), ventral medial prefrontal cortex (vMPFC) and posterior cingulate cortex (PCC). Activity within the vMPFC and PCC were reduced during the exercise. Differences between the 5% and 35% trials were observed in the HR response and vMPFC activity but not PCC activity. The bars representing standard errors are only shown at the end of the exercise for clarity. The red-orange and blue-white brain highlights represent the activation and deactivation clusters, respectively. (Reprinted from (3). Copyright © 2007 Elsevier. Used with permission.)

(reduced activation) that scaled with the intensity of exercise and HR. Other regions that are observed frequently include reduced activity in the dorsal anterior cingulate (dACC), HC, and dorsal bilateral IC (21), as well as increased activity in the bilateral anterior IC. The reproducibility of these findings is presented in Figure 3, which provides a meta-analysis of 124 distinct individuals across nine studies performed in our laboratory (23). This figure provides a general overview of the regions considered to be the human CAN, at least in cardiovascular control studies. Using the same meta-analysis approach, we have illustrated the reproducibility of these regions and their association with HR and HR variability across many laboratories who studied cognitive, emotive, and physical stimuli (24). Based on limited data, these reported changes occur similarly in men and women, albeit to a smaller extent in women (3,25).

Therefore, there seems to be a group of cortical regions whose generalized activation patterns correlate with HR fluctuations, including the bilateral IC, MPFC, dACC, and HC. Other regions related to cardiac function during specific tasks that include emotive arousal (but not exercise *per se*) include the amygdala and dorsolateral prefrontal cortex (21).

The regions identified as a CAN for exercise generally are part of the "default mode network" (26). This default mode network is characterized by its high level of activity during vegetative periods, with regions that oscillate in synchrony. This corresponds to the understanding that the vegetative state involves high vagal outflow to the heart and low levels of sympathetic outflow. In a sample (n = 29) of apparently healthy individuals ranging in age from 18 to 80 years, we observed that the correlations of HR with activity patterns in the MPFC, HC, and

anterior IC during brief handgrips shared the same temporal pattern and were, therefore, functionally connected (27). These functional outcomes are supported by structural neuroimaging findings that indicate neural connections exist between the MPFC, HC, and PCC (28). Importantly, an analysis of effective connectivity, which provides a metric of temporal order to the patterns in the two regions, suggests that the MPFC changes occur before the HC, suggesting the direction of information in this context is from MPFC to HC. This observation suggests a dominant role for the MPFC in cardiovascular control. This interpretation is consistent with available experimental research in rodents. For example, electrical stimulation of the CA1 region of the HC in anesthetized rats elicited a variety of visceral or autonomic modifications, such as decreases in HR and increases in pulse pressure (29,30), but this effect only is observed in the presence of an intact MPFC (31). However, bilateral excitotoxin lesions of the rat MPFC (32) or surgical unilateral MPFC lesions in human patients (33) did not alter baseline HR or blood pressure. Therefore, the MPFC region seems to exert little direct impact on *baseline* cardiovascular stability but, rather, exerts obligatory influence on the ability of the CAN to exert its cardiovascular effects.

The depressor response to MPFC stimulation is enabled by cortico-brainstem projections that activate the intramedullary baroreflex pathway. Pharmacological lesion models (32), anterograde tracing methods (17), and electrophysiological recordings in rat models (34) illustrate that the vMPFC is involved in baroreflex control through excitatory pathways that elevate parasympathetic baroreflex function (35). Therefore, one may speculate that the MPFC may not be responsible for exerting direct tonic influence on cardiovascular control, but instead, acts as a critical relay center that modulates in real time the baroreflex set point in conjunction with, or because of, alterations in communications from the HC and IC regions. In this manner, high baseline MPFC activation (as part of the default mode network) would keep brainstem parasympathetic outflow at high levels. In contrast, reduced MPFC activation with volitional exercise would, logically, lead to reduced parasympathetic outflow.

But what of the HC? The direct role of this region in cardiovascular responses to stress remain speculative. The aforementioned description suggests that *elevating* HC neuronal activity through electrical stimulation will also elevate MPFC activity thereby causing a depressor cardiovascular outcome. In contrast, at the exercise onset, HC activity is *reduced*, which may be caused by reduced MPFC activity. The HC also may exert more direct effects. For example, neural tracing studies in rodents indicate neural connections exist between the HC and brainstem autonomic nuclei (36,37). However, the lack of information regarding the mechanisms mediating the need for an intact MPFC for physiologically relevant outcomes from HC stimulation, or more direct hippocampal effects on cardiovascular control, remain critical gaps in our knowledge.

Must the MPFC and HC act in synchrony to achieve a robust tachycardiac at the exercise onset? In limited studies, we have observed diminished HR responses to 35%–40% maximal strength handgrip contractions in older compared with younger individuals (1), a response that was diminished further in older adults with ischemic heart disease (6). In these older groups, the changes in MPFC and HC activity often were heterogenous such that a pattern of reduced activity was observed in only one of the two sites. Therefore, the smaller (or absent) HR responses to handgrip exercise in these groups may represent cortical "decoupling", similar to reports that suggest altered compensatory cortical activation patterns are needed in older adults to achieve similar behavioral outcomes in psychological tests (38). Notably, older individuals and those with ischemic heart disease also are characterized by low levels of baseline cardiovagal influence (39), suggesting an age and disease effect on baseline MPFC activity, which remains a possible explanation for a lack of *reduced* activation to handgrip in these groups; that is, there is little activity left to inhibit or withdraw. Much remains to be understood regarding the basic functioning of brain-heart interactions that could contribute to mechanistic knowledge regarding disease-related aberrations that include conditions of the heart (cardiac arrhythmias and ischemia) as well as brain and mind (*e.g.*, cognition and mental health disorders) (22).

The IC seems to hold a key role in integrating viscerosensory inputs with autonomic responses to exercise. Using anterograde tracing methods in a mouse model, Shipley (40) reported IC projections to the medullary solitary nucleus tract that contain preganglionic parasympathetic neurons. As well, the IC expresses a great deal of bidirectional neural connections with many limbic brain regions including the MPFC (41). Early structural studies using white matter degeneration in response to insula ablations suggest neural projections link the insula, frontal, parietal, temporal, cingular, and olfactory, as well as subcortical brain areas such as the HC and amygdala (42). Recent magnetic resonance tractography approaches suggest robust connections between the HC with the anterior and posterior IC (43) in nonhuman primates, findings that correspond with imaging-based measures of functional connectivity in humans (27). Nonetheless, reports using direct neural tracing methods have not supported the concept of direct neural projections between the IC and HC subregions (although they seem to exist for parahippocampal regions) (44).

Functionally, clinical lesion models and direct electrical stimulation models in both rodents and humans point to an important role for the IC in cardiac function (45). However, some results are contradictory. For example, using electrical stimulation of more than 100 sites in the IC of patients with epilepsy, Chouchou (46) reported that elevated activity (via electrical stimulation) of the anterior and median IC regions primarily caused bradycardia, with posterior IC stimulation primarily causing tachycardia. In contrast, as illustrated in Figure 3, volitional handgrip exercise that *elevates* HR also is associated with anterior IC activation. Reconciling the conflicting data of similar anterior IC activation patterns but disparate HR responses outlined herein remains speculative. The answer may lie in the complex attributes of the IC such as its many subdivisions (51), its highly viscerotopic organization for sensory inputs from muscle, gut, and vagus nerve (*i.e.*, cardiac inputs) (52,53), and its role in processing viscerosensory with motor/behavioral outcomes. In addition, the integrated contributions of IC may vary when engaged during volitional mechanisms that engage an entire network versus local stimulation of a single site within the network.

ROLE OF SENSORY AFFERENTS IN CORTICAL ACTIVATION PATTERNS DURING EXERCISE

The cortical activation patterns during volitional exercise are expected to represent two fundamental functions. First, they
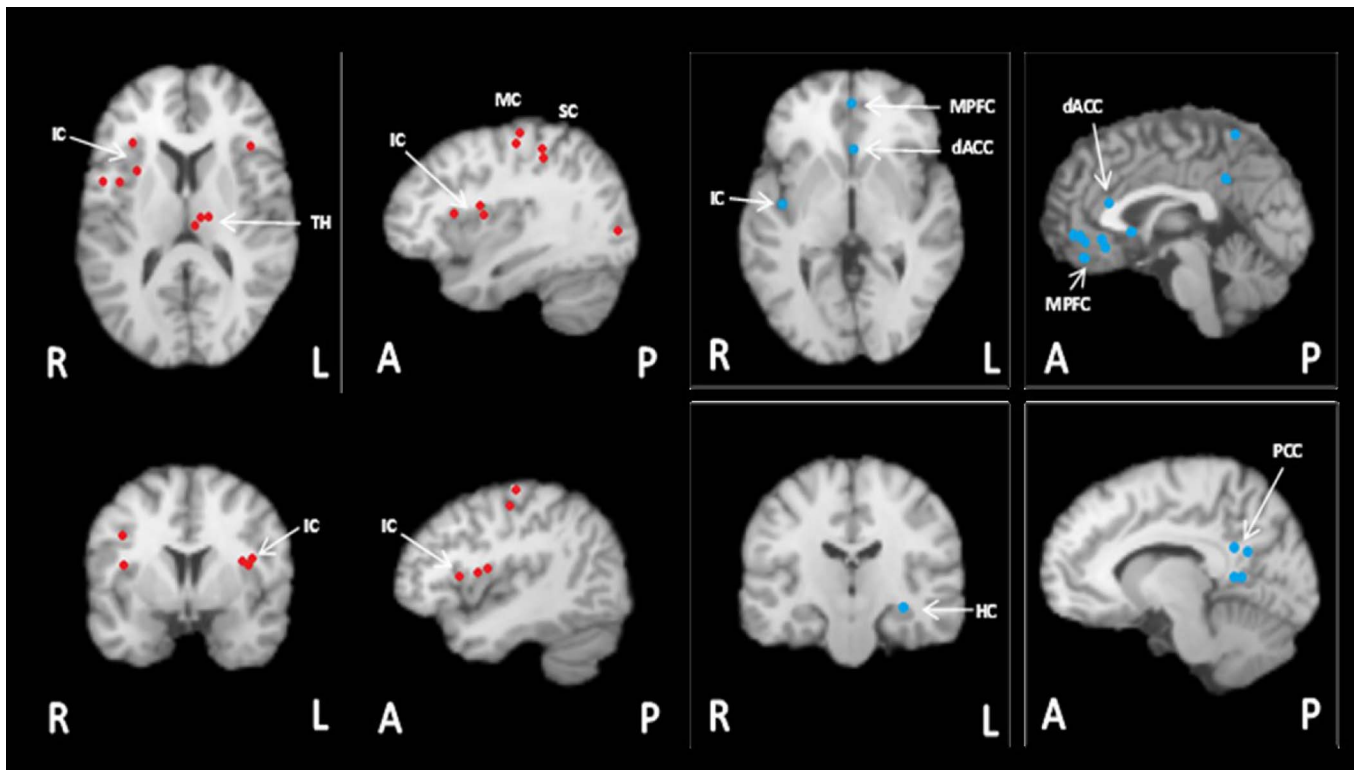
Figure 3. Summary of common regions associated with the handgrip exercise task. Data represent nine groups (n = 124) from four published articles (3,25,27,47) and two unpublished studies from our laboratory. These participants each performed repeated bouts (27,47–50) of moderate intensity (35%–40% maximal strength) handgrip tasks, each lasting 30s. Right panels: Cortical areas of decreased activation relative to baseline in response to short-duration, moderate intensity isometric handgrip exercise. Left panels: Cortical areas of increased activation relative to baseline in response to short-duration, moderate intensity isometric handgrip exercise. False Discovery Rate pN = 0.01; minimum volume (mm^3) = 200. Analysis performed using GingerALE (Version 2.3.2; BrainMap) and Mango (Version 3.1.2; Research Imaging Institute, University of Texas Health Science Center, San Antonio, TX) (48–50). dACC, dorsal anterior cingulate cortex; HC, hippocampus; IC, insula cortex; MC, motor cortex; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; SC, sensory cortex; TH, thalamus. Images are in radiological presentation with right side of the brain (R) on left, and left side of the brain (L) on the right. A, anterior; P, posterior. (Reprinted from (23). Copyright © 2015 Elsevier. Used with permission.)

could represent top-down "central" processes of a feed-forward control system that anticipates or modifies brainstem neural control of the circulation in the absence of visceral inputs. Second, they could represent bottom-up or feedback sensory inputs related to cardiac function, muscle contraction, and blood pressure (baroreceptors). Each of these sensory inputs must be accounted for in the testing of the Brain-Heart hypothesis for exercise-based HR responses.

Heart Rate

A major concern with interpretations based on correlations between changes in HR and cortical activation patterns is the lack of directional knowledge. Although the hypothesis being tested refers to cortical regions that determine HR changes, uncertainty remains regarding how changes in HR alter cortical activation patterns. Statistical approaches to assess the influence of HR on the BOLD signal under baseline conditions have been provided (54,55) with the conclusions that the low-frequency cardiac rate regressors displayed significant but not total shared variance with the global signal.

Direct electrical stimulation of the MPFC or IC is one approach to study the direct impact of these regions on cardiac outcomes. This model also provides an opportunity to address the ensuing hypothesis that preventing the reduction in chronic activity in those regions of the brain that demonstrated reduced activity during handgrip contractions should minimize the HR response. Using

surgical implantation of depth electrodes, as applied for clinical reasons in patients with intractable epilepsy, we provided a case study whereby direct stimulation of the posterior IC region diminished HR responses to handgrip contractions and had a modest bradycardic effect at baseline when isolated to the posterior inferior, but not posterior superior IC (56). More studies of this nature will complement BOLD imaging studies with direct neural recordings as well as provide experimental evidence regarding the direct role of these regions in HR regulation.

Muscle Sensory Afferents

The neural signals arising from contracting skeletal muscle exert powerful influence on cardiovascular adjustments. In contrast to the sympathoexcitatory influence of the Type III and IV afferents that reflect muscle tension and fatigue (57), those Type I and II afferents emanating from muscle spindles produce a vegetative influence on cardiovascular function (58). As both Type I and II muscle afferents are activated simultaneously with muscle contractions that elicit rapid HR changes, it is important to determine whether these muscle afferents are confounding the cortical activation patterns that also correlate with HR. We assume that the 30-s duration and moderate intensity workloads used in our studies (3,24,27,47) produce minimal involvement of fatigue-representing afferents (i.e., Type III and IV afferents) or sympathetic activation in young, healthy individuals. The Brain-Heart hypothesis regarding rapid HR responses to

exercise predicts that the depressor effects of isolated Type I and II afferent stimulation (58) should produce cortical activation patterns that oppose (or are opposite to) those observed during volitional contractions.

To isolate these sensory afferents in humans and establish their cortical representation, as well as their associations with cardiovascular arousal during exercise, Goswami et al. (47) compared the cortical and cardiac patterns observed during submotor electrical stimulation of the forearm muscle with those observed during motor-level electrical stimulation and moderate intensity volitional handgrip (Fig. 4). In this study, bilateral posterior IC activity was increased in graded fashion from submotor to motor-level electrical stimulation (that matched 5% maximal volitional strength) of the forearm, suggesting a
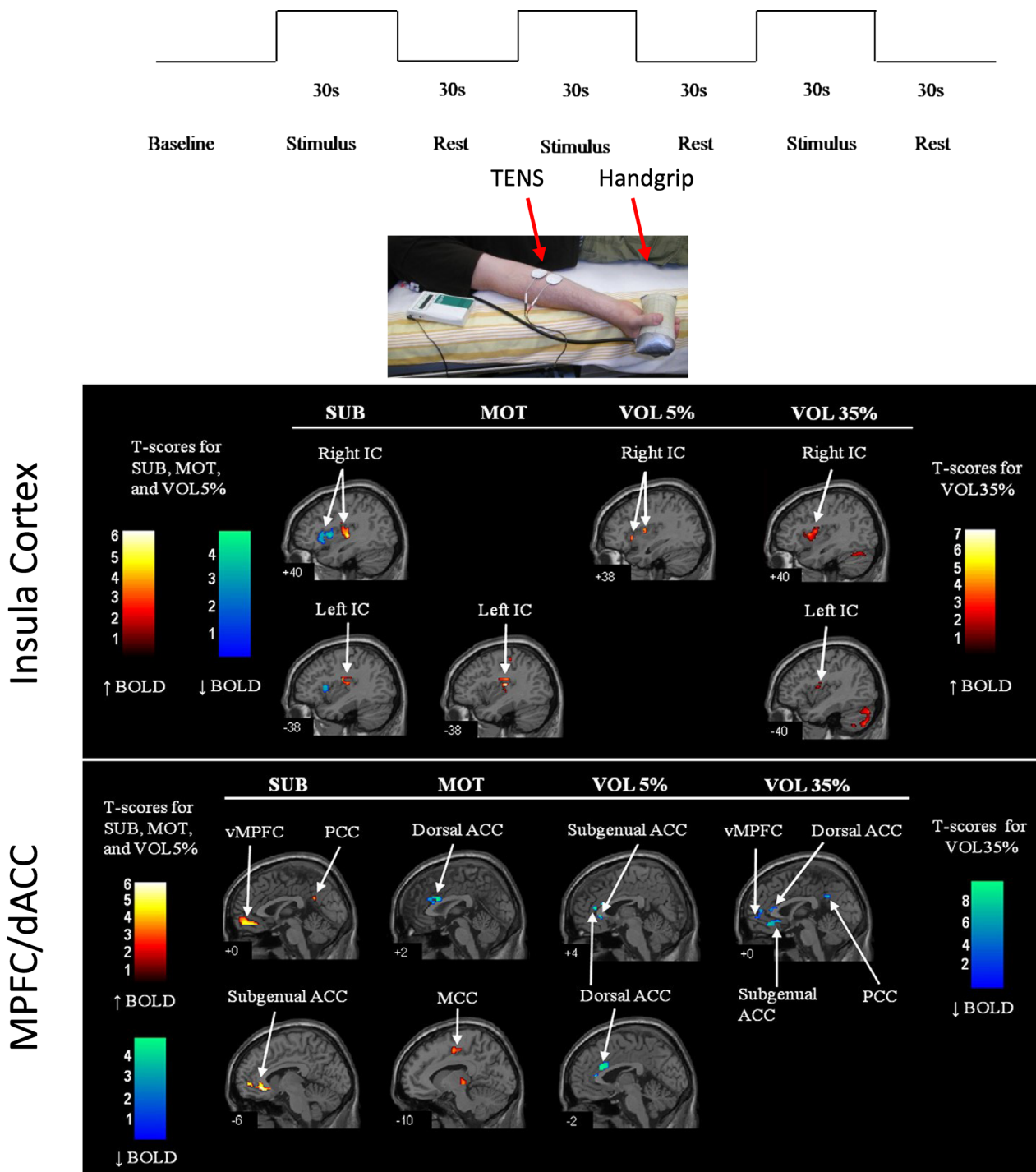
Figure 4. BOLD responses in the insula (Top Panel) as well as cingulate and ventral medial prefrontal cortex (vMPFC) during sub-motor threshold stimulation (SUB), motor threshold stimulation (MOT), 5% MVC volitional wrist flexion (VOL5%), and 35% MVC volitional handgrip exercise (VOL35%) versus rest. IC, insular cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; MCC, middle cingulate cortex. SUB and Motor conditions were induced by Transcutaneous Electrical Stimulation (TENS). Volitional handgrip assessed by a magnetic resonance imaging-compatible bladder (inset) or force transducer device (see Figure 2). (Adapted from [47]. Copyright © 2011 Elsevier. Used with permission.)

somatosensory role of this region for Type I and II afferent stimulation. Of note, in addition to the insula, activity in the vMPFC and subgenual ACC also was *increased* relative to baseline during submotor stimulation. Moreover, these activation patterns, which are opposite to those observed during volitional exercise, elicited a tendency toward lower HR and elevated HR variability indicative of elevated parasympathetic (or vagal) influence at the heart. Furthermore, differences between electrically stimulated muscle and centrally driven tasks were noted in insular and cingulate subregions. The results suggest that Type I and II afferents from muscle are functionally represented in the forebrain regions associated with HR regulation, but in a way that directly opposes the exercise patterns so that they depress cardiovascular arousal through elevation of parasympathetic drive to the heart. Two interesting possibilities emerge from this study. First, during volitional activity that engages top-down influences as well as the bottom-up somatosensory response, the net outcome in young, healthy individuals reflects a potential modulatory or fine tuning effect of somatosensory inputs to the cortical network. Second, and conversely, the network-wide patterns during volitional contractions may be caused by a pathway emanating from sites related to volitional effort that cancel the influence of somatosensory stimulation that occurs concurrently with muscle activation. These pathways are not known, and a lack of known neural projections from the MC to IC, HC, or MPFC regions suggests this switch occurs elsewhere. In either case, the somatosensory inputs do not replicate those cortical activation patterns observed during volitional exercise and may, if anything, diminish the magnitude of the observed patterns.

Baroreceptors

Increased blood pressure represents a key and appropriate response to fatiguing exercise. This rise in blood pressure may be represented in the cortical circuitry through afferent baroreceptor pathways that project beyond the brainstem synapses and, thereby, confounding interpretations regarding the role of an IC-MPFC-HC axis in HR regulation. Therefore, it is necessary to consider how blood pressure is represented in the brain independent of concurrent changes in HR or volitional effort.

Baroreceptor cardiovascular control represents a key negative feedback mechanism that retains mean arterial blood pressure around a modifiable set point (10,60,61). As previously mentioned, a primary mechanism by which changes in MPFC activity affect HR seems to involve its influence on the parasympathetic (vagal) arm of the baroreflex (62). Therefore, we expect some interweaving of baroreceptor afferent input to the forebrain CAN structures. Yet, few studies have explored forebrain neurocircuitry that represents a pure baroreceptor input.

Baroreceptor inputs to CAN sites can be studied by reducing pulsatile pressure in the baroreceptive regions and through studying cortical activation periods under conditions of elevations in blood pressure. Only the latter pertains to the pressor response observed during exercise in healthy individuals but, as part of the overall baroreflex regulatory mechanism, tests of both elevated and reduced baroreceptor activation will be instructive. Importantly, the challenge is to study baroreceptor activation changes under conditions of minimal confounds from concurrent sensory alterations (such as pain-induced hypertensive episodes) or pharmacological vasoactive stimuli (*e.g.*, α-adrenergic receptor activation) that could also affect regional cerebral perfusion that independently modify the BOLD outcome. To avoid these complications, we have used graded levels of lower body negative pressure to study cortical activation patterns associated with cardiovascular arousal during baroreceptor unloading (59) as a preliminary approach. Specifically, this model produces titratable reductions in cardiac and then cardiac plus vascular baroreceptor activity with corresponding graded increases in sympathetic

MAST trousers to control cardiovascular stress during a background of LBNP

Laboratory studies of cardiovascular variables

fMRI-based studies of BOLD response to LBNP

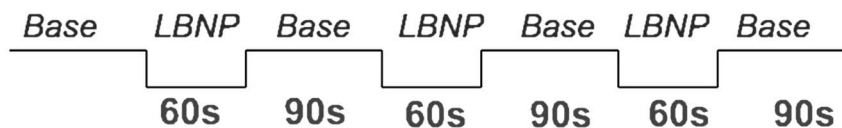| Base	LBNP	Base	LBNP	Base	LBNP	Base
	60s	90s	60s	90s	60s	90s

Figure 5. Illustration of an approach to conduct simulated orthostatic stress using lower body negative pressure while removing body movement when used during magnetic resonance imaging studies. Medical antishock trousers are fitted to the participant inside the lower body negative pressure chamber. By venting the trousers either to atmospheric or intrachamber pressures, they can be filled or emptied against a background of constant lower body suction. In this manner, the cardiovascular stress of the simulated orthostatic stress can be applied in box-car experimental models with minimal body movement at the onset or offset of suction.

TABLE. Patterns of regional cortical autonomic network change during handgrip and baroreceptor unloading reflexes that elevate heart rate

	R Post IC	R Ant IC	HC	MPFC	dACC	Amyg
Isometric handgrip	↓	↑	↓	↓	↓	NC
Lower body negative pressure	↑	↑	NC	↓	↑	↓

Amyg, amygdala; dACC, dorsal anterior cingulate; HC, hippocampus; IC, insula cortex; MPFC, medial prefrontal cortex; NC, no change; R, right. Direction of arrows indicates increase or decrease in regional activity relative to baseline.

outflow. In this model, HR changes are minimal at low levels of suction, and it is difficult to isolate baroreflex-medicated changes to vagal excitation with this model. (Fig. 5 provides a basic illustration of our approach to apply cyclic and graded baroreceptor unloading with limited head movements by inflating or deflating military antishock trousers against a constant background of lower body suction). Nonetheless, the Table contrasts the major findings in CAN patterns between the nonfatiguing isometric handgrip model and the lower body negative pressure model. The primary similarities include reduced MPFC activity and increased right anterior IC activation. Conspicuous differences in activation patterns are observed in the HC, right posterior IC, and dACC. Thus, these data support the overall idea that MPFC and anterior IC are part of a generalized cardiovascular arousal network and that baroreflex unloading *per se* does not wholly replicate patterns elicited by short-duration volitional handgrip. This model of CAN assessment is challenged by difficulties in separating HR and efferent sympathetic responses to the simulated orthostatic stress and the changes in cerebral blood volume (63) that may affect the blood oxygenation signal.

The simulated orthostatic challenge discussed earlier creates a baroreceptor unloading scenario through reductions in stroke volume and pulse pressure. In contrast, baroreceptor activation requires an elevation in pulsatile or steady state blood pressure. Direct IC neural recordings in anesthetized cats illustrated important findings that many IC neurons reflect cardiac rhythms, illustrating either cardiopulmonary or arterial baroreceptor inputs (64). Although most of these neurons did not respond during phenylephrine-induced increases in blood pressure, others increased in activity, probably reflecting baroreceptor inputs. Of note, in this study, none of the afferents that reflected changes in blood pressure overlapped with those that were activated by electrically induced muscle contraction. These findings are consistent with the role of the IC in viscerosensory processing of blood pressure. In 2003, Williamson *et al.* (12) used single-photon emission computed tomography (SPECT) magnetic resonance imaging to study regional cerebral blood flow patterns across the brain during a handgrip protocol that was titrated carefully to achieve a sustained blood pressure elevation during volitional isometric handgrip that could be sustained by a period of postexercise circulatory occlusion. In this approach, they were able to observe blood flow patterns in response to a change in blood pressure independent of concurrent changes in HR or volitional effort. This study indicated the elevations in action within the right inferior anterior IC and right inferior thalamus were related to the blood pressure response to
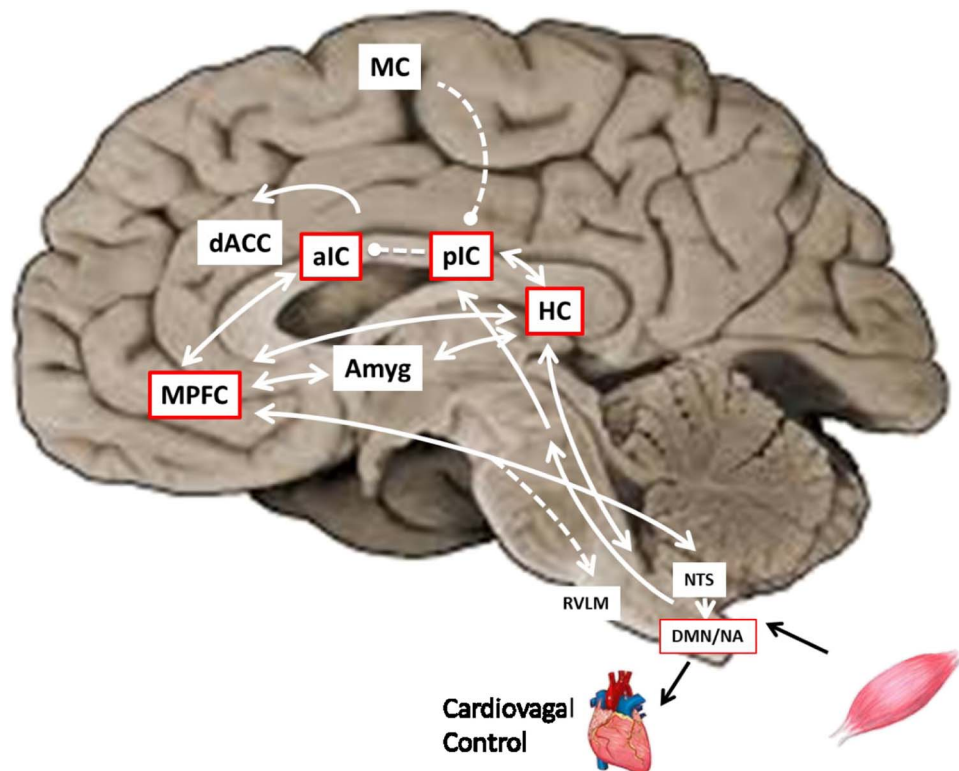

Figure 6. Schematic of proposed neurocircuitry associated with the rapid heart rate response at the exercise onset that includes the integration of ascending somatosensory information from the Type I and II afferents from the contracting muscle. See text for description. aIC, anterior IC; Amyg, amygdala; dACC, dorsal anterior cingulate cortex; DMN, dorsal motor nucleus; HC, hippocampus; MC, motor cortex; MPFC, medial prefrontal cortex; NA, nucleus ambiguous; NTS, nucleus tractus solitarius; pIC, posterior IC; RVLM, rostral ventrolateral medulla; represent key regions in this pathway in the context of rapid heart rate changes at the exercise onset.

exercise. Using a different approach but with the same experimental aim, we have presented preliminary data that relate to the specific rise in blood pressure that occurs after a strong (70% maximal strength) 2-s handgrip contraction when the HR response generated during the handgrip is returning to baseline (*i.e.*, a period when vagal dominance of the heart is being reestablished) (21). In this model, the rise in blood pressure was represented as increased activity within the mid-IC, a pattern that supports the observations of Williamson *et al.* (12), as well as those previously mentioned, whereby electrical stimulation of this region under baseline conditions produced bradycardia (46). Therefore, the available data do not negate the idea that the MPFC-HC-IC cortical patterns during volitional handgrip are specific to cardiac acceleration. These observations do not address the additional hypothesis that MPFC-HC-IC patterns in exercise elicit tachycardia through a rightward and upward resetting of baroreflex set point for HR, which leads to a reduction in vagal outflow. The role that central command exerts on baroreflex resetting during exercise has been reviewed in detail previously (10).

SUMMARY

The evidence to date regarding the hypothesis that a cortical network links volitional exercise and tachycardiac at the exercise onset because of reduced cardiovagal dominance is portrayed in Figure 6. Functional neuroimaging approaches have revealed patterns of change in the IC, HC, and MPFC that predictably correlate with rapid changes in HR at the exercise onset. Based on available information, these cortical patterns do not seem to be replicated by somatosensory or baroreceptor inputs. Reduction in MPFC activity at the exercise onset seems to be key to the HR response. At present, the overarching hypothesis suggests the following narrative and subhypotheses: baseline activity is high in the HC and MPFC affecting a level of baroreflex set point that favors high vagal outflow to the heart. With activation of volitional skeletal muscle motor pathways (or probably even anticipation of MC activation), this high activity in MPFC is reduced in concert with decreased activity in the HC and increased anterior IC activity. In turn, reduced MPFC activation affects a reduction in activity within the brainstem parasympathetic nuclei or a shift in the activity needed in these regions to achieve a desired blood pressure (also linked in some unknown way to the perceptual concept called "central command"). Subsequently, HR increases. Although many details remain to be established, the current information indicates that this network synthesizes the integration of central as well as peripheral sensory afferent signals from muscle during exercise that oppose the patterns induced by volitional muscle contractions. Clearly, the net effect of the somatosensory and baroreceptor inputs does not dominate those related to muscle contractions. The mechanisms that link and initiate the neural network into a functional unit that can adapt instantly to motor activity remain to be discovered.

Acknowledgments

References

1. Lalande S, Sawicki CP, Baker JR, Shoemaker JK. Effect of age on the hemodynamic and sympathetic responses at the onset of isometric handgrip exercise. *J. Appl. Physiol.* 2014; 116(2):222–7.
2. Seals DR, Victor RG. Regulation of muscle sympathetic nerve activity during exercise in humans. *Exerc. Sport Sci. Rev.* 1991; 19:313–49.
3. Wong SW, Masse N, Kimmerly DS, Menon RS, Shoemaker JK. Ventral medial prefrontal cortex and cardiovagal control in conscious humans. *NeuroImage.* 2007; 35(2):698–708.
4. Fagraeus L, Linnarsson D. Autonomic origin of heart rate fluctuations at the onset of muscular exercise. *J. Appl. Physiol.* 1976; 40(5):679–82.
5. Hollander AP, Bouman LN. Cardiac acceleration in man elicited by a muscle-heart reflex. *J. Appl. Physiol.* 1975; 38(2):272–8.
6. Norton KN, Badrov MB, Barron CC, Suskin N, Heinecke A, Shoemaker JK. Coronary artery disease affects cortical circuitry associated with brain-heart integration during volitional exercise. *J. Neurophysiol.* 2015; 114(2):835–45.
7. Hughson RL, Shoemaker JK, Tschakovsky ME, Kowalchuk JM. Dependence of muscle VO$_2$ on blood flow dynamics at onset of forearm exercise. *J. Appl. Physiol.* 1996; 81:1619–26.
8. Grassi B, Porcelli S, Salvadego D, Zoladz JA. Slow VO$_2$ kinetics during moderate-intensity exercise as markers of lower metabolic stability and lower exercise tolerance. *Eur. J. Appl. Physiol.* 2011; 111(3):345–55.
9. Spyer KM. Annual review prize lecture. Central nervous mechanisms contributing to cardiovascular control. *J. Physiol.* 1994; 474:1–19.
10. Raven PB, Young BE, Fadel PJ. Arterial baroreflex resetting during exercise in humans: underlying signaling mechanisms. *Exerc. Sport Sci. Rev.* 2019; 47(3):129–41.
11. Krogh A, Lindhard J. The regulation of respiration and circulation during the initial stages of muscular work. *J. Physiol.* 1913; 47(1–2):112–36.
12. Williamson JW, McColl R, Mathews D. Evidence for central command activation of the human insular cortex during exercise. *J. Appl. Physiol.* 2003; 94(5):1726–34.
13. Williamson JW, McColl R, Mathews D, Mitchell JH, Raven PB, Morgan WP. Brain activation by central command during actual and imagined handgrip under hypnosis. *J. Appl. Physiol.* 2002; 92(3):1317–24.
14. Mitchell JH, Victor RG. Neural control of the cardiovascular system: insights from muscle sympathetic nerve recordings in humans. *Med. Sci. Sports Exerc.* 1996; 28(Suppl. 10):S60–9.
15. Shoemaker JK, Goswami R. Forebrain neurocircuitry associated with human reflex cardiovascular control. *Front. Physiol.* 2015; 6:240.
16. Iwamoto GA, Botterman BR. Peripheral factors influencing expression of pressor reflex evoked by muscular contraction. *J. Appl. Physiol.* 1985; 58(5):1676–82.
17. Allen GV, Saper CB, Hurley KM, Cechetto DF. Organization of visceral and limbic connections in the insular cortex of the rat. *J. Comp. Neurol.* 1991; 311(1):1–16.
18. Yasui Y, Breder CD, Saper CB, Cechetto DF. Autonomic responses and efferent pathways from the insular cortex in the rat. *J. Comp. Neurol.* 1991; 303(3):355–74.
19. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin. Proc.* 1993; 68(10):988–1001.
20. Williamson JW, Fadel PJ, Mitchell JH. New insights into central cardiovascular control during exercise in humans: a central command update. *Exp. Physiol.* 2006; 91(1):51–8.
21. Cechetto DF, Shoemaker JK. Functional neuroanatomy of autonomic regulation. *NeuroImage.* 2009; 47(3):795–803.
22. Silvani A, Calandra-Buonaura G, Dampney RAL, Cortelli P. Brain-heart interactions: physiology and clinical implications. *Philos. Trans. A. Math Phys. Eng. Sci.* 2016; 374(2067):20150181.
23. Shoemaker JK, Norton KN, Baker J, Luchyshyn T. Forebrain organization for autonomic cardiovascular control. *Auton. Neurosci.* 2015; 188:5–9.
24. Ruiz Vargas E, Sörös P, Shoemaker JK, Hachinski V. Human cerebral circuitry related to cardiac control: a neuroimaging meta-analysis. *Ann. Neurol.* 2016; 79(5):709–16.
25. Wong SW, Kimmerly DS, Masse N, Menon RS, Cechetto DF, Shoemaker JK. Sex differences in forebrain and cardiovagal responses at the onset of isometric handgrip exercise: a retrospective fMRI study. *J. Appl. Physiol.* 2007; 103(4):1402–11.
26. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc. Natl. Acad. Sci. U. S. A.* 2001; 98(2):676–82.

27. Norton KN, Luchyshyn TA, Kevin SJ. Evidence for a medial prefrontal cortex-hippocampal axis associated with heart rate control in conscious humans. *Brain Res.* 2013; 1538:104–15.

28. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb. Cortex.* 2009; 19(1):72–8.

29. Anand BK, Dua S. Circulatory and respiratory changes induced by electrical stimulation of limbic system (visceral brain). *J. Neurophysiol.* 1956; 19(5): 393–400.

30. Kaada BR, Jasper H. Respiratory responses to stimulation of temporal pole, insula, and hippocampal and limbic gyri in man. *A.M.A. Arch. Neurol. Psychiatry.* 1952; 68(5):609–19.

31. Ruit KG, Neafsey EJ. Hippocampal input to a "visceral motor" corticobulbar pathway: an anatomical and electrophysiological study in the rat. *Exp. Brain Res.* 1990; 82(3):606–16.

32. Verberne AJ, Lewis SJ, Worland PJ, et al. Medial prefrontal cortical lesions modulate baroreflex sensitivity in the rat. *Brain Res.* 1987; 426:243–9.

33. Hilz MJ, Devinsky O, Szczepanska H, Borod JC, Marthol H, Tutaj M. Right ventromedial prefrontal lesions result in paradoxical cardiovascular activation with emotional stimuli. *Brain.* 2006; 129(Pt 12):3343–55.

34. Owens NC, Sartor DM, Verberne AJ. Medial prefrontal cortex depressor response: role of the solitary tract nucleus in the rat. *Neuroscience.* 1999; 89(4):1331–46.

35. Resstel LB, Correa FM. Medial prefrontal cortex NMDA receptors and nitric oxide modulate the parasympathetic component of the baroreflex. *Eur. J. Neurosci.* 2006; 23(2):481–8.

36. Castle M, Comoli E, Loewy AD. Autonomic brainstem nuclei are linked to the hippocampus. *Neuroscience.* 2005; 134(2):657–69.

37. Westerhaus MJ, Loewy AD. Central representation of the sympathetic nervous system in the cerebral cortex. *Brain Res.* 2001; 903(1–2):117–27.

38. Reuter-Lorenz PA, Park DC. Human neuroscience and the aging mind: a new look at old problems. *J. Gerontol. B. Psychol. Sci. Soc. Sci.* 2010; 65B(4):405–15.

39. Kaye DM, Esler MD. Autonomic control of the aging heart. *NeuroMolecular Med.* 2008; 10(3):179–86.

40. Shipley MT. Insular cortex projection to the nucleus of the solitary tract and brainstem visceromotor regions in the mouse. *Brain Res. Bull.* 1982; 8(2):139–48.

41. Hurley KM, Herbert H, Moga MM, Saper CB. Efferent projections of the infralimbic cortex of the rat. *J. Comp. Neurol.* 1991; 308(2):249–76.

42. Showers MJ, Lauer EW. Somatovisceral motor patterns in the insula. *J. Comp. Neurol.* 1961; 117:107–15.

43. Ghaziri J, Tucholka A, Girard G, et al. Subcortical structural connectivity of insular subregions. *Sci. Rep.* 2018; 8(1):8596.

44. Mathiasen ML, Hansen L, Witter MP. Insular projections to the parahippocampal region in the rat. *J. Comp. Neurol.* 2015; 523(9):1379–98.

45. Cechetto DF, Hachinski V. Cardiovascular consequence of experimental stroke. *Baillieres Clin. Neurol.* 1997; 6(2):297–308.

46. Chouchou F, Mauguière F, Vallayer O, et al. How the insula speaks to the heart: cardiac responses to insular stimulation in humans. *Hum. Brain Mapp.* 2019; 40(9):2611–22.

47. Goswami R, Frances MF, Shoemaker JK. Representation of somatosensory inputs within the cortical autonomic network. *NeuroImage.* 2011; 54(2): 1211–20.

48. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. *NeuroImage.* 2012; 59(3):2349–61.

49. Eickhoff SB, Bzdok D, Laird AR, et al. Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *NeuroImage.* 2011; 57(3):938–49.

50. Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Hum. Brain Mapp.* 2012; 33(1):1–13.

51. Macey PM, Wu P, Kumar R, et al. Differential responses of the insular cortex gyri to autonomic challenges. *Auton. Neurosci.* 2012; 168(1–2):72–81.

52. Cechetto DF. Central representation of visceral function. *Fed. Proc.* 1987; 46(1):17–23.

53. Cechetto DF, Saper CB. Role of the cerebral cortex in autonomic function. In: Loewy AD, Spyer KM, editors. *Central Regulation of Autonomic Functions.* New York (NY): Oxford University Press; 1990. p. 208–23.

54. Chang C, Cunningham JP, Glover GH. Influence of heart rate on the BOLD signal: the cardiac response function. *NeuroImage.* 2009; 44(3): 857–69.

55. Chang C, Glover GH. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *NeuroImage.* 2009; 47(4):1448–59.

56. Al-Otaibi F, Wong SW, Shoemaker JK, Parrent AG, Mirsattari SM. The cardioinhibitory responses of the right posterior insular cortex in an epileptic patient. *Stereotact. Funct. Neurosurg.* 2010; 88(6):390–7.

57. Mitchell JH. J.B. Wolffe memorial lecture. Neural control of the circulation during exercise. *Med. Sci. Sports Exerc.* 1990; 22:141–54.

58. Hollman JE, Morgan BJ. Effect of transcutaneous electrical nerve stimulation on the pressor response to static handgrip exercise. *Phys. Ther.* 1997; 77(1):28–36.

59. Kimmerly DS, O'Leary DD, Menon RS, Gati JS, Shoemaker JK. Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans. *J. Physiol.* 2005; 569(Pt 1):331–45.

60. Fadel PJ, Raven PB. Human investigations into the arterial and cardiopulmonary baroreflexes during exercise. *Exp. Physiol.* 2012; 97(1):39–50.

61. Raven PB, Fadel PJ, Smith SA. The influence of central command on baroreflex resetting during exercise. *Exerc. Sport Sci. Rev.* 2002; 30(1):39–44.

62. Resstel LBM, Fernandes KBP, Correa FMA. Medial prefrontal cortex modulation of the baroreflex parasympathetic component in the rat. *Brain Res.* 2004; 1015(1–2):136–44.

63. Wilson TD, Shoemaker JK, Kozak R, Lee TY, Gelb AW. Reflex-mediated reduction in human cerebral blood volume. *J. Cereb. Blood Flow Metab.* 2005; 25(1):136–43.

64. Ichiyama RM, Waldrop TG, Iwamoto GA. Neurons in and near insular cortex are responsive to muscular contraction and have sympathetic and/or cardiac-related discharge. *Brain Res.* 2004; 1008(2):273–7.