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Cortical Circuitry Associated With Reflex Cardiovascular Control in Humans: Does the Cortical Autonomic Network "Speak" Or "Listen" During Cardiovascular Arousal

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ABSTRACT

Beginning with clinical evidence of fatal cardiac arrhythmias in response to severe stress, in epileptic patients, and following stroke, the role of the cerebral cortex in autonomic control of the cardiovascular system has gained both academic and clinical interest. Studies in anesthetized rodents have exposed the role of several forebrain regions involved in cardiovascular control. The introduction of functional neuroimaging techniques has enabled investigations into the conscious human brain to illuminate the temporal and spatial activation patterns of cortical regions that are involved with cardiovascular control through the autonomic nervous system. This symposia report emphasizes the research performed by the authors to understand the functional organization of the human forebrain in cardiovascular control during physical stressors of baroreceptor unloading and handgrip exercise. The studies have exposed important associations between activation patterns of the insula cortex, dorsal anterior cingulate, and the medial prefrontal cortex and cardiovascular adjustments to physical stressors. Furthermore, these studies provide functional anatomic evidence that sensory signals arising from baroreceptors and skeletal muscle are represented within the insula cortex and the medial prefrontal cortex, in addition to the sensory cortex. Thus, the cortical pathways subserving reflex cardiovascular control integrate viscerosensory inputs with outgoing traffic that modulates the autonomic nervous system. Anat Rec, 295:1375–1384, 2012. © 2012 Wiley Periodicals, Inc.

Key words: cortical autonomic network; medial prefrontal cortex; insula cortex; cingulate cortex; handgrip; baroreflex

Cardiovascular homeostasis requires reflex-mediated changes in cardiac and vascular function. The reflexive nature of cardiovascular control indicates the presence of afferent and efferent arms of neural processes that sense and alter conditions in the target tissues. With regards to cardiovascular control, the successful control of blood pressure and distribution of blood flow in response to stress is under the control of, and is dependent upon, rapid adjustments in the outflow of the parasympathetic (PNS) and sympathetic (SNS) nervous systems. Our interests in understanding reflex cardiovascular control are within the context of physical stressors such as orthostasis or exercise. In the case of orthostatic stress, the baroreflex loop is the primary mechanism in place to defend inappropriate oscillations in blood pressure through rapid adjustments in heart rate and vascular resistance. The neural control strategies become more complicated in the context of volitional effort, such as exercise, where, in addition to descending feed-forward processes that coordinate muscle activation with cardiovascular adjustments (Krogh and Lindhard, 1913; Mitchell, 1990), reflex feedback information from muscle sensory afferents as well as the baroreceptor afferents converge upon the neural structures involved in adjusting SNS and PNS outflow. Whereas considerable effort has been applied to understanding the autonomic neural pathways and nuclei of the brainstem in the service of SNS and PNS outflow (Loewy and McKellar, 1980; Spyer, 1994; Guyenet, 2006), less is known about the pathways from higher cortical centers that modulate autonomic outflow, particularly in conscious humans. However, considerable clinical observations, as well as experimental evidence from rodents, indicate that these supramedullary centers play a critical role in the neural control of the cardiovascular system. The introduction of noninvasive neuroimaging technology has opened opportunities to explore the conscious human brain and expose the cortical regions associated with cardiovascular control.

Following a brief historical perspective, this review will outline the major observations from studies in our laboratory regarding the organization of the cerebral cortex for autonomic cardiovascular control in conscious humans. Earlier, investigations using anesthetized rodent models established the primary cortical regions of interest, and these have been reviewed extensively (Cechetto and Saper, 1990; Cechetto and Shoemaker, 2009). This article will emphasize our more recent work in conscious humans using functional magnetic resonance imaging (fMRI) techniques. Where applicable, reference will be made to earlier rodent studies. A fundamental issue with fMRI studies is the ambiguity of the blood-oxygenation-level-dependent (BOLD) signal. Therefore, we also present our recent studies examining the cortical representation of sensory inputs from muscle and baroreceptor afferents. The collective outcomes of the cortical architecture related to cardiovascular arousal, as well as those cortical regions associated with viscerosensory activation, provide a deeper understanding of cortical activation patterns within the context of cardiovascular control.

HISTORICAL PERSPECTIVE

The term "reflex cardiovascular control" refers to the ongoing adjustments in sympathetic and parasympathetic outflow that modify cardiac and vascular tissue in the pursuit of tightly controlled blood pressure (Fadel et al., 2001). Within this context, considerable research has established the reflexive behavior, as well as the anatomical brainstem pathways (reviews indicated above) that subserve sensory and efferent signals that reflexively control cardiovascular arousal (O'Leary, 1993, 1996; Augustyniak et al., 2000; Fadel et al., 2001; Machado, 2001; Raven et al., 2002; Boushel, 2010; Fadel and Raven, 2011). Nonetheless, several observations point to the cerebral cortex as a site of important modulatory influence over autonomic cardiovascular control. Some examples of such observations are listed below:

1) Based on observations of respiratory and heart rate responses at the exercise onset, Krogh and Lindhard (Krogh and Lindhard, 1913) proposed the concept of "central command" to describe the ability of the brain to coordinate concurrently the cardiovascular, respiratory, and skeletal muscle responses to volitional or effortful exercise. Of course, the details of the brain's involvement in such rapid and coordinated adjustments to exercise were not available at that time.
2) Walter B. Cannon's characterization of "voodoo death" in 1942 illustrated the important and sometimes fatal role that psychologic stress can have on cardiovascular function (Cannon, 2002).
3) Clinical observations made in the 1980s indicated that fatalities following cerebral stroke often were due to catastrophic cardiac arrhythmias (Myers et al., 1982; Cheung and Hachinski, 2003). Of particular importance were the outcomes of stroke in the insula cortex region. Subsequent experimental studies in rodents, summarized below, established the insula cortex as a region with critical impact on cardiopathologic outcomes from hyperadrenergic activation (Oppenheimer et al., 1991; Yasui et al., 1991; Yoon et al., 1997).
4) Studies on patients with cortical lesions demonstrate the role of the medial prefrontal cortex in modulating sympathetic nerve activity. In particular, such patients show blunted emotion, poor decision-making and a failed alteration in the skin conductance response that is mediated mainly by the sympathetic nervous system (Damasio, 1994; Bechara et al., 1996, 1997). These data link the autonomic nervous system to many cognitive tasks and emotive experiences.

EXPERIMENTAL STUDIES IN RODENTS

The rat cortex and forebrain have been studied extensively within the context of cardiovascular control and cardiopathology. In addition to documenting the important role of the insula cortex in cardiac arrythmias, introduced above, Cechetto et al. outlined the important role of the insula as a somatotopically organized region that receives visceral sensory information and is somehow involved in subsequent adjustments to cardiovascular control (Cechetto et al., 1989; Oppenheimer and Cechetto, 1990; Oppenheimer et al., 1990, 1991; Yasui et al., 1991; Butcher et al., 1993; Butcher and Cechetto, 1995; Cechetto and Chen, 1995; Cheung et al., 1997). Through these studies, and others, the reciprocal innervations of various cortical regions associated with afferent and efferent cardiovascular control were established (Cechetto and Saper, 1990). Collectively, the studies in rodents established the

important role of various regions within the forebrain for cardiovascular control including the insula, thalamus, infralimbic cortex, amygdala, and basal ganglia regions. Thus, these studies identified the cortical organization for cardiovascular control and emphasized the regions of interest involved in autonomic outflow. Subsequently, studies in humans were conducted to establish the translational success of the rodent models, and also to avoid concerns regarding the negative impact of anesthesia on neural adjustments to stress and the subsequent neurovascular outcomes. Electrophysiologic interventions during surgery of epileptics supported the idea that the insula affected cardiovascular control and further pointed to the possibility of important lateralization of the insula cortices such that the left insula affected PNS whereas the right insula was predominantly SNS in their cardiovascular effects (Oppenheimer et al., 1992, 1996). Through these approaches, the forebrain architecture associated with cardiovascular control was mapped and experimental evidence was provided that exposed the forebrain as a critical site in the modulation, or restraint, of autonomic balance. The concerns regarding the role of the cortex in fatal cardiac arrhythmias are replicated in cases of sudden unexplained death in epileptic seizures (SUDEP) (Scorza et al., 2009).

As noted above, a challenge in examining cortical function from an experimental rodent model is the inability to study the brain in its unanesthetized intact state and from a perspective of what various regions are doing together rather than just one at a time. Concurrent with the buildup of clinical understanding, and experimental work in rodents, the 1990s were the decade in which functional magnetic resonance imaging (fMRI) technology was introduced (Ogawa et al., 1990, 1992), opening a new era in neuroscience. As a nonradioactive and noninvasive method, fMRI enables advanced understanding of the brain in its natural state of activation without the confounding impact of anesthesia on the autonomic nervous system. Specifically, this method enables detection of the group of brain regions that changed their activity patterns in real time, all at the same time. We have used fMRI to establish the group of cortical regions whose activity levels change predictably and reproducibly in response to orthostatic or exercise-based cardiovascular arousal. The exact physiologic purpose of each region of interest cannot be determined solely by the use of fMRI methods. However, using a variety of volitional, passive and sensory stimulation experimental paradigms along with physiologic outcomes, the roles of two particular regions are becoming clearer, namely the insula and medial prefrontal cortex.

EXPLORING THE CORTICAL ARCHITECTURE ASSOCIATED WITH CARDIOVASCULAR CONTROL IN CONSCIOUS HUMANS

Functional magnetic resonance imaging (fMRI) is one technique that enables noninvasive assessment of real-time changes in cortical activation patterns that can be applied in experimental settings. Functional MRI takes advantage of the paramagnetic properties of hemoglobin that vary with the degree of oxygenation (Ogawa et al., 1990). Thus, changes in blood flow in response to changes in neural activity can be detected and used to quantify and locate the range of regions involved in response to particular stimuli. The blood-oxygenation-level-dependent (BOLD) signal provided by fMRI is complex in its origin (Arthurs and Boniface, 2002) but reflects well the temporal and spatial aspects of regional or focal cortical activation patterns in response to particular stimuli. As such, this method complements invasive electrophysiologic and/or pharmacologic approaches that study single neurons or regions.

A commonly used approach to understand the functional impact of cortical activation patterns is to correlate these with patterns of change in blood pressure, heart rate, efferent sympathetic nerve activity or a stimulus signal such as strain gauge force, during maneuvers that elicit cardiovascular stress such as handgrip exercise or lower body negative pressure (to mimic orthostatic stress). Because of difficulties in measuring peripheral physiologic signals in the MRI scanner concurrent measures that reflect autonomic nervous system variables are limited to indirect analog measurements such as heart rate or skin conductance responses (Wong et al., 2011). To bring further meaning to cortical activation patterns studies are replicated in the fMRI session as well as a physiology laboratory session. In this context, reproducibility of cortical patterns associated with identical stimuli are required, and have been established in our hands (Kimmerly et al., 2004, 2005). Moreover, the regions associated with cardiovascular adjustments to stress are more-or-less replicated across many stressors from many laboratories. Specifically, many groups have examined the cortical patterns associated with cardiovascular responses (primarily heart rate) during physical (King et al., 1999; Critchley et al., 2000, 2003; Gianaros et al., 2004, 2005; Critchley, 2005; Kimmerly et al., 2005; Wong et al., 2007b; Goswami et al., 2011), cognitive (Gianaros et al., 2004, 2005; Critchley et al., 2000, 2003), and emotional (Lane et al., 2008) stressors. Overall, the regions outlined below appear to form the core cortical regions associated with cardiovascular control.

Cortical Circuitry Associated With Cardiovascular Arousal

The inaugural study of King et al. (1999) illustrated the utility of fMRI to expose the complexity of cortical activation that occurs during straining efforts that induced large cardiovascular responses. Using short but maximal handgrip exercise, Valsalva's maneuver and a maximal inspiration task, these authors observed increased cortical activation that was localized in the insular cortex, the posterior regions of the thalamus, and the medial prefrontal cortex (MPFC). Notably, increased MPFC activity during the recovery phase of Valsalva's maneuver occurred concurrently with a decline in heart rate. This point becomes important below when HR correlations with MPFC activation or deactivation begin to expose an important role for this frontal region in cardiovagal control. Regions of brain that were less activated compared with baseline were not explored in this early study. Also, each of the handgrip, maximal inspiration and Valsalva's maneuver segments elicited significant changes in blood pressure, heart rate, and volitional effort sense (straining). Thus, the cortical patterns were

observed within the context of complex stimuli from muscle, baroreceptor and top-down neural sources.

To examine the forebrain architecture associated with baroreflex-mediated sympathetic activation in the absence of volitional effort or changes in blood pressure, a model of graded lower body suction was developed to simulate orthostasis while the participant remains supine (Kimmerly et al., 2005). With lower body suction it is possible to grade the orthostatic stress, and thereby the magnitude of baroreflex unloading, so that either a change in sympathetic nerve activity occurs without a change in heart rate (−15 mmHg) or both sympathetic activation and heart rate changes occur (such −35 mmHg suction). Cortical regions demonstrating increased activity that correlated with higher HR and greater levels of lower body suction included the right superior posterior insula, frontoparietal cortex and the left cerebellum. Conversely, using the identical statistical paradigm, bilateral anterior insular cortices, the right anterior cingulate, orbitofrontal cortex, amygdala, mediodorsal nucleus of the thalamus and midbrain showed decreased neural activation. These findings were replicated in additional studies using direct unloading of baroreceptors (Kimmerly et al., 2007a,b). Such locations also covary with changes in cardiovagal baroreflex sensitivity induced by psychological stress in humans (Gianaros et al., 2011). Further, the insula cortex has long been associated with baroreflex cardiovascular control in anesthetized rodents (Saleh and Connell, 1998; Zhang et al., 1998).

To study the forebrain regions and patterns involved with exercise, the cortical response to graded moderate intensity handgrip (HG) exercise was assessed (Wong et al., 2007a,b; Goswami et al., 2011). When performed at <40% of maximal contractile force for brief (e.g., <30 sec) in young adults, HG elicits an intensity-dependent tachycardia (in most individuals) that is apparent within the first 1–2 sec of the handgrip onset, growing to about 10–15 bpm increase over the 30-sec contraction duration (Fig. 1). Pharmacologic blockade evidence suggests that PNS withdrawal mechanistically controls the bulk of this rapid HR response (Hollander and Bouman, 1975; Fagraeus and Linnarsson, 1976; Mitchell et al., 1989). It follows that regions of the brain that change their activity in association with these rapid HR changes may reflect sites that modulate PNS. With HG, the motor cortex, bilateral insula, thalamus, cerebellum, and basal ganglia regions are all increased in their activation (Wong et al., 2007b). However, the ventral medial prefrontal cortex (vMPFC) was the only region to correlate strongly and inversely with heart rate changes with a time course and magnitude of change that reflected variations in exercise intensities. This patterned response was not affected by one's handedness or sex although females tend to produce smaller HR and cortical responses for the same relative workload (Wong et al., 2007a). Similar deactivation patterns within the medial prefrontal/genual ACC region that correlated inversely with HR were noted in the LBNP study above. Thus, handgrip maneuvers that appear to emphasize parasympathetic withdrawal elicit increased cortical responses in the posterior inferior bilateral insula activation and deactivation within the MPFC. This pattern has been observed in repeated studies (Wong et al., 2007a,b; Goswami et al., 2011). Furthermore, this strong relationship
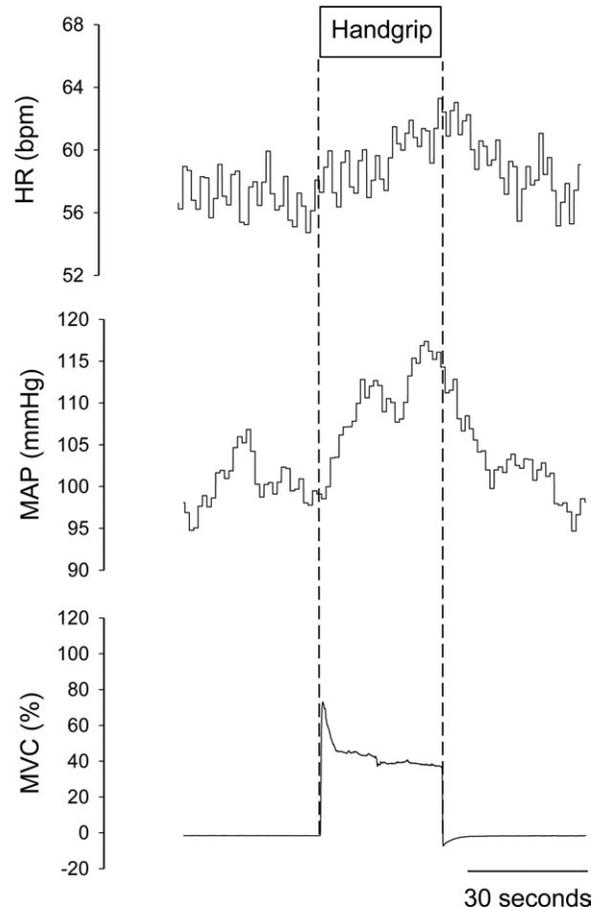

Fig. 1. Time course of changes in heart rate (HR; top panel), mean arterial pressure (MAP; middle panel) during a 30-sec of handgrip exercise performed at 40% of maximal voluntary contraction (MVC) strength.

between MPFC and HR is consistent with other reports examining the brain-heart relationship during cognitive and emotional stressors (Critchley et al., 2000, 2003, 2004; Critchley, 2004, 2005; Gianaros et al., 2004, 2005; Lane et al., 2008).

Thus, the evidence from lower body suction and handgrip exercise models indicates that changes in HR are consistently associated with reduced activation within the vMPFC and subgenual ACC complex. These observations are consistent with extensive functional anatomical studies in lower animals which indicate the extensive projections from this region to brain stem cardiovascular centers (Verberne and Owens, 1998). While pharmacologic evidence discussed above suggests that PNS withdrawal mediates this rapid HR response, there may be a similar time course of sympathetic activation of visceral organs (Momen et al., 2005; Frances et al., 2008). However, conditions under which sympathetic activation may be responsible for the rapid HR change have not been studied. Of note, moderate intensity handgrip exercise also elicits increased activation within the supplementary motor area, basal ganglia, hippocampus, motor cortex, thalamus, and cerebellum. Of these, the cerebellum vermis (Bradley et al., 1991) and hippocampus (Ansakorpi et al., 2004; Castle et al., 2005) have been associated with

autonomic cardiovascular modification. Otherwise, these regions have received minimal attention with regard to human cardiovascular control.

The above studies were performed under conditions of short-term and moderate-intensity handgrip to minimize concurrent blood pressure and sympathetic responses that occur with exercise. Nonetheless, these studies are still complicated by the complex neural patterns that occur at the onset of exercise. In particular, concurrent cardiovascular arousal, ventilatory activation, and motor control are coordinated at the exercise onset and are enveloped in the concept of "central command" (Krogh and Lindhard, 1913). The cortical activation patterns associated with central command in general have been studied in a series of complex studies by Williamson and colleagues using both SPECT and fMRI imaging (Williamson et al., 1996, 1999, 2002, 2003). These studies collectively demonstrate involvement of the insula in particular as an important region associated with volitional and effortful muscular exercise. These data raise the important question of the purposefulness of cortical activation during cardiovascular arousal. Particularly, to what extent does the insula–amygdala–medial prefrontal/anterior cingulate complex impact heart rate alone versus a broader coordination of physiologic responses required to initiate and sustain, effortful exercise?

In summary, the regions that consistently are associated with cardiovascular arousal include the dorsal anterior cingulate, medial prefrontal cortex/subgenual anterior cingulate, and insula cortex. Another site commonly observed is the amygdala. Sympathetic activation, studied in our hands only in the context of baroreflex unloading, is most consistently associated with the superior, posterior insula cortex (right side) and dorsal ACC. In our experience, HR responses always correlate negatively with the medial prefrontal cortex. From these temporal and spatial patterns, the collective evidence suggests that these regions reflect portions of a network that processes and supports the complex features associated with reflex cardiovascular control. Nonetheless, evidence supporting the concept of an integrated network is required.

Interpretational Issues

Attempts to interpret the role of particular cortical regions based on BOLD responses must be considered carefully due to the limitations of this methodological approach. These challenges include the following: (1) uncertainty regarding the physiological basis of the BOLD response, (2) need for short but repeated stimuli to enhance signal-to-noise, (3) sensitivity to artifacts generated by movement, or tissue/air interfaces and global changes in brain blood volume (such as might occur with changes in blood pressure or ventilation patterns), and, (4) ambiguity in interpretation of the BOLD signal. Generally, our study designs aim to deal with such limitations by optimizing the levels of lower body negative pressure (LBNP) or handgrip to elicit important cardiovascular reflex adjustments with minimal movement or minimal changes in blood pressure and ventilation. Such practices are important to consider further. As mentioned, BOLD imaging offers advantages of relatively high temporal and spatial resolution, an advantage that makes this technique sensitive to changes in heart rate, blood pressure, and ventilation. This sensitivity to pulsatile or rhythmic physiologic events can interfere with detection of other signals that are unrelated to cardiovascular or ventilatory control. Thus, some neuroimaging specialists treat BOLD oscillations due to these autonomic variables as nuisance outcomes to be removed from the overall signal (Iacovella and Hasson, 2011). For example, increases in blood pressure can, in fact, enhance BOLD signal detection (Wang et al., 2006; Qiao et al., 2007). This effect likely includes somatosensory inputs from baroreceptors, an issue presented in detail below. In contrast, many other laboratories, such as those reflected in this review, consider these autonomic outcomes to be a theoretically meaningful component of the BOLD signal. Further, the sensitivity of cerebrovasculature to changes in blood oxygen and/or carbon dioxide create a concern for ventilatory patterns and their integration with task-specific brain activation patterns that may be specific to different brain regions (Hall et al., 2011).

The issue of interpretational ambiguity in BOLD responses (i.e., problem no. 4 above), requires special attention as well. Specifically, although relationships between cortical activation/deactivation patterns are exposed by correlations with heart rate or the stimulus time course, these correlations cannot convey causality or directional relationships. Two interpretational challenges arise from this latter limitation. First, by itself, the BOLD signal does not indicate whether the regions of activation form an integral network or discreet regions that are processing information directly or indirectly related to the stimulus. Second, a single activation pattern cannot inform the viewer regarding the inhibitory or excitatory nature of the brain's response or whether various regions are (a) "listening" to afferent sensory signals arising in the brain that reflect a cardiovascular change or (b) "talking" in the sense that they are directing an efferent motor response to adjust the cardiovascular status. To illustrate this point, the rapid increase in heart rate and blood pressure with handgrip exercise, or the elevated HR during lower body suction, will stimulate mechanosensor or baroreceptor afferents in the cardiac chambers, aortic arch and carotid sinus' whose neural pathways link into the nucleus tractus solitaries in the brain stem, with possible subsequent pathways that project through the thalamus to the insula, amygdala and other forebrain areas (Cechetto and Saper, 1990). Furthermore, sensory signals from muscle spindles arise during muscular work and these may cause a change in cortical activation; the cortical irradiation of such muscle sensory signals in humans is not reported. Finally, even mild handgrip exercise requires cognitive engagement during volitional effort, an aspect of the task that will carry its own and perhaps variable cortical activation pattern. The problem then arises as to whether the activation patterns observed in the cortex during handgrip or other cognitive tasks, are causing (or at least modulating) the heart rate or blood pressure change or, rather, are representing that change in sensory input as a cortical activation that does not influence cardiovascular control. Stated more specifically, the reduced activation of the vMPFC during HG may reflect a sensory response to afferent neural signals arising from the heart or skeletal muscle that signal a change in cardiac function or muscle tension within the
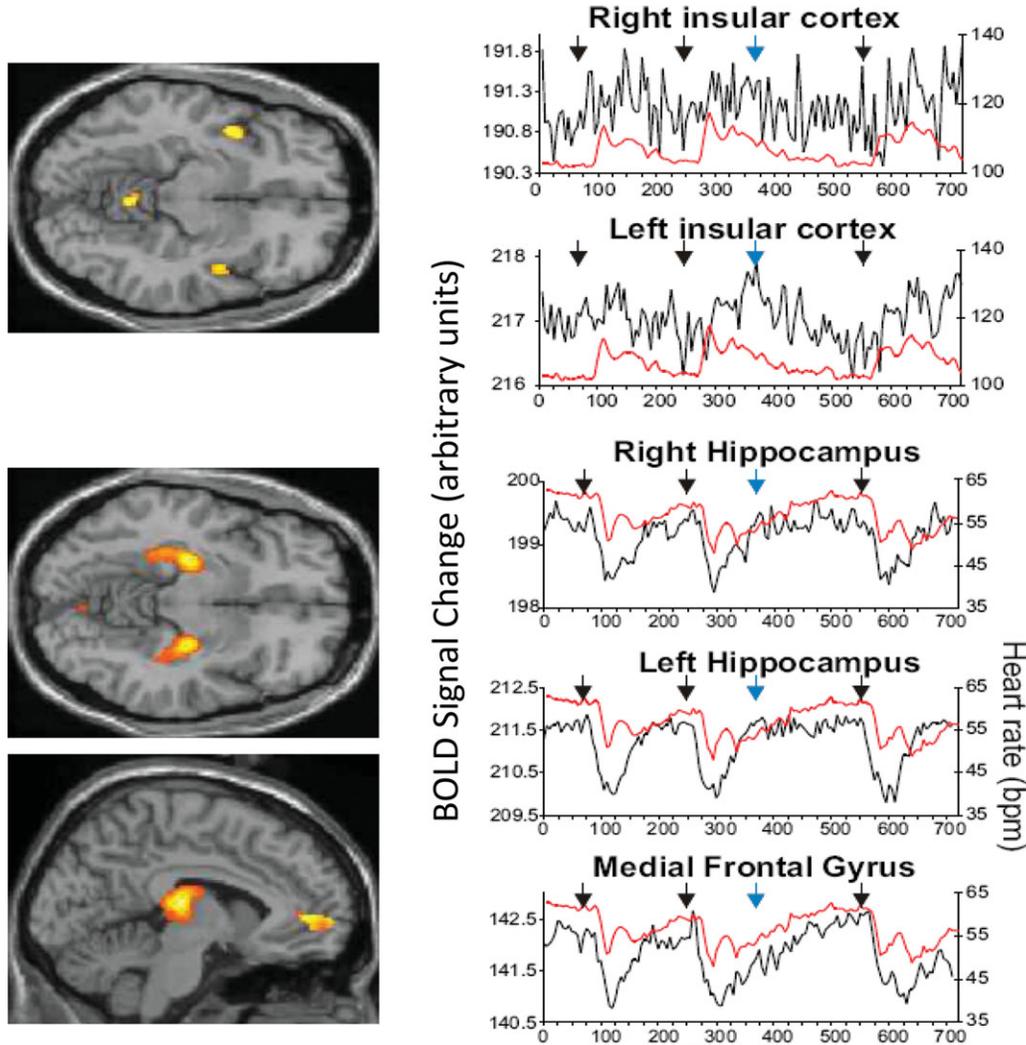
Fig. 2. Association between the blood oxygenation level dependent (BOLD) location (left panels), their response time course (black lines in graphs) and the heart rate time course (red lines). Cortical patterns of increased (right and left insula; top panels) and decreased activation (right and left hippocampus, medial frontal gyrus (or medial prefrontal cortex) associated with infusions of phenylephrine (black down-ward pointed arrows) or saline (blue arrow). Unpublished results from Topolovec et al.

MPFC region. Thus, studies are being conducted to address sensory representation within cortical autonomic regions and the concurrent cardiovascular outcomes.

SENSORY SIGNALS REFLECTED IN THE CORTICAL AUTONOMIC NETWORK

Baroreceptor Inputs

Given the concurrent rise in blood pressure and heart rate at the onset of HG exercise (e.g., Fig. 1), we have attempted to experimentally separate these two responses and study their independent effects on cortical activation patterns. We reasoned that a rise in blood pressure in the absence of volitional effort or cardiac responses would expose baroreceptor-mediated sensory pathways in the forebrain. Such separation can be accomplished using both pharmacologic and volitional models. As outlined above, the cardiovascular responses

to the exercise onset in young individuals include a tachycardia that develops within the first cardiac cycle. This is followed by the pressor response with a ~4 sec delay. Using this delay, Wong developed an event-related protocol that included a two-sec handgrip at either 30% or 70% of maximal contraction effort followed by variable periods of recovery [preliminary data presented in (Cechetto and Shoemaker, 2009)]. By constructing hemodynamic response models that emphasized either the handgrip period to capture the HR response, or the delayed blood pressure response after the cessation of HG, the cortical responses reflecting only the blood pressure response could be examined in the absence of the confounding patterns associated with volitional muscular effort and/or HR changes. These data indicated that the bilateral insula cortices and MPFC were activated in response to baroreceptor activation in a manner that was graded with the magnitude of the pressor response. It may be important to note that HR was declining as

the blood pressure was rising in this post-HG period. In contrast, during volitional effort the HR response is always associated with MPFC deactivation, as outlined above. Therefore, the MFPC pattern of response continued to be inversely related to HR. Further, this approach infers that the bilateral insula, and primarily the left insula, receives barosensory information, as clearly demonstrated in the rat.

To further assess the cortical organization associated with baroreceptor inputs in the absence of volitional effort or HR increases we have produced preliminary data reflecting the impact of phenylephrine-induced blood pressure increases (Topolovec et al., unpublished results; Fig. 2). In this approach, cortical regions associated with mean arterial pressure included increased activation in the bilateral insula cortices. A challenge with this model is the reflexive bradycardia induced by the drug-induced pressor response. Nonetheless, when correlated with HR (bradycardia), phenylephrine infusion was associated with increased activation in the MPFC. Recall that the rise in HR with volitional exercise correlates with deactivation within the MPFC region. Thus, MPFC responses to volitional or passive stimuli are consistently inversely related to HR. Together, these data indicate that baroreceptor-based sensory signals are directly associated with insula cortex activation and inversely associated with MPFC activation.

Somatosensory Inputs

During volitional handgrip, there are descending neural signals from higher cortical centers that coordinate the immediate cardiovascular (and respiratory) responses with muscular contractions to support the metabolic as well as blood flow and pressure needs associated with volitional exercise (Krogh and Lindhard, 1913; Mitchell, 1990). In addition, there are sensory signals arising from muscle spindles with the onset of the contraction. To study the isolated effect of muscle afferent, Goswami et al. (2011) examined the forebrain patterns associated with somatosensory afferent stimulation achieved by submotor electrical stimulation of forearm muscles through anesthetized skin. This approach preferentially recruits the large and myelinated muscle spindle afferent fibers (Radhakrishnan and Sluka, 2005). This somatosensory stimulation elicited increased activation within the thalamus, the posterior insula and the MPFC. In addition, important deactivation of the anterior insula cortex was observed. These observations are summarized in Fig. 3. Concurrently, heart rate was reduced and the spectral power of high frequency oscillations in heart rate, reflecting PNS activation, was increased. These findings indicate that muscle sensory afferents are represented within the insula and MPFC and subsequently affect an increase in PNS outflow. These data provide a backdrop against which the responses to volitional handgrip can be interpreted. Specifically, the MPFC is inversely related with HR levels and directly related to high frequency power in the heart rate variability. Thus, the combined information suggests that the MPFC exerts important influence over parasympathetic modulations of heart rate.

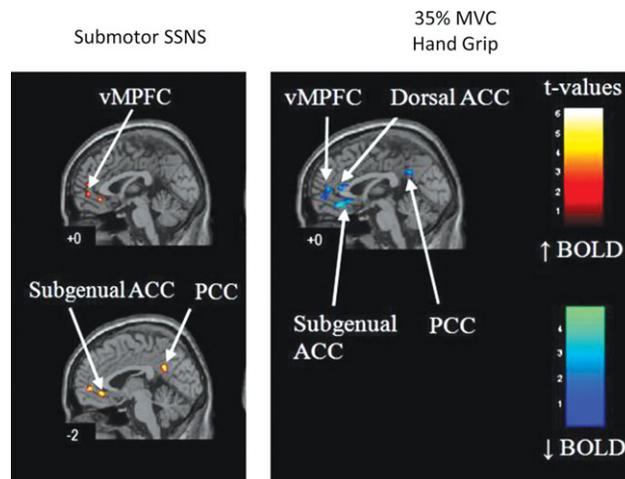This conclusion confirms the associative conclusions drawn in previous reports from various laboratories

Fig. 3. Cortical activation maps illustrating the average response (n = 12) of the ventral medial prefrontal cortex (vMPFC), subgenual anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC) and dorsal anterior cingulate during either submotor levels of forearm somatosensory nerve stimulation (SSNS) or volitional handgrip exercise performed at 35% of each individual's maximal voluntary contraction strength (MVC). The noteworthy patterns of increased activation (left panel; SSNS) and decreased activation (right panel, volitional handgrip) are illustrated. Adapted from (Goswami et al., 2011).

using different stimuli (Critchley, 2004; Gianaros et al., 2004; Wong et al., 2007b; Lane et al., 2008). In contrast to the MPFC, the posterior insula cortex is increased in its activation levels during volitional or passive stimuli suggesting that this BOLD response reflects a sensory region. These observations are consistent with evidence in rats which indicate the anatomical linkages of viscerosensory inputs to the insula (Oppenheimer and Cechetto, 1990; Allen et al., 1991), as well as the cardiovascular outcomes of posterior insula activation (Oppenheimer et al., 1991; Yasui et al., 1991; Butcher and Cechetto, 1995). Finally, the anterior insula is deactivated by sensory signals from muscle but not by baroreflex afferents or top-down signals during volitional work. The functional implications of this response have not been studied.

These data indicate that the cortical responses to volitional handgrip exercise observed with fMRI methods do, in fact, reflect a patterned response that, in the MPFC region, is diametrically different from that achieved by sensory inputs. Therefore, the brain appears to handle sensory information from skeletal muscle and baroreceptor afferents along similar pathways. If HR is reduced either by increased blood pressure or muscle sensory stimulation, the MPFC activity is increased. Because muscle and baroreceptor sensory inputs are engaged during 30-sec HG, it must be that the descending signals from cortical regions associated with volitional exercise dominate the sensory signals arising from these peripheral regions. The cortical pathways mediating this effect, culminating in MPFC deactivation despite sensory inputs that exert a net excitatory influence, remain to be determined. Overall, the available data provide strong support for a functional cortical network that processes and integrates information regarding muscle activation with cardiovascular responses.

RED: Increased Activation
BLUE: Decreased Activation

□ Lower Body Negative Pressure
○ Handgrip
△ Swallowing
✿ Submotor Somatosensory Muscle Stimulation
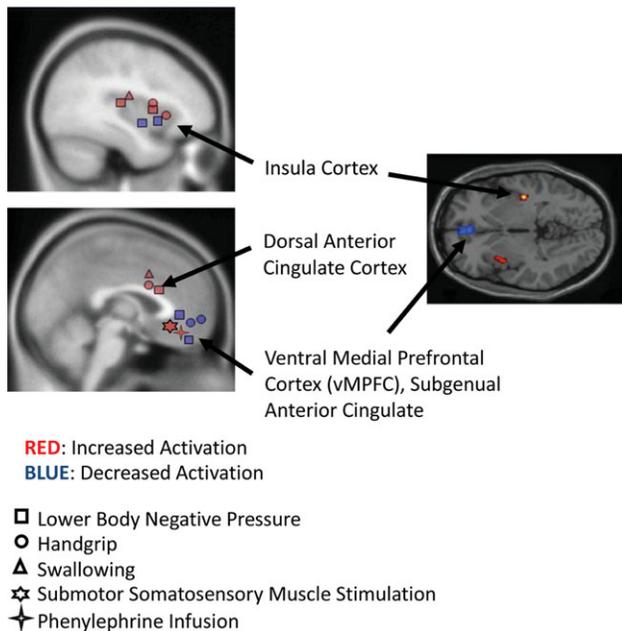✛ Phenylephrine Infusion

Fig. 4. The commonly observed regions of the forebrain where cortical activity is increased (red) or decreased (blue) during the physical stressors listed. Other regions that are commonly observed but have yet to be associated strongly with heart rate or sympathetic nerve activity in humans performing the physical stressors listed include the following: Amygdala, cerebellum, thalamus, hypothalamus, basal ganglia, and hippocampus.

SUMMARY

Overall, our studies in conscious humans using fMRI indicate that a set of forebrain regions are commonly associated either directly or inversely with reflex-mediated cardiovascular arousal or its depression. These regions, the pattern of activation (increased or decreased), and the reflexes with which they are associated (although more reflex studies could be performed) are illustrated in Fig. 4. In our experience, these regions represent the fundamental and reproducible cortical regions associated with cardiovascular adjustments to various reflex maneuvers in our experience. Furthermore, it is not uncommon to observe associations between changes in heart rate and the hippocampus and basal ganglia regions during baroreflex or handgrip-induced cardiovascular arousal. The role or relationship of these regions in the reflex cardiovascular response also remains to be determined.

To conclude, recent studies have outlined the anatomical and functional architecture of the forebrain in conscious humans that are associated with reflex-mediated cardiovascular control. Our evidence indicates that these regions are involved in both sensory representation of cardiovascular adjustments once they have been made, as well as in the active modulation of efferent neural changes that elicit the cardiovascular response. With these observations it is tempting to allocate a networked functionality to these regions although further anatomical and experimental approaches are required to examine this hypothesis.

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