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Forebrain organization for autonomic cardiovascular control

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ABSTRACT

This brief review discusses the current state of knowledge regarding the cortical circuitry associated with autonomic cardiovascular responses to volitional exercise in conscious humans. Studies to date have emphasized the autonomic nervous system adjustments that occur through top-down central command features as well as bottom-up signals arising from skeletal muscle. While in its infancy, the pattern of cortical circuitry associated with exercise seem to depend on the nature of the exercise but with common patterns arising in the insula cortex, dorsal anterior cingulate cortex, medial prefrontal cortex, and hippocampus.

1. Introduction

Physical exercise elicits rapid and large changes in autonomic nervous system outflow that affect cardiovascular adjustments in support of the effortful task. The neural circuitry involved in these autonomic responses includes sites in the brainstem and supramedullary centres. This brief review deals specifically with the current state of knowledge regarding the cortical circuitry associated with autonomic cardiovascular responses to volitional exercise in conscious humans. The following topics are discussed: 1) an overview of the background to the developing story surrounding the cortical autonomic patterns during exercise, 2) a description of the forebrain and midbrain neural circuitry associated with the cardiovascular arousal observed during volitional exercise models, and 3) new evidence regarding the cortical representation of sensory information from activated skeletal muscle and efferent autonomic outflow.

2. Section 1: overview

Brainstem nuclei and the interconnecting neural pathways that modulate autonomic nervous system outflow are well known (Benarroch, 1993; Dampney, 1994; Dampney et al., 2003; Loewy and McKellar, 1980; Potts et al., 2000). These brain stem pathways receive modulatory inputs from supramedullary centres (Barron and Chokroverty, 1993; Castle et al., 2005; Goswami et al., 2011; Owens and Verberne, 2000) providing the anatomical basis to suspect the cortex as an important contributor to cardiovascular arousal. Krogh and Lindhard (1913) provided the first hint that the cortex was involved in cardiovascular arousal during exercise with their observations of a change in heart rate and respiration at, or prior to, the onset of volitional exercise, ushering the "central command" hypothesis of neural control in exercise states. Since that time, considerable clinical (Critchley et al., 2003; Macey et al., 2008; Norris et al., 1978; Norton et al., 2013; Oppenheimer et al., 1991; Soros and Hachinski, 2012; Woo et al., 2003), and experimental work in rodents (Cechetto and Saper, 1990) outlined the functional cardiovascular outcomes due to stimulation of, or damage to, the insula, thalamus, hypothalamus, amygdala, and medial prefrontal regions. Benarroch (1993) outlined the "central autonomic network" as a group of brainstem and supramedullary regions suspected of being associated with modulation over the autonomic nervous system, although with less emphasis on forebrain or parietal regions than provided by others (Butcher and Cechetto, 1995a,1995b; Cechetto and Chen, 1995; Oppenheimer et al., 1991; Verberne et al., 1987, 1988, 1997).

The difficulty in studying the brain in its un-anesthetized intact state, along with limitations in the number of sites that can be examined simultaneously, represent some challenges in interpreting cortical function from clinical or experimental rodent models. Thus, an important experimental goal has been the establishment of models that expose functional brain patterns in the conscious animal. Two models have been used to accomplish this goal in humans. First, electrical stimulation of brain regions have been performed in conscious epileptic patients with indwelling electrodes (Al-Otaibi et al., 2010; Oppenheimer et al., 1992). To our knowledge, these studies are few, and are limited to insula cortex stimulation. Nonetheless, this model illustrates the ability of the insula cortex to affect heart rate through either bradycardia or

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tachycardia. The outcomes likely depend on a lateralized effect (Oppenheimer et al., 1992) or the location within the insula. Second, neuroimaging approaches, such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and to a greater extent, functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990, 1992) have provided a critical technological breakthrough to examine the temporal and spatial patterns of cortical activation in conscious humans performing volitional exercise.

3. Section 2: forebrain circuitry associated with exercise

Williamson et al. (1996, 2002) were the first to use the power of functional neuroimaging techniques to explore cortical metabolic changes under various conditions of volitional fatiguing handgrip exercise, or imagined exercise, in attempts to isolate regions related to descending "central" control. Using SPECT these authors observed changes in regional cerebral blood flow, representative of increased neural activity, within the anterior cingulate cortex (ACC) and bilateral insula cortex (IC) that were associated with the perceptual/volitional aspects of performing exercise (Williamson et al., 2003). Thus, these two regions repeatedly were associated with an efferent "motor" cardiovascular outcome.

In contrast to the steady-state and relatively long-term requirements of SPECT imaging, fMRI assesses the blood oxygenation level dependent (BOLD) signal with high temporal and spatial resolution. The first fMRI report to study reflex cardiovascular control in humans (King et al., 1999) outlined a large group of forebrain regions co-activated during brief maximal effort handgrip exercise. During these tasks increased cortical activation was observed in the hand regions of the contralateral motor and sensory cortices, medial prefrontal cortex (MPFC), ACC, bilateral IC, thalamus, amygdala and regions of the cerebellum. What these patterns mean in terms of autonomic balance (i.e., parasympathetic and/or sympathetic efferent changes) in such a model is difficult to determine because concurrent changes are expected in sensory feedback, cognitive or affect aspects of maximal effort, or peripheral hemodynamic changes. Each of these factors will cause changes in cortical neural activity, representing a major challenge for functional imaging studies in the exercise context. Regardless, this study laid the groundwork that exercise elicits wide-ranging cortical activation patterns.

Our approach to the study of the cortical network associated with autonomic adjustments has attempted to minimize the number of factors that potentially confound fMRI outcomes during heavy and fatiguing exercise. When performed by young adults at <40% of maximal contractile force for brief periods (e.g., <30 s), handgrip elicits an intensity-dependent tachycardia that is apparent within the first 1–2 s of the handgrip onset, growing to about 10–15 bpm above baseline levels over the contraction period. Pharmacologic blockade evidence suggests that reduced parasympathetic dominance, rather than sympathetic activation, mechanistically controls the bulk of this rapid heart rate response (Fagraeus and Linnarsson, 1976; Hollander and Bouman, 1975; Mitchell et al., 1989). Leg muscle sympathetic nerve activation does not increase in this model (Lalande et al., 2014) further supporting the interpretation that this maneuver, and some of the brain activation patterns that correlate with changes in heart rate (or heart rate variability), may reflect the reduction of parasympathetic cardiac inhibition. The handgrip task itself is associated with *increased* activation in the motor cortex, bilateral insula, thalamus, cerebellum, and basal ganglia (Wong et al., 2007b) as well as *decreased* activity relative to baseline within the posterior cingulate cortex and ventral MPFC (vMPFC) regions. In some participants, dorsal anterior cingulate cortex (dACC) activity decreases as well (see Fig. 1). However, only the decreased vMPFC activity correlated strongly and inversely with heart rate changes with a time course and magnitude of change that reflected variations in exercise intensities. This pattern has been observed in repeated studies (Goswami et al., 2011; Wong et al., 2007a, 2007b) and was not affected by one's sex or hand with which the task was performed (Wong et al., 2007a). Other reports examining the brain–heart relationship during cognitive and emotional stressors also emphasize the strong inverse relationship between MPFC and heart rate responses (Critchley, 2004, 2005; Critchley et al., 2000, 2003, 2004; Gianaros et al., 2004, 2005; Lane et al., 2009).

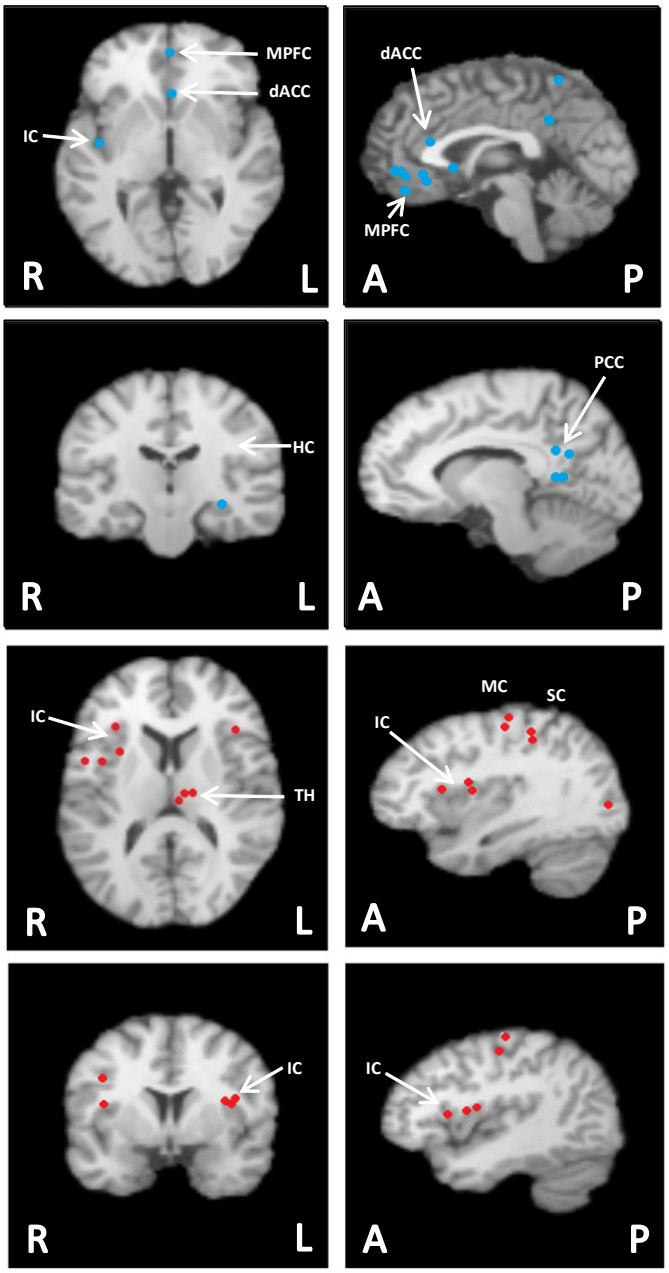

Fig. 1. Summary of common regions associated with the handgrip exercise task. Data represent 9 groups ($n = 124$) from 4 published papers (Wong et al., 2007a; Wong et al., 2007b; Norton et al., 2013; Goswami et al., 2011 and two unpublished studies from our laboratory). These participants each performed repeated bouts (3–7) of moderate intensity (35–40% maximal strength) handgrip tasks each lasting 30 s. Top panel: Cortical areas of *decreased* activation relative to baseline in response to short duration, moderate intensity isometric handgrip exercise. Bottom panel: Cortical areas of *increased* activation relative to baseline in response to short duration, moderate intensity isometric handgrip exercise. FDR pN = 0.01; Min 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) (Eickhoff et al., 2011, 2012; Turkeltaub et al., 2012). MPFC; medial prefrontal cortex, IC; insula cortex, dACC; dorsal anterior cingulate cortex, PCC; posterior cingulate cortex, MC; motor cortex, SC; sensory cortex, TH; thalamus, HC; hippocampus. 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.

In addition to the MPFC, the hippocampus (HC) may also participate in cardiac adjustments to exercise. Specifically, neural connections exist