SYMPOSIUM REVIEW

Defining the neurocircuitry of exercise hyperpnoea

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Abstract One hundred years ago in this journal, Krogh and Lindhard published a seminal paper highlighting the importance of the brain in the control of breathing during exercise. This symposium report reviews the historical developments that have taken place since 1913, and attempts to place the detailed neurocircuitry thought to underpin exercise hyperpnoea into context by focusing on key structures that might form the command network. With the advent of enhanced neuroimaging and functional neurosurgical techniques, a unique window of opportunity has recently arisen to target potential circuits in humans. Animal studies have identified *a priori* sites of interest in mid-brain structures, in particular the subthalamic locomotor region (subthalamic nucleus, STN) and the periaqueductal grey (PAG), which have now been recorded from in humans during exercise. When all data are viewed in an integrative manner, the PAG, in particular the lateral PAG, and aspects of the dorsal lateral PAG, appear to be key communicating circuitry for 'central command'. Moreover, the PAG also fulfils many requirements of a command centre. It has functional connectivity to higher centres (dorsal lateral prefrontal cortex) and the basal ganglia (in particular, the STN), and receives a sensory input from contracting muscle, but, importantly, it sends efferent information to brainstem nuclei involved in cardiorespiratory control.

Abbreviations dPAG, dorsal periaqueductal grey; dlPAG, dorsal lateral periaqueductal grey; dmPAG, dorsal medial periaqueductal grey; DLPFC, dorsal lateral prefrontal cortex; lPAG, lateral periaqueductal grey; MLR, mesencephalic locomotor region; PAG, periaqueductal grey; PMA, premotor area; PPN, pedunculopontine nucleus; SMA, supplementary motor area; STN, subthalamic nucleus; vlPAG, ventrolateral periaqueductal grey.

One hundred years ago, *The Journal of Physiology* published a classic paper by the Nobel Prize winning physiologist August Krogh and his colleague Johannes Lindhard (Krogh & Lindhard, 1913) concerning the regulation of respiration and circulation during the initial stages of muscular work. This publication became a landmark study for those interested in understanding how ventilation and the cardiovascular system are controlled during exercise. Since then, many animal and human studies have built on their initial observation showing

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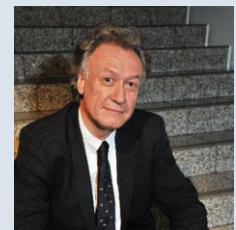
the importance of higher centre control. A wealth of information has been published, forgotten and latter re-discovered (e.g. Mateika & Duffin, 1995; Forster *et al.* 2012). This symposium report reviews the historical developments that have taken place since 1913, and attempts to place the detailed neurocircuitry thought to underpin exercise hyperpnoea into context by focusing on key structures that might form the command network.

It has been known for some time that the stimulation of skeletal muscle can affect ventilation and cardiovascular function (Zuntz & Geppert, 1886; Geppert & Zuntz, 1888; Johansson, 1893). Given the difficulty of studying the central nervous system in humans, much of the effort in the last century focused on the peripheral neural and chemical factors targeting areas of known chemoreception (Heymans & Heymans, 1927) as putative drivers for exercise hyperpnoea (e.g. Haldane & Priestley, 1905; Douglas & Haldane, 1909; Paterson, 1928; Comroe & Schmidt, 1943; Grodins, 1950; Bannister & Cunningham, 1954; Dejours, 1959; Wasserman & Whipp, 1975; Dempsey & Forster, 1982). Several by-products of muscle contraction received considerable attention in the 1970–80s, in particular H^+ (e.g. Wasserman *et al.* 1973; Wasserman & Whipp, 1975) and arterial potassium (e.g. Linton & Band, 1985, Burger *et al.* 1988; Paterson & Nye, 1988; Paterson *et al.* 1989), were mooted as being factor x (Haggard & Henderson, 1920), later renamed the 'hyperpnein' (Henderson, 1938) or 'anaerobic work substance' (Asmussen & Nielsen, 1946). However, studies with McArdle's patients (myophosphorylase deficiency – hence no acid on exercise) still show a relatively normal respiratory and hyperkalaemic response to exercise (Paterson *et al.* 1990). Circumstantial evidence supports a role for potassium as the 'work substance', although there is no direct proof of whether it is critical in exercise hyperpnoea (Paterson, 1992).

It is clear that exercise rhythm can entrain breathing frequency to a subharmonic of that rhythm (e.g. Bechbache & Duffin, 1977; Paterson *et al.* 1986) and hypoxia can reduce this coupling (Paterson *et al.* 1987). However, the removal of peripheral signals in humans does not appreciably change the steady-state isocapnic ventilatory response to exercise. This is seen following surgical denervation of the carotid bodies (Wasserman *et al.* 1975), in subjects with no functional chemoreception (congenital central hypoventilation syndrome) (Shea *et al.* 1993), following heart–lung transplantation (Banner *et al.* 1988), and in patients with spinal chord transection (Adams *et al.* 1984) or following epidural anaesthesia during exercise (Fernandes *et al.* 1990). However, recent work using selective afferent blockade during exercise suggests that muscle afferents play a significant role in the respiratory response (Amann *et al.* 2010). For some, these observations merely reinforce the notion that the essential nature of the control system resides in the brain (e.g. Rauch

et al. 2013; 'central governor' hypothesis), whereas others would argue that these studies confirm that the control is multifactorial, and is based on a high degree of redundancy (Cunningham, 1987).

Evidence for 'central command'

Krogh and Lindhard (1913) provided the first evidence for the concept of central command. They suggested that the rise in ventilation and heart rate (data provided by Miss Florence Buchanan in Haldane's laboratory at Oxford) was not produced reflexly, but by the 'irradiation of impulses from the motor cortex'. The experiment was simple yet informative. In anticipation of exercise, subjects showed greater ventilation in the transition from rest to work. When one subject (JL) was told to expect a heavy load (when in fact it had not changed), the resulting ventilation during the first few seconds of exercise was essentially the same as if the extra load was present (see Fig. 4 from Krogh & Lindhard, 1913). The power of this observation in respiratory control is further illustrated when hypnotic suggestion is used to focus attention (Daly & Overly, 1966; Morgan *et al.* 1973). Figure 1 is an example that attests to the reproducibility of Krogh & Lindhard's original observation, when hypnotized subjects who are exercising on a cycle ergometer are told to imagine cycling 'uphill' at the same pedal frequency. Here, isocapnic buffering is lost as the subjects breathe disproportionately to the metabolic rate until they are told the imagined 'hill' has disappeared (Thornton, 1999). A similar response is seen at rest with no movement feedback when subjects are told to imagine cycling up a hill (Thornton *et al.* 2001).

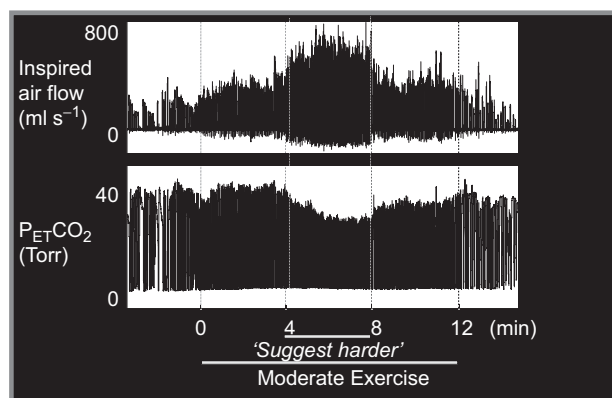The significance of the earlier observation by Krogh & Lindhard was recognized by Goodwin *et al.* 1972, who first

Figure 1. Breathing response to altered perception of effort
Respiratory responses during exercise under hypnotic suggestion. Note the increase in inspired air flow and loss of isocapnic buffering when subjects are told to imagine ('*Suggest harder*' line on *x* axis) the exercise has become hard whilst maintaining a constant pedal frequency and exercise intensity. From Thornton (1999) with permission.

used the term 'central command'. In a clever experiment, they showed that ventilation, heart rate and arterial blood pressure would follow a change in central command brought about by tendon vibration on either the triceps or biceps muscle during isometric exercise at constant muscle tension. For example, when the triceps was contracting, tendon vibration of the biceps muscle would cause reflex inhibition, so that more central command would be required to maintain the same tension in the muscle during biceps contraction. This resulted in a greater cardio-respiratory response (Fig. 2). The converse was true for vibration of the biceps muscle. So, where are the command neurons for 'central command'?

Higher central circuits

In humans, there have been several approaches to address this question employing a combination of neuroimaging techniques (e.g. Fink *et al.* 1995; Williamson *et al.* 2001), transcranial stimulation (e.g. Gandevia & Rothwell, 1987) and functional neurosurgical interventions (deep brain stimulation; Green *et al.* 2005). Penfield and Foerster, both leading neurosurgeons of their day, first showed that discrete electrical stimulation of the primary motor cortex excited the diaphragm (e.g. Foerster, 1936; Penfield & Boldrey, 1937). Others have refined this approach using percutaneous stimulation (Gandevia & Rothwell, 1987) or transcranial magnetic stimulation of
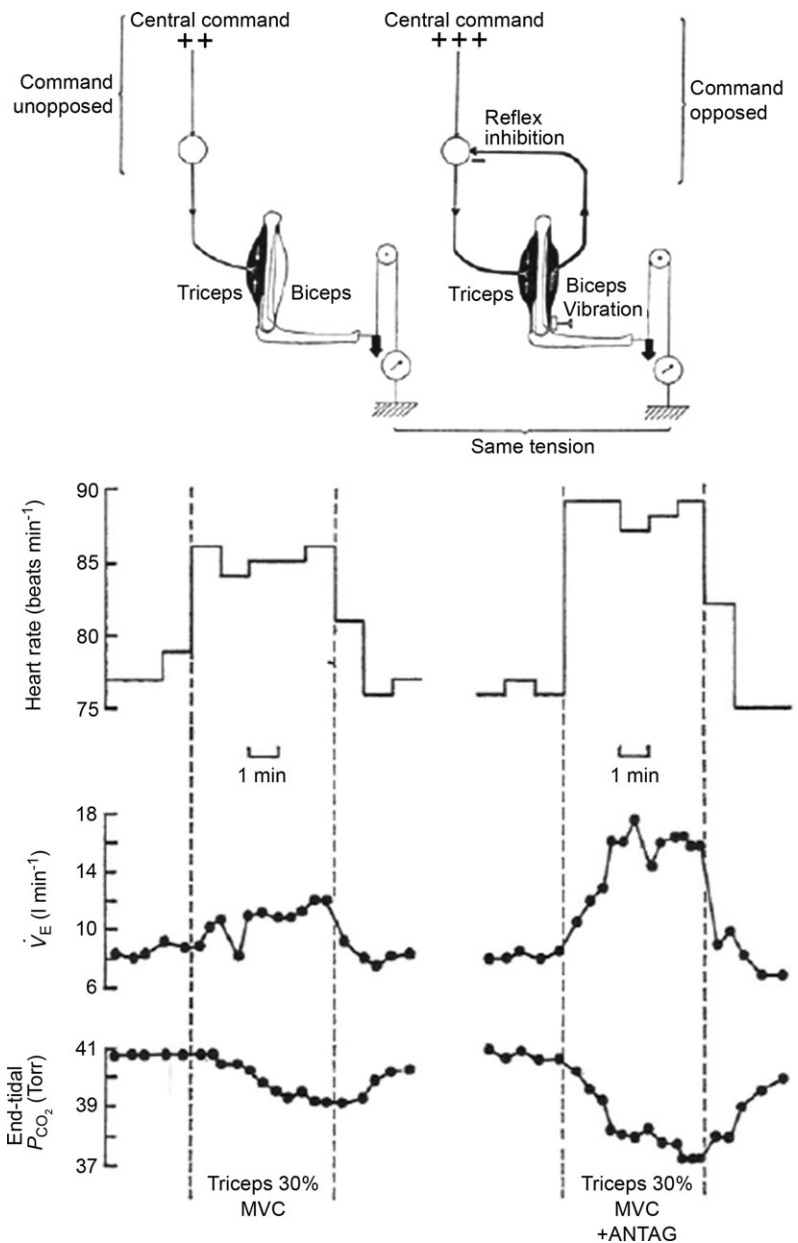

Figure 2. Altered central command using tendon vibration

Top panel: principle of experiment to increase central command required to achieve the same muscle tension. On the left is the force exerted by the forearm through voluntary contraction of the triceps muscle: the magnitude of central command is given as ++. On the right is the vibration of the biceps; an antagonist of the contracting muscle is used to excite the primary afferents from the muscle spindles in the biceps. This contributes an element of reflex inhibition to the motor neurons innervating the contracting triceps. The same downward force can thus be exerted by a contraction of the triceps, only if a greater central command (here +++) is given. Bottom panel: increase in central command. On the right are the responses to a contraction of the same force in which the central command required was greater because of vibration applied to the antagonist, the biceps. Note the greater breathing and heart rate responses. ANTAG, antagonist; MVC, maximum voluntary contraction. Modified from Goodwin *et al.* (1972) with permission.

the motor cortex (Corfield *et al.* 1998) to support the idea of a fast conducting oliosynaptic motor pathway that activates the diaphragm via a cortico-spinal tract that presumably 'by-passes' the brainstem respiratory centre. Fink *et al.* (1995) employed positron emission tomography and showed that the hyperpnoea observed during and immediately after exercise in humans was correlated with the activation of motor cortical sites, specifically, the left and right superomedial primary motor cortex and left and right superolateral primary cortex, areas associated with volitional breathing.

In an attempt to uncouple 'central command' from movement feedback, Thornton *et al.* (2001) used hypnotic suggestion of exercise during concurrent positron emission tomography scanning. Three cognitive conditions were used, involving the imagination of: (i) free-wheeling downhill on a bicycle; (ii) cycling up a hill; and (iii) volitional hyperventilation with the CO_2 clamped to match the breathing observed in (ii). Similar to Fink *et al.* (1995), significant activation was seen in the supplementary motor area (SMA) and premotor area

(PMA). In addition, the thalamus, bilateral cerebellum and right dorsal lateral prefrontal cortex (DLPFC Brodmann area 9) were also activated (fig. 3). These areas are concerned with volitional/motor control that also includes respiratory muscle. However, when breathing was driven voluntarily, only the SMA and sensorimotor cortex were activated. The lack of activation of the dorsal lateral precortex is particularly interesting, because this area is important for working memory and executive function, which also includes the regulation of thinking and tasks (Frith *et al.* 1991). It projects to the SMA/PMA but not to the motor cortex itself. Moreover, it also has a projection to the lateral periaqueductal grey (lPAG) (An *et al.* 1998), which is an area that is widely believed to be important in cardiorespiratory control during stress and emotional states (Bandler & Shipley 1994; Dampney *et al.* 2013). Emerging evidence now suggests that the dorsal lateral periaqueductal grey (dlPAG)/lPAG, which is activated during exercise, could form a key part of the circuitry involved in 'central command' (Green *et al.* 2007; Basnayake *et al.* 2011 see below).
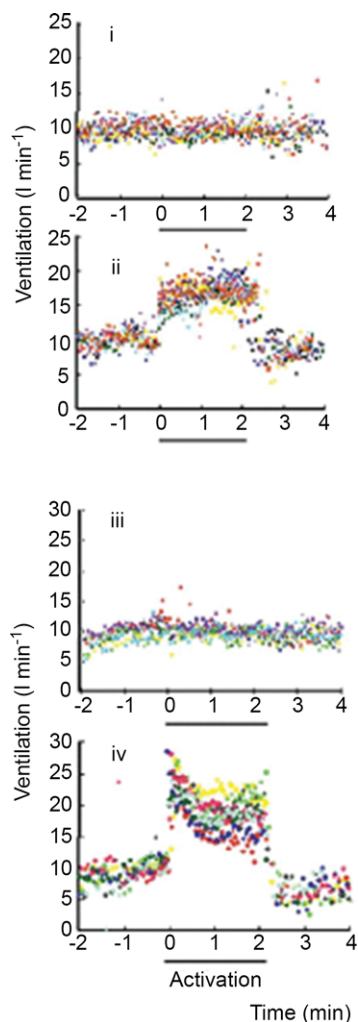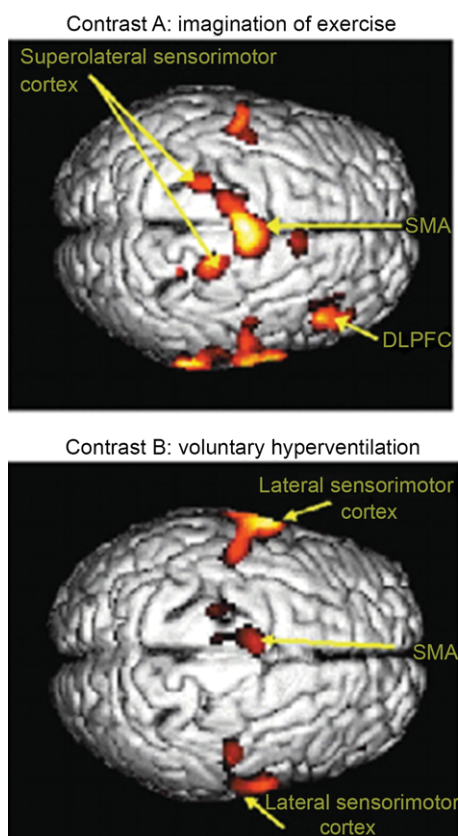

Figure 3. Activations during imagination of exercise and voluntary hyperventilation with associated respiratory responses

Left panel: main activations during contrasts A and B rendered on the dorsal aspect of a representative brain in a transverse view from above (right edge, anterior) shown at $P < 0.01$ (uncorrected for multiple comparisons), for clarity. Right panel: breath-by-breath ventilatory data in one subject for contrast A, imagining cycling uphill (ii), and for contrast B, breathing to an instructed frequency (iv) copying that in (ii). Graphs (i) (contrast A) and (iii) (contrast B) record the absence of effect when imagining freewheeling downhill. Each point represents a single breath and the eight colours represent each repeat of the protocol. Experimental periods of 2 min 10 s are marked by the full lines (*x* axis) when the scan was performed. DLPFC, dorsal lateral prefrontal cortex; SMA, supplementary motor area. Activations within 2 cm of the brain surface are represented. From Thornton *et al.* (2001) with permission.

Mid-brain circuits

Subthalamic nucleus. The visualization of deep brain structures during exercise with neuroimaging techniques is technically challenging, given the blurring effects that can be detected as a result of the smallest of head movements caused by whole body exercise. Until relatively recently, direct electrophysiological evidence came from early animal investigations that focused on the sub-thalamic locomotor region of the posterior hypothalamus and the broader mesencephalic locomotor region (MLR) as key structures in cardiorespiratory neurocircuits. Pitts *et al.* (1941) provided some of the first evidence for increases in sympathetic discharge and arterial blood pressure following stimulation of the hypothalamic region in anaesthetized cats. Similarly, Smith *et al.* (1960) and Eldridge *et al.* (1981) refined this approach, and showed that the activation of the H2 fields of Forel, which include the dorsal aspect of the subthalamic nucleus (STN) in dogs, mimicked their arterial blood pressure response to exercise (Smith *et al.* 1960). Eldridge *et al.* (1981) then went on to elegantly demonstrate that the stimulation of the mesencephalic locomotor region (including the STN) in the decorticate cat caused a parallel activation of both cardiovascular and respiratory activity. Importantly, they observed that blocking all movement feedback during stimulation with curae (fictive locomotion) still caused an increase in arterial blood pressure, heart rate and phrenic nerve activity (Fig. 4). Other areas of the MLR, such as the pedunculopontine nucleus (PPN), can also cause a rise in cardiorespiratory variables following muscle contraction in the rat (Plowey & Waldrop 2004); moreover, c-fos studies confirmed that the PPN is activated during treadmill running (Iwamoto *et al.* 1996). Of interest, the reflex diaphragmatic response caused by muscle contraction was attenuated by a cobalt injection into the rostral PPN, whereas the cardiovascular response remained intact, suggesting a differential neural integration (Plowey & Waldrop 2004).

As compelling as these studies might seem, they do not represent 'central command' *per se*, but rather sub-cortical control that can drive a cardiorespiratory response independent of movement feedback. Furthermore, the loss of descending cortical–thalamic inhibition in the exercising cat model also calls into question the exact quantitative role played by the MLR in exercise hyperpnoea. Nevertheless, these pioneering animal studies paved the way for deep mid-brain neural sites to be targeted directly in humans with the advent of improved neuroimaging coupled with precise stereotaxic neurosurgical techniques (Fig. 5).
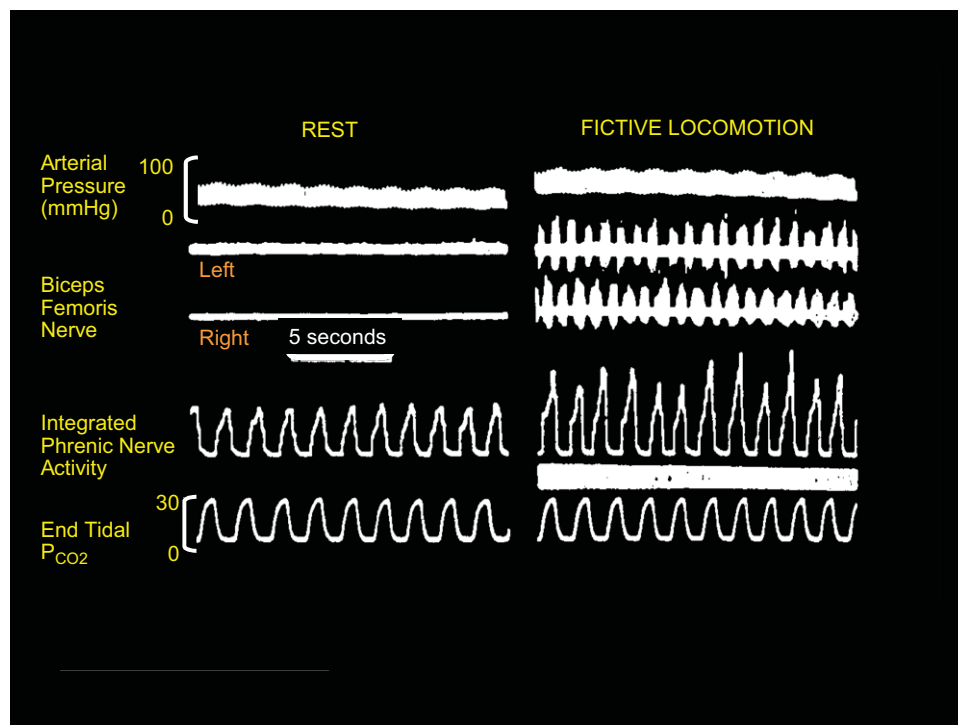

Figure 4. Activation of mid-brain nuclei to drive locomotion and cardiorespiration independent of peripheral feedback
Left panel: example of locomotion induced by electrical stimulation of the subthalamic locomotor region. Right panel: example of cardiovascular and respiratory responses during fictive locomotion induced by stimulation of the subthalamic locomotor region. Here the decorticate animals were paralyzed and ventilated. Note the increase in phrenic nerve activity during stimulation. Modified from Eldridge *et al.* (1981) with permission.

Thornton *et al.* (2002) targeted the STN in patients with a Parkinsonian phenotype and reported that high-frequency stimulation (depolarization block) facilitated movement, but also increased the heart rate and systolic and diastolic blood pressure by removing an inhibitory 'break' on the system (Thornton *et al.* 2002). Advancing this study further, Basnayake *et al.* (2012) recently re-visited the 'Goodwin *et al.*' paradigm using muscle vibration during constant tension-based isometric contraction, whilst recording field potentials in the STN. Here, a decrease in the inhibitory action of the STN during biceps muscle contraction was further potentiated when the triceps tendon was vibrated, thereby activating the muscle spindle afferents to cause reflex inhibition. This resulted in more 'central command' in order to maintain the same tension (Basnayake *et al.* 2012). It is clear that the basal ganglia is a complex circuit and may form only a part of the circuitry involved in central command itself (e.g. Williamson *et al.* 2001), especially for cardiovascular control during exercise (Williamson, 2010). In particular, the posterior hypothalamus receives a heavy projection from the periaqueductal grey (PAG) (Mantyh, 1983), which appears to be diffuse in nature, rather than from distinct regions of the PAG, although Sakai *et al.* (1990) reported notable connectivity from the lPAG and dlPAG.

Periaqueductal grey. This structure provides a functional interface between the forebrain and lower brainstem, and has been referred to as a visceral, nociceptor and 'cognitive integrator' (Mantyh, 1983). Its well-established role in the
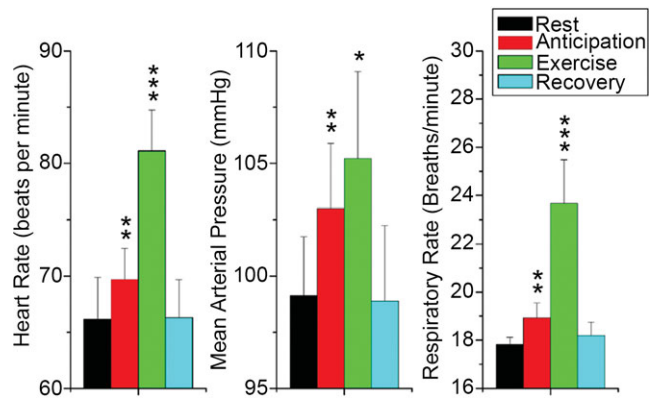

Figure 6. Changes in cardiorespiratory parameters with exercise and anticipation of exercise
Note that all three parameters, i.e. heart rate, mean arterial pressure and respiratory rate, increased with anticipation, and further with exercise. Similarly, all parameters recovered after exercise was stopped. Error bars show one standard error of the mean; $**P < 0.01$, $***P < 0.001$, $*P < 0.05$. From Green *et al.* (2007) with permission.
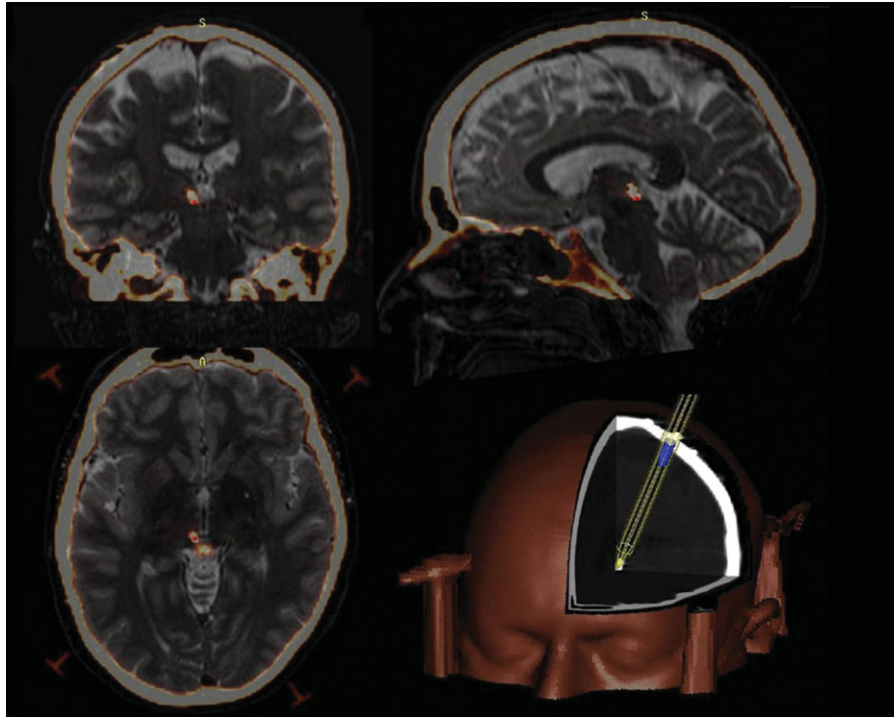

Figure 5. Targeting mid-brain structures using functional neurosurgical techniques
Fused pre-operative magnetic resonance imaging and post-operative computed tomography images highlighted using heat mapping (axial, coronal and sagittal clockwise from bottom left) showing left periaqueductal grey electrode placement. Three-dimensional reconstruction of the electrode trajectory is shown bottom right. From Pereira *et al.* (2013) with permission.
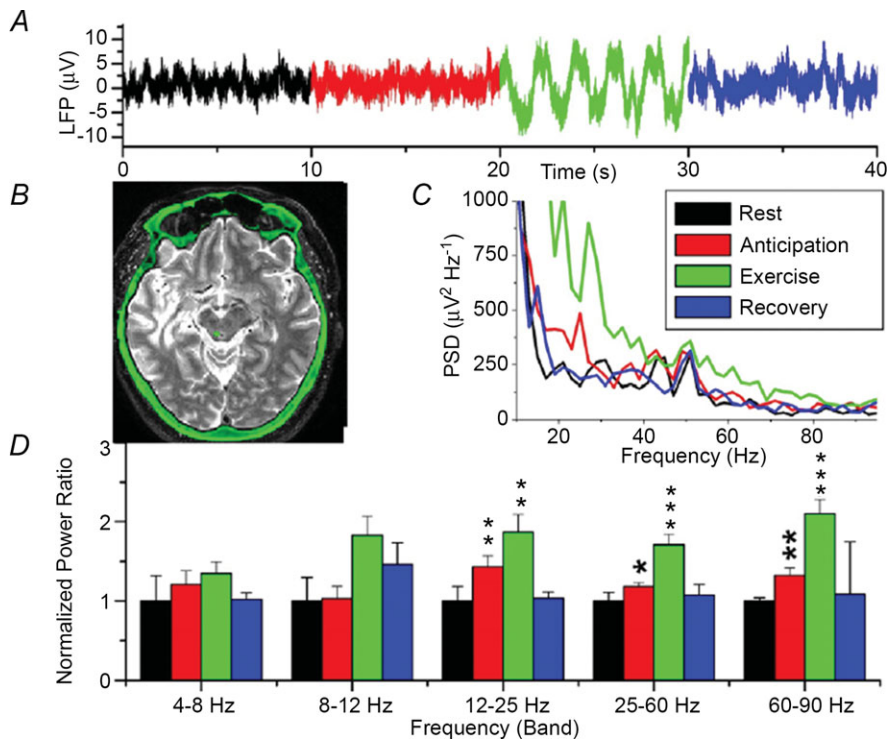
Figure 7. Local field potential (LFP) changes in the periaqueductal grey (PAG) during rest, anticipation, exercise and recovery

A, raw data trace. *B*, post-operative magnetic resonance image showing a unilateral electrode in the left PAG (green dot). *C*, mean power spectral density (PSD) for all three patients (recovery not shown for clarity). *D*, normalized spectral changes (rest = 1.0) divided into frequency bands. *P < 0.05, **P < 0.01, ***P < 0.001. Note increase in neural activity during both anticipation of exercise and actual exercise. From Green *et al*. (2007) with permission.
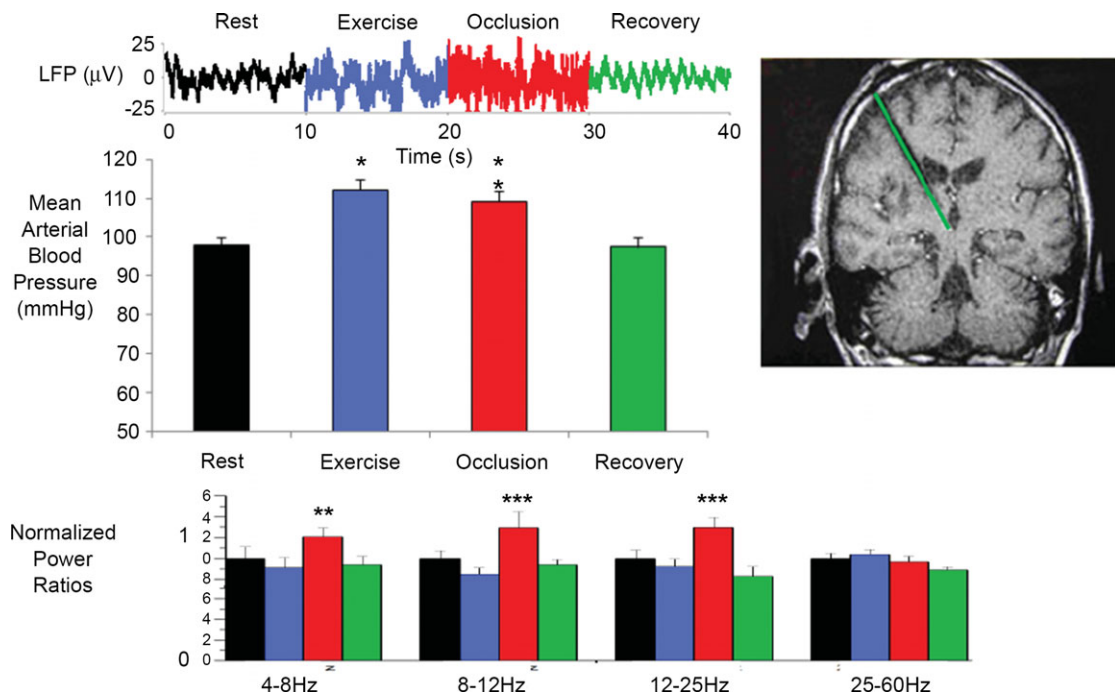
Figure 8. Local field potential (LFP) changes in the periaqueductal grey (PAG) during activation of muscle pressor reflex

Top panel: raw data trace. Middle left panel: activation of muscle pressor reflex during light muscle contraction. Middle right panel: post-operative image (post-operative computed tomography fused to pre-operative magnetic resonance) showing a unilateral electrode in the right PAG. Bottom panel: normalized spectral changes (rest = 1.0) divided into frequency bands. *n* = 6, **P < 0.01, ***P < 0.001. Note that PAG remains elevated when the pressor reflex is active. Modified from Basnayake *et al*. (2011) with permission.

modulation of pain (internal stress) and defensive action (fight/flight or coping: external stress) (e.g. Benarroch, 2012) is now being extended to our understanding of cardiorespiratory control during exercise (Green *et al.* 2007; Basnayake *et al.* 2011). Interestingly, removal of the PAG through lesioning results in immediate loss of consciousness (Watt *et al.* 2000), mutism (Esposito *et al.* 1999), attenuation of carbon dioxide sensitivity (Lopes *et al.* 2012), loss of the muscle pressure reflex (Williams *et al.* 1990) and instances of respiratory failure in the case of subacute necrotizing encephalomyelopathy (Leigh's syndrome) (Arii & Tanabe, 2000). The neural architectural of the PAG is very heterogeneous where it is divided into four distinct longitudinal columns comprising the dorsal medial periaqueductal grey (dmPAG), dlPAG, lPAG and ventrolateral periaqueductal grey (vlPAG) (Dampney *et al.*

2013). This structure is closely related to function. Each column has its own cytoarchitecture comprising neurons that are heterogeneous in size and shape with over-lapping connections (Mantyh, 1983). The PAG circuits associated with cardiovascular responses are now well established in animals (Kabat *et al.* 1935; Lovick, 1985; Carrive *et al.* 1988) and human studies (Green *et al.* 2005), whereas we are only now obtaining a fuller understanding of the circuitry to and from the PAG that can control breathing (Horn & Waldrop 1998; Horiuchi *et al.* 2009; Subramanian, 2013).

An *et al.* (1998), Benarroch (2012) and Dampney *et al.* (2013) have provided a comprehensive review of the inputs and outputs of the PAG. In brief, the rat PAG receives selective inputs from the medial prefrontal cortex, amygdala, hypothalamus and nociceptive pathways, and
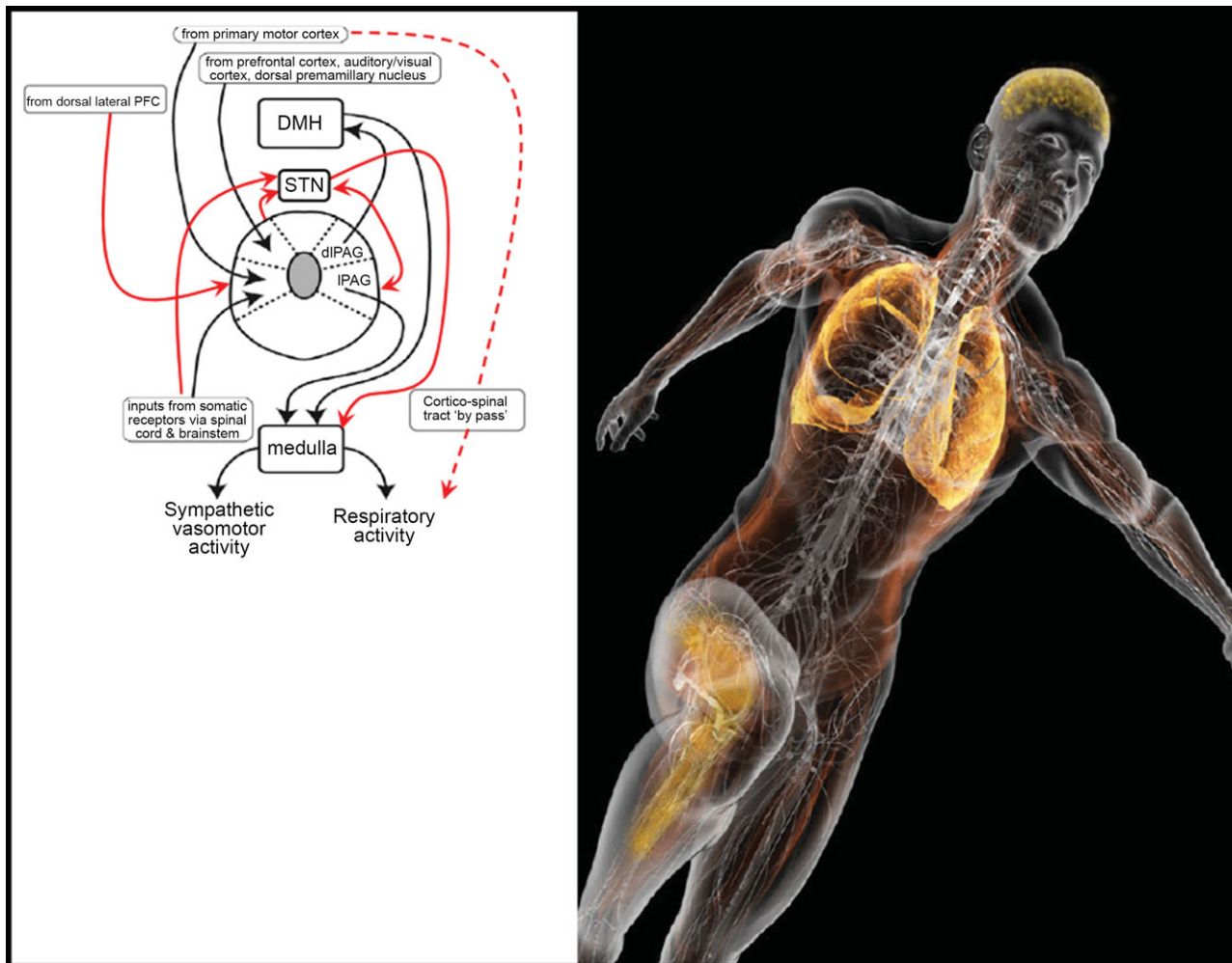
Figure 9. Proposed circuitry for exercise hyperpnoea
Left panel illustrates, in schematic form, the key circuits that may underpin the networks and structures involved in exercise hyperpnoea. dlPAG, dorsal lateral periaqueductal grey; DMH, dorsal medial hypothalamus; lPAG, lateral periaqueductal grey; PFC, prefrontal cortex; STN, subthalamic nucleus. Modified from Dampney *et al.* (2013) with permission. New proposed circuits in red. In particular, this network may underpin the 'central governor hypothesis' proposed by Noakes (Rauch *et al.* 2013). Running man image with permission from Bryan Christie Design.

sends outputs via the dorsal medial and lateral columns to thalamic and brainstem areas, especially those involved in cardiovascular regulation (e.g. rostral and caudal ventrolateral medulla) associated with 'fight and flight' responses (Bandler & Carrive, 1988). Conversely, coping responses, such as hypotension, bradycardia and hypopnoea, are observed when the ventrolateral column of the PAG is activated (Benarroch, 2012). Indeed, there is an especially close relationship between the PAG and the hypothalamus, given the functional connectivity reported by Horiuchi *et al.* (2009). In particular, there is a prominent synaptic connection from the dlPAG to the dorsal medial hypothalamus, which has been shown to increase respiratory activity when stimulated (e.g. Dampney *et al.* 2013).

Subramanian *et al.* (2008) and Subramanian (2013) have undertaken a detailed electrophysiological profile of various aspects of the rat PAG, and have shown different respiratory patterns depending upon the site of stimulation. Activation of the dlPAG causes active breathing and tachypnoea, consistent with a defence response, whereas stimulation of the medial part of the lPAG causes apneusis (Subramanian *et al.* 2008). However, stimulation of the dorsal aspect of the lPAG increases diaphragm electromyogram activity twofold as a consequence of increases in inspiratory time and decreases in expiratory time (Subramanian, 2013). Taken together, these data provide a framework to suggest that the PAG can serve as a strong modulator of breathing. Of interest, the DLPFC that is activated during 'exercise' (see Thornton *et al.* 2001) projects to the lateral PAG (An *et al.* 1998). Two big questions then arise. First, are all the PAG-activated cardiorespiratory responses only related to internal or external stress? Second, is it possible that neurons in the lPAG are activated in a reciprocal fashion to increase and decrease respiratory activity associated with exercise and recovery?

Treadmill running and static muscle contraction in rats increase c-fos activation of the PAG (Iwamoto *et al.* 1996; Li & Mitchell, 2003). When Green *et al.* (2007) re-visited the 'Krogh and Lindhard' paradigm of anticipation of exercise, they observed marked increases in PAG activity when their patients were alerted to impending exercise. Neural activity increased further during actual exercise and then subsided during recovery as cardio-respiratory variables returned to baseline values (Figs 6 and 7). This study provided direct neurophysiological support in an exercising human for the idea that the dorsal periaqueductal grey (dPAG) may be a key part of the sub-cortical neurocircuitry of central command. What was not established was the precise location of the electrodes in the dPAG. If the PAG is a 'cognitive integrator', what is its relationship with the peripheral nervous system given the abundance of information travelling into the brain during exercise? There is convincing evidence that muscle

contraction brought about by ventral root stimulation increases activity in both the posterior hypothalamus (Waldrop & Stremel 1989) and the PAG in the cat (Kramer *et al.* 1996). Group III and IV afferents connect to the PAG and carry important sensory information from muscle regarding nociception, but they also transmit the signal underpinning the exercise pressor reflex (Coote *et al.* 1971; McCloskey & Mitchell 1972). Basnayake *et al.* (2011) provided direct evidence for excitation of the dPAG in patients during activation of the exercise pressor reflex, confirming the functional significance of the PAG as an integrator of this reflex (Fig. 8).

Conclusion

When all data are viewed in an integrative manner, the PAG, in particular the lPAG and aspects of the dlPAG, appears to be a key communicating circuit for 'central command'. Moreover, the PAG also fulfils many requirements of a command centre. It has functional connectivity to higher centres (DLPFC) and the basal ganglia (in particular, the STN), and receives a sensory input from contracting muscle, but, importantly, it sends efferent information to brainstem nuclei involved in cardiorespiratory control (see Fig. 9).

The future challenge will be to build on these observations to test the robustness of the PAG as an essential structure in the circuitry underpinning exercise hyperpnoea, but to also establish the connections to other structures that are coupled to the exercise response. We have come a long way since Krogh and Lindhard (1913), although, in many ways, we are also now at the beginning of a new effort to re-assemble the neural circuits responsible for exercise hyperpnoea.

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Additional information