Identification of higher brain centres that may encode the cardiorespiratory response to exercise in humans

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1. Positron emission tomography (PET) was used to identify the neuroanatomical correlates underlying 'central command' during imagination of exercise under hypnosis, in order to uncouple central command from peripheral feedback.

2. Three cognitive conditions were used: condition I, imagination of freewheeling downhill on a bicycle (no change in heart rate, HR, or ventilation, $\dot{V}_I$): condition II, imagination of exercise, cycling uphill (increased HR by 12 % and $\dot{V}_I$ by 30 % of the actual exercise response): condition III, volitionally driven hyperventilation to match that achieved in condition II (no change in HR).

3. Subtraction methodology created contrast A (II minus I) highlighting cerebral areas involved in the imagination of exercise and contrast B (III minus I) highlighting areas activated in the direct volitional control of breathing ($n = 4$ for both; 8 scans per subject). End-tidal P_{CO_2} (P_{ET,CO_2}) was held constant throughout PET scanning.

4. In contrast A, significant activations were seen in the right dorso-lateral prefrontal cortex, supplementary motor areas (SMA), the right premotor area (PMA), superolateral sensorimotor areas, thalamus, and bilaterally in the cerebellum. In contrast B, significant activations were present in the SMA and in lateral sensorimotor cortical areas. The SMA/PMA, dorso-lateral prefrontal cortex and the cerebellum are concerned with volitional/motor control, including that of the respiratory muscles.

5. The neuroanatomical areas activated suggest that a significant component of the respiratory response to 'exercise', in the absence of both movement feedback and an increase in CO_2 production, can be generated by what appears to be a behavioural response.

How humans can match the cardiorespiratory responses to the increase in metabolic rate caused by exercise has proved difficult to unravel. Removal of putative peripheral drives or their absence in some pathological conditions does not significantly affect the steady-state cardiorespiratory response to exercise (Wasserman *et al.* 1975; Adams *et al.* 1984; Shea *et al.* 1993; Pan *et al.* 1995; Banner *et al.* 1988). Circumstantial evidence supports the existence of cortical control (Krogh & Lindhard, 1917); moreover, the superlateral motor cortical areas that are known to be concerned with volitional inspiration (Gandevia & Rothwell, 1987; Colebatch *et al.* 1991) are activated during exercise (Fink *et al.* 1995). In both decorticate cats and anaesthetized paralysed dogs, subcortical command centres have also been shown to drive locomotion together with an associated cardiorespiratory response that can be independent of afferent feedback (Smith *et al.* 1960; Eldridge *et al.* 1981, 1985). However, uncoupling the role of higher centre command from the movement itself and identifying its neuroanatomical correlates has never been achieved, since precision imaging of the brain with positron emission tomography (PET) or functional magnetic resonance imaging (MRI) requires an immobile head; a condition that is not yet possible to achieve during dynamic leg exercise.

Imagining movement (Decety *et al.* 1991) or attempting to contract muscles before and after regional anaesthesia (Gandevia & Hobbs, 1990; Jørgensen *et al.* 1993) or neuromuscular blockade (Secher, 1985; Gandevia *et al.*

1993) has been used to dissociate peripheral neural signals from central command. Attempted muscle contraction in these studies enhances the cardiovascular response. Nowak *et al.* (1999) reported that before axillary blockade, handgrip exercise activated the contralateral sensory motor area, supplementary motor area and ipsilateral cerebellum. This pattern of activation was not affected by regional anaesthesia even though the strength of contraction was reduced (Nowak *et al.* 1999), suggesting that the activated areas may be involved in generating command-related cardiovascular responses to exercise.

Mental imagery of treadmill exercise at rest (Decety *et al.* 1991) has been shown to increase heart rate (HR) and ventilation ($\dot{V}_I$); however, in more recent work (Wuyam *et al.* 1995) the response was only seen in athletes. Imagination of exercise has also been studied under hypnosis (Levin & Egolinsky, 1936; Nemtzova & Shatenstein, 1936; Agosti & Camerota, 1965; Daly & Overley, 1966; Morgan *et al.* 1976; Wang & Morgan, 1992) with all studies showing increases in $\dot{V}_I$ and one (Arvidsson *et al.* 1970) showing increases in cardiac output. Hypnosis allows isolation from the environment and therefore permits a more directed imagination than is possible when awake (Morgan *et al.* 1973; Coe *et al.* 1980). In this state, we have used imagination of exercise at rest in experimentally naive volunteers as a cognitive tool to uncouple central command from peripheral feedback. We show in humans that a significant component of the cardiorespiratory response to the imagination of exercise can be generated in the absence of both movement feedback and any increase in carbon dioxide production. Using PET we have identified higher brain areas that may encode a cardiorespiratory motor programme.

A part of this study has been presented in abstract form (Thornton *et al.* 1997; Paterson *et al.* 2000).

METHODS

All volunteers gave their informed consent whilst remaining experimentally naive regarding cardiorespiratory control. Experiments were carried out with local ethics committee approval and with permission from the Administration of Radioactive Substances Advisory Committee, London, to administer radioactivity to male subjects over 25 years of age. All experiments conformed to the Declaration of Helsinki.

Two studies were undertaken, all under hypnosis. Study 1: imagination of exercise whilst at rest. Study 2: neuroimaging during imagination of exercise whilst at rest.

Throughout this paper, 'awake' is used to describe the normal conscious state and 'under hypnosis' refers to the hypnotized state, which is clearly distinguishable from sleep.

Subject selection and familiarization

Initial assessments were performed on athletically untrained, healthy, experimentally naive subjects ($n = 27$; 22 men and 5 women), who were hypnotized using a standard induction procedure (a combination of visual fixation and progressive relaxation suggestions) and assessed for their hypnotic susceptibility and trance depth by experienced medical hypnotists (D.L.P./A.R.G.). Subjects were scored according to a modified version of the Stanford hypnotic susceptibility scale form B (Weitzenhoffer & Hilgard, 1959). Those scoring 6 or more during this assessment proceeded to the rest of the study (the scale being graded from 0 to 12, with 12 being the most susceptible). These subjects would typically show features associated with deep hypnosis, including partial amnesia, an altered perception of the passage of time and rapid responses to suggestions of visual, auditory and olfactory imagery. Seven subjects were rejected at this stage owing to low susceptibility scores and the group for study 1 then consisted of 18 men and 2 women, aged 26 ± 1 years (mean ± S.E.M.).

In study 2, eight experimentally naive men who scored 6 or more out of 12 on the Stanford scale were familiarized with leg exercise cycle ergometry in the semi-reclined position in the awake state.

Assigning exercise levels

Subjects performed an incremental exercise test in the semi-reclined position on an electromagnetically braked cycle ergometer (Elema-Schonander, Sweden) at a pedalling frequency of 60 r.p.m. achieved with the aid of a metronome. Work rate started at 16 W and increased in 16 W increments every minute until the subject's HR was 75% of the predicted maximum above his/her resting level (HR_{max} taken to be 220 beats min^{-1} minus age in years). Subsequently, each subject was familiarized with a load corresponding to 50% of his/her HR_{max} ('heavy' load). Ventilation was measured as described below. Subjects performed imagination of 'heavy exercise' in the awake state and separately under hypnosis.

Cardiorespiratory measurements

Except during the assessment of hypnotic susceptibility, subjects breathed via a facemask (one-way valves, separate nose compartment giving mouth-only breathing, total dead space ~100 ml, resistance at 50 l min^{-1} was 0.8 cmH_2O; 7920, 7930, 7940, Hans Rudolph, USA). A pneumotachometer (Fleisch size 4, unheated) was fixed to the inspired side of the facemask; the pressure across it was measured with a differential pressure transducer (Anodyne), the signal was then amplified and integrated (transducer, amplifier and integrator, P. K. Morgan, UK) for analysis of tidal volume (V_T) and breathing frequency (f). Calibration of the flow signal was performed prior to each experimental session using a 3 l syringe (Hans Rudolph). Valve imperfections resulted in a slight backflow through the pneumotachometer with each expiration; these were of negligible volume. Where indicated, CO_2 was added to the inspired air to prevent hypocapnia developing with hyperventilation. The amount of CO_2 added was manually controlled using a rotameter (0–1100 ml min^{-1}, Platon). Expired gases were analysed for O_2 and CO_2 (Servomex 570A, Servomex 1400) and minute averages of O_2 uptake ($\dot{V}_{O_2}$) were obtained. End-tidal P_{CO_2} (P_{ET,CO_2}) was recorded (Datex Normocap 200) from a sampling line attached to the facemask. The Servomex gas analysers were calibrated daily using a cylinder of 20% O_2, 5% CO_2. HR was measured from lead II of the ECG (Minimon 7136, Kontron Instruments, UK). In five subjects (study 1) electromyograms (EMGs) were obtained during study 1 (protocol 1) from left and right quadriceps and hamstrings (Neurolog System, NL820, 135, 824, Digitimer, UK).

Positron emission tomography

A cannula was inserted into an antecubital vein for the infusion of the positron-emitting ^{15}O in the form of 5 mCi of $H_2{}^{15}O$. Subjects were then hypnotized on the scanning table, after which the head was positioned to minimize movement under laser beam alignment. The immobility of the subjects under hypnosis and their automatic response to instructions, together with the vividness of their descriptions of the experience, e.g. the altered state of consciousness,

the sense of deep relaxation and the altered perception of the passage of time, made the medical hypnotists confident that the subjects were in a deep hypnotic state.

A transmission scan was performed using an external ^{137}Cs positron source to permit compensation for the field distortion occurring due to the subject's head. Scans occurred at 6 min intervals. Each consisted of a 30 s background scan (to allow correction for background activity), followed after a 15 s delay by a 20 s infusion of radiotracer. An activation scan of 90 s was then taken to coincide with the steady-state cardiorespiratory response. Suggestion of the required imagination was made just before the infusion of radiotracer commenced. The integrated counts for the activation scan, corrected for background activity, gave an estimate of regional cerebral blood flow. All subjects studied with PET had a structural MRI scan on a different date.

Experimental protocols

Hypnotic induction was performed using the same technique as for the susceptibility assessment and was followed by manoeuvres designed to increase the depth of the hypnotic state (arm levitation, sensory imagery). These manoeuvres were repeated in-between experimental protocols if hypnotic depth was judged to have decreased (assessed by pupil dilatation, relaxation of facial muscles; Waxman, 1989). The time taken from the beginning of the induction to starting the protocols was approximately 20 min. The order of the protocols was randomized with the exception of volitional hyperventilation being always performed last in order not to alert the subjects to our interest in breathing. Great care was taken to avoid mentioning cardiorespiratory variables at any stage during the investigations, except during instructions for volitional hyperventilation (described below). All protocols were performed without use of a metronome and the subjects breathed room air except where indicated.

Study 1

Protocol 1: imagination of exercise, awake and under hypnosis. Hypnotized subjects ($n = 17$) imagined themselves exercising for 2 min at the 'heavy' work rate with which they had been familiarized. It was suggested to the subjects that they were cycling up a steep hill with a grade equivalent to the heavy work rate. In order to assess the repeatability of the response, four of these subjects performed the protocol eight times at 6 min intervals. Imagination of exercise was repeated in eight of the subjects in the awake state. In five subjects bipolar surface EMGs were obtained during imagination of exercise under hypnosis from left and right quadriceps and hamstrings.

Protocol 2: imagination of freewheeling downhill under hypnosis. In order to examine the cardiorespiratory effects of cognitive effort *per se*, hypnotized subjects ($n = 8$) were asked to imagine themselves on a bicycle freewheeling down a hill, whilst applying the brakes gently. This protocol was performed for 2 min.

Protocol 3: volitional hyperventilation under hypnosis. Hypnotized subjects ($n = 6$) were told to 'breathe faster' for 2 min. Feedback on the breathing frequency required was provided by the hypnotist and was set at the level achieved during imagination of exercise.

In order to examine whether the magnitude of any hyperventilation was limited by hypocapnia, seven subjects during study 1 (protocol 3) had CO_2 added to the inspired air to maintain isocapnia.

Study 2

Neuroimaging imagination of exercise at rest. PET scanning was used to image neuro-anatomical correlates of 'central command'. We employed cognitive subtraction methodology to create two contrasts (A and B) in two separate protocols with different subjects ($n = 4$ for both; 8 scans per subject). Three cognitive conditions were used: condition I, imagination of freewheeling downhill on a safe country road; condition II, imagination of exercise, cycling uphill on the same road; condition III, volitionally driven increase in f (under instruction of the hypnotist) to match that achieved in condition II whilst imagining a safe country road. The order of the conditions was randomized in a balanced design, with the restriction that condition III was always the last to be studied. In the first protocol, freewheeling was compared with cycling uphill to produce contrast A, highlighting cerebral areas involved in the imagination of exercise. In the second protocol, freewheeling was compared with a voluntary increase in f to produce contrast B, highlighting areas activated in the direct volitional control of f as opposed to indirect activation as a consequence of imagination of exercise. Any effects of both imagination and hypnosis were therefore constant throughout all conditions. All subjects in this study had CO_2 added to the inspired air to maintain isocapnia.

Data acquisition and analysis

Breathing. Analog signals were sampled at 200 Hz (Biopac MP100WS) and recorded on a Power Macintosh computer using Acqknowledge software for subsequent analysis. Breath-by-breath data from each subject were divided into 15 s epochs (study 1, protocols 1 and 3; study 2) or 30 s epochs (study 1, protocol 2) and averages were calculated for each epoch. The average value from 30 to 15 s prior to the onset of the instruction to imagine was taken as the control value; this was then subtracted from each epoch average. Changes were then averaged across the group and all data were expressed as means ± S.E.M. Comparison of imagined exercise with and without inspired CO_2 was evaluated by a repeated measures ANOVA and *post hoc* Tukey test.

Positron emission tomography. Analysis of the PET data was performed using statistical parametric mapping (SPM96) (Frackowiak *et al.* 1997). Images were reconstructed as axial planes and realigned to remove the effects of head motion. They were spatially normalized to the Montreal Neurological Institute (MNI) template using the subject's own T1 MRI to guide this process and then smoothed by an isotropic 10 mm, full-width half-maximum, isotropic Gaussian kernel filter to account for individual variation in gyral anatomy and to improve the signal-to-noise ratio. The standard stereotaxic space was that of the Montreal Neurological Brain (Evans, 1993) but the coordinates presented in Table 2 have been corrected (A. Meyer-Lindenberg, unpublished data: http://www.mailbase.ac.uk/lists/spm/1998-06/0079.html) to those of Talairach space (Talairach & Tournoux, 1988) to facilitate comparison with previous studies.

A small volume correction factor was applied only to areas activated where a prior hypothesis existed concerning areas known to be involved in the control of breathing (Worsley *et al.* 1996). These regions of interest were hand-edited on a copy of the SPM canonical T1 template, using Analyze AVW software (Robb *et al.* 1989). Each region of interest image was entered into SPM96 and the corrected P value for peak voxels within these regions was calculated (M. Brett, unpublished data: http://www.mrc-cbu.cam.ac.uk/Imagining/vol-corr.html). SPM96 corrects for multiple comparisons using a Euler characteristic. This characteristic is dependent on the number of resolution elements (resels) with a given image, which itself depends on the number of voxels within the image and the 3-D smoothness of that image. A small volume correction reduces the number of resels in the search volume to that of the brain region of interest in question; thus the threshold for accepting a given Z score as significant ($P < 0.05$) is reduced (Worsley *et al.* 1996).

Table 1. Cardiorespiratory data in subjects, awake and hypnotized, in both actual and imagined heavy exercise

		$\dot{V}_I$ (l min^{-1})	f (breaths min^{-1})	V_T (l)	P_{ET,CO_2} (Torr)	HR (bpm)	n
A	Awake: rest	10.5 ± 0.6	16.0 ± 0.6	0.7 ± 0.1	40.7 ± 0.7	68 ± 3	20
	Hypnosis: rest	8.6 ± 0.5†	15.6 ± 0.9	0.6 ± 0.1	40.9 ± 0.0	67 ± 3	20
B	Awake: rest	10.0 ± 1.0	16.0 ± 1.0	0.6 ± 0	40.1 ± 0.6	67 ± 2	8
	Awake: imagined heavy exercise	10.0 ± 1.0	19.0 ± 2.0	0.5 ± 0	39.1 ± 0.8	67 ± 2	8
C	Hypnosis: imagined heavy exercise	15.5 ± 1.2‡	26.7 ± 2.1‡	0.6 ± 0.1	35.2 ± 0.8‡	75 ± 2‡	17
	Hypnosis: actual heavy exercise	34.8 ± 1.9‡	23.7 ± 0.9‡	1.5 ± 0.1‡	45.8 ± 0.4‡‖	128 ± 4‡	17
D	Hypnosis: rest	9.9 ± 0.4	15.5 ± 1.0	0.7 ± 0.1	43.0 ± 1.0	61 ± 3	8
	Hypnosis: imagined freewheeling downhill	9.8 ± 0.4	15.5 ± 1.3	0.7 ± 0.1	43.3 ± 0.9	61 ± 3	8
E	Hypnosis: rest	8.3 ± 1.2	16.6 ± 1.3	0.5 ± 0.1	42.5 ± 1.3	62 ± 6	6
	Volitional hyperventilation	12.9 ± 1.1*	30.4 ± 2.7*	0.4 ± 0.1	37.1 ± 1.3*	65 ± 2	6
	Hypnosis: rest	9.2 ± 1.2	16.2 ± 0.7	0.6 ± 0.1	43.6 ± 0.9	62 ± 6	6
	Volitional hyperventilation + CO_2	12.2 ± 0.7§	26.0 ± 1.4§	0.5 ± 0.1	41.7 ± 1.0§	63 ± 1	6

Data are expressed as means ± S.E.M. bpm, beats per minute. † $P < 0.001$ hypnosis rest *vs.* awake rest. ‡ $P < 0.001$ hypnosis: imagined heavy exercise and actual exercise *vs.* hypnosis rest. * $P < 0.05$ hypnosis: volitional hyperventilation *vs.* hypnosis rest. § $P < 0.05$ hypnosis: volitional hyperventilation + CO_2 *vs.* hypnosis rest (paired t test). ‖ At this f, V_T and estimated $\dot{V}_{CO_2}$, $P_{ET,CO_2} > P_{a,CO_2}$ by 2–4 Torr (Jones *et al.* 1979).

RESULTS

The peak work rate attained during the incremental exercise test was 172 ± 8 W (mean ± S.E.M.), corresponding to a peak $\dot{V}_{O_2}$ of 2332 ± 187 ml min^{-1}. The heavy work rate assigned to each subject was of the order of 103 ± 5 W ($\dot{V}_{O_2}$ of 1356 ± 83 ml min^{-1}).

Study 1

Effect of hypnosis on cardiorespiratory variables at rest and subjects' perception of the hypnotic state. Hypnosis resulted in small significant decreases in $\dot{V}_I$, and in $\dot{V}_{O_2}$ from 298 ± 22 to 266 ± 21 ml min^{-1} ($P < 0.05$, Table 1A). Subjects' comments on the hypnotic state *per se* included descriptions of intense relaxation and altered self-perception (e.g. '... I felt all warm and tingly and it was like I wasn't actually anywhere at all ...'). Subjects consistently underestimated how long they had been in the hypnotic state; they also had periods of amnesia (e.g. '... I would just suddenly realise that I had no idea what had been happening for the last half an hour ...').

Imagination of exercise under hypnosis (protocol 1). In the absence of hypnosis there was no effect on cardiorespiratory parameters of imagining heavy exercise ($n = 8$, Table 1B). In 17 resting hypnotized subjects, imagination of the previously performed heavy exercise task resulted in hyperventilation and hypocapnia (Table 1C, Figs 1 and 2) and an increase in HR (Table 1C). The dynamics of the $\dot{V}_I$ and HR responses over the 2 min period of imagination were well fitted by monophasic exponentials (group data; $\dot{V}_I$: $t_{50\%} = 16$ s, goodness of fit of

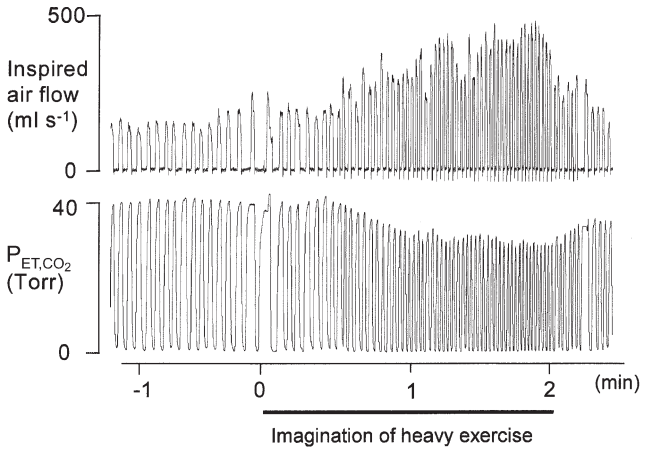

Figure 1. Imagination of exercise under hypnosis at rest

Imagination of heavy exercise for 2 min whilst under hypnosis (protocol 1) resulted in an increase in inspired air flow (top panel) and a decrease in P_{ET,CO_2} (bottom panel). Raw data from one subject. Filled bar indicates period of imagination of heavy exercise.

regression coefficient $r^2 = 0.98$; HR: $t_{50\%} = 5$ s, $r^2 = 0.96$). The magnitude of the increase in ventilation was *ca* 30% of that seen during actual performance of the exercise task under hypnosis (Table 1A and C) but occurred via an increase in f with no change in V_T. The magnitude of the ventilatory response to imagination of exercise was not affected by the addition of CO_2 to the inspired air to maintain eucapnia ($n = 7$, repeated measures ANOVA, $P = 0.345$, Fig. 3). The magnitude of the HR response to the imagination of exercise was 12% of that seen during actual exercise (Table 1A and C).

In the four subjects who repeated the protocol eight times, the magnitude of the ventilatory responses was similar between repeats. In this subgroup, the coefficient of variation of the steady-state ventilatory response was 9%. There was no obvious movement in the legs during imagination of exercise, and in five subjects the lack of rhythmic motor activity was confirmed by the absence of any significant increase in quadriceps or hamstring EMG activity (Fig. 4).

When asked about the experience, subjects gave vivid accounts ('...I was really into it, I felt like I had to give

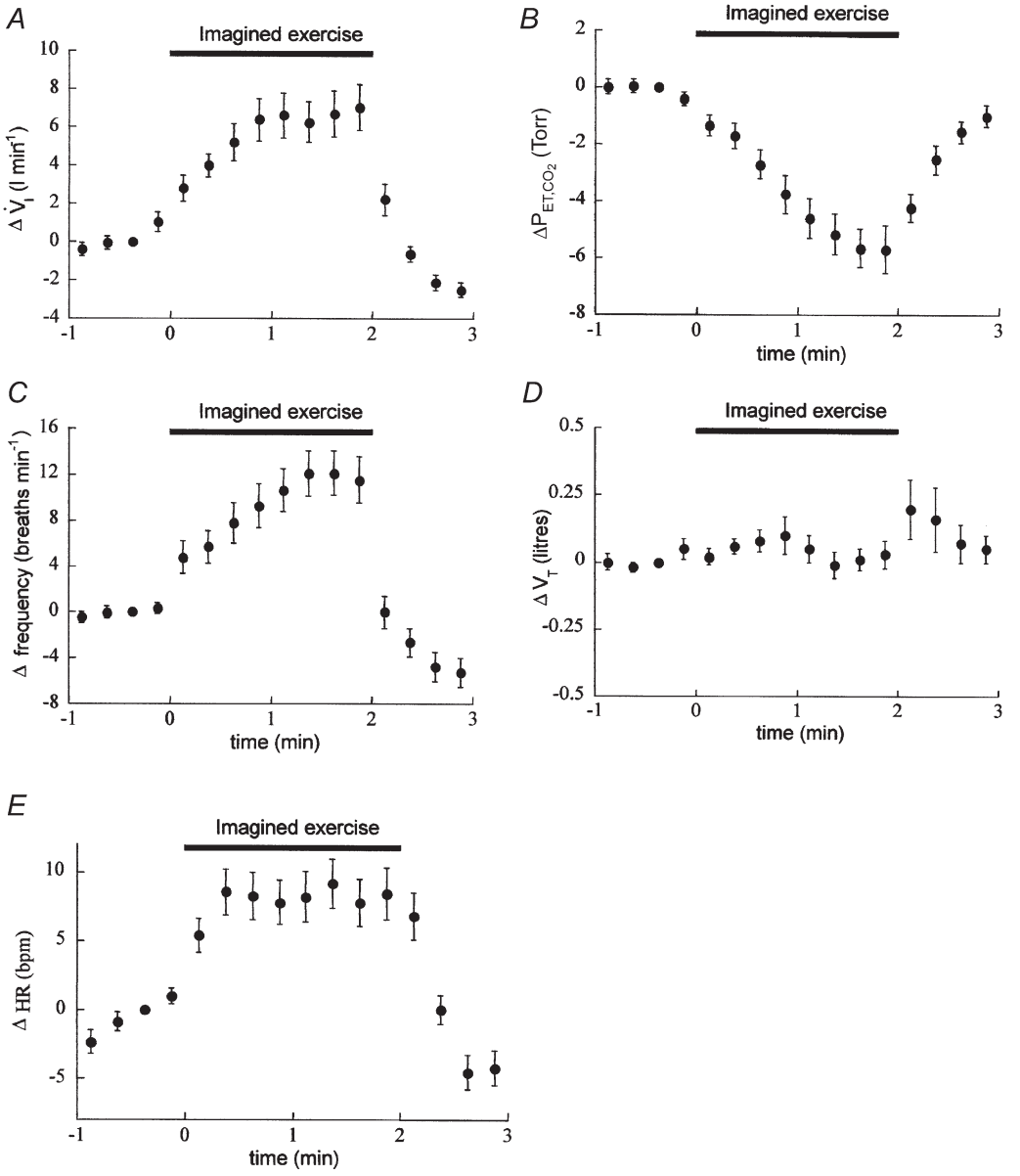

Figure 2. Imagination of heavy exercise under hypnosis

Group data for the imagination of heavy exercise under hypnosis (protocol 1, $n = 17$). Each data point represents the mean ± S.E.M. of a 15 s epoch, with the resting value (taken as the mean of the variable between 30 and 15 s prior to the onset of imagined exercise) subtracted from it. *A*, $\Delta\dot{V}_I$; *B*, $\Delta P_{ET,CO_2}$; *C*, Δf; *D*, ΔV_T; *E*, ΔHR (bpm, beats per minute).

Table 2. Brain activations under hypnosis during imagination of exercise and voluntary hyperventilation

Site	Left							Right						
	x	*y*	*z*	*Z*	Hyp	Psmvc	Pm	*x*	*y*	*z*	*Z*	Hyp	Psmvc	Pm
Contrast A (imagined exercise)														
Dorsolateral prefrontal cortex	—	—	—	—	No	—	—	43	24	36	4.8	No	—	0.04
Supplementary motor area	—	—	—	—	Yes	—	—	4	−9	64	5.0	Yes	—	0.01
Premotor area	—	—	—	—	Yes	—	—	59	3	19	4.4	Yes	0.013	0.19
Superolateral sensorimotor cortex	−17	−34	56	3.5	Yes	0.02	0.98	18	−29	63	4.0	Yes	0.004	0.52
Cerebellum	−12	−50	−27	4.2	Yes	0.05	0.31	22	−60	−26	4.2	Yes	0.05	0.31
Thalamus	—	—	—	—	Yes	—	—	1	−9	15	4.1	Yes	0.007	0.44
Contrast B (voluntary hyperventilation)														
Supplementary motor area	−4	−11	54	4.7	Yes	0.003	0.06	—	—	—	—	Yes	—	—
Lateral sensorimotor cortex	−48	−5	19	7.0	Yes	—	0.001	55	−5	21	5.1	Yes	—	0.008

Stereotactic coordinates (mm) (Talairach & Tournoux, 1988) of voxels maximally activated within sites that are significant ($P < 0.05$) either (a) after correction for multiple comparisons (Pm – from SPM, Frackowiak *et al.* 1997) or (b) where *a priori* hypothesis (Hyp) exists, after a small volume correction (Psmvc – Worsley *et al.* 1996). Voxels are unit cubes of 2 mm side length. *x*, lateral to midline, positive to right; *y*, anterior/posterior to anterior commisure, positive anterior; *z*, superior/inferior to anterior/posterior commisural plane, positive superior. *Z*, normal distribution statistic.

the pedals a real shove to get them to go round . . .') and reported sensations that included tiredness in the legs ('I knew that my legs weren't moving, but they felt really tired and I was battling against myself to keep going.') and sweating ('. . . my legs started tingling as if I was about to break out into a sweat, it was like I was blushing . . .'). Seven subjects mentioned that they noticed their breathing had increased.

Imagination of freewheeling downhill under hypnosis (protocol 2). Imagination of freewheeling downhill under hypnosis did not result in any changes in cardiorespiratory variables ($n = 8$, Table 1D).

Volitional hyperventilation under hypnosis (protocol 3). The instruction to breathe faster resulted in an immediate and sustained increase in ventilation with a

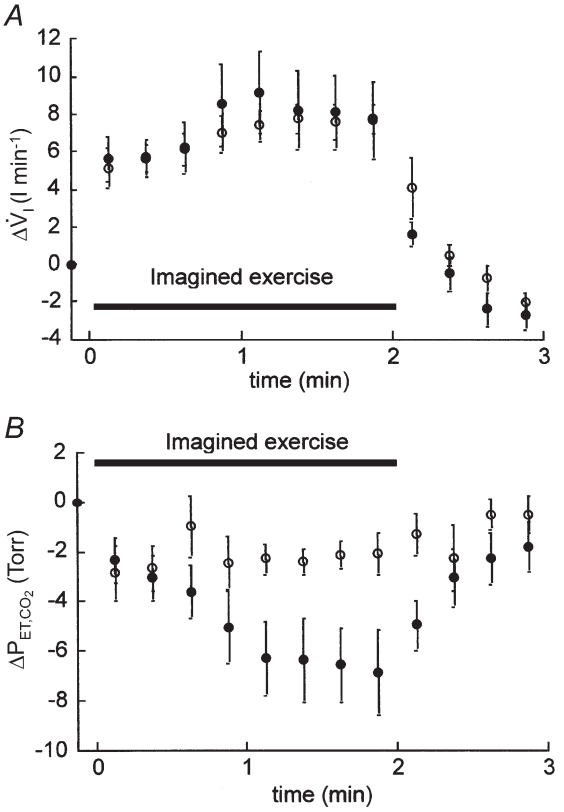

Figure 3. Imagination of exercise under hypnosis at rest whilst maintaining isocapnia

Addition of CO_2 to the inspired air to maintain isocapnia did not alter the magnitude of the ventilatory response to the imagination of exercise under hypnosis. Each data point represents the mean ± S.E.M. of a 15 s epoch, with the resting value (taken as the mean of the variable between 30 and 15 s prior to the onset of imagined exercise) subtracted from it ($n = 7$). *A*, $\Delta\dot{V}_I$; *B*, $\Delta P_{ET,CO_2}$ (●, control; ○, isocapnic).

square-wave response. The magnitude of volitional hyperventilation was not affected by maintaining isocapnia ($n = 6$, Table 1E).

Study 2

The depth of hypnosis within the PET scanner was judged to be of a similar order to that achieved in study 1, and the $\dot{V}_I$ and HR responses were also similar. $\dot{V}_I$ and HR did not change in condition I (Fig. 5i and iii), whereas they increased during conditions II (exercise) and III (voluntary hyperventilation). The f during volitional hyperventilation was well matched to the f during imagination of exercise. The dynamics of the increase in $\dot{V}_I$ and f in condition II followed an exponential (Fig. 5ii); in contrast f rose immediately during voluntary hyperventilation (Fig. 5iv).

Table 2 shows the coordinates for the most activated voxels within relevant brain areas that are also significant ($P < 0.05$). For contrast A (imagined exercise), these areas are shown in Fig. 6 as through projections in three anatomical views; some of these areas are further illustrated (Fig. 5) on a rendered representative brain (Evans, 1993). The activations in the right dorso-lateral prefrontal cortex and supplementary motor areas in the midline remained significant after correction for multiple comparisons (Pm). The activations in the right premotor area, both superolateral sensorimotor cortices, midline thalamus and the cerebellum bilaterally were significant following small volume correction (Psmvc), but not following multiple comparsions. A further analysis correlating the intensity of a given voxel with $\dot{V}_I$ for all data in contrast A showed that the right premotor area,

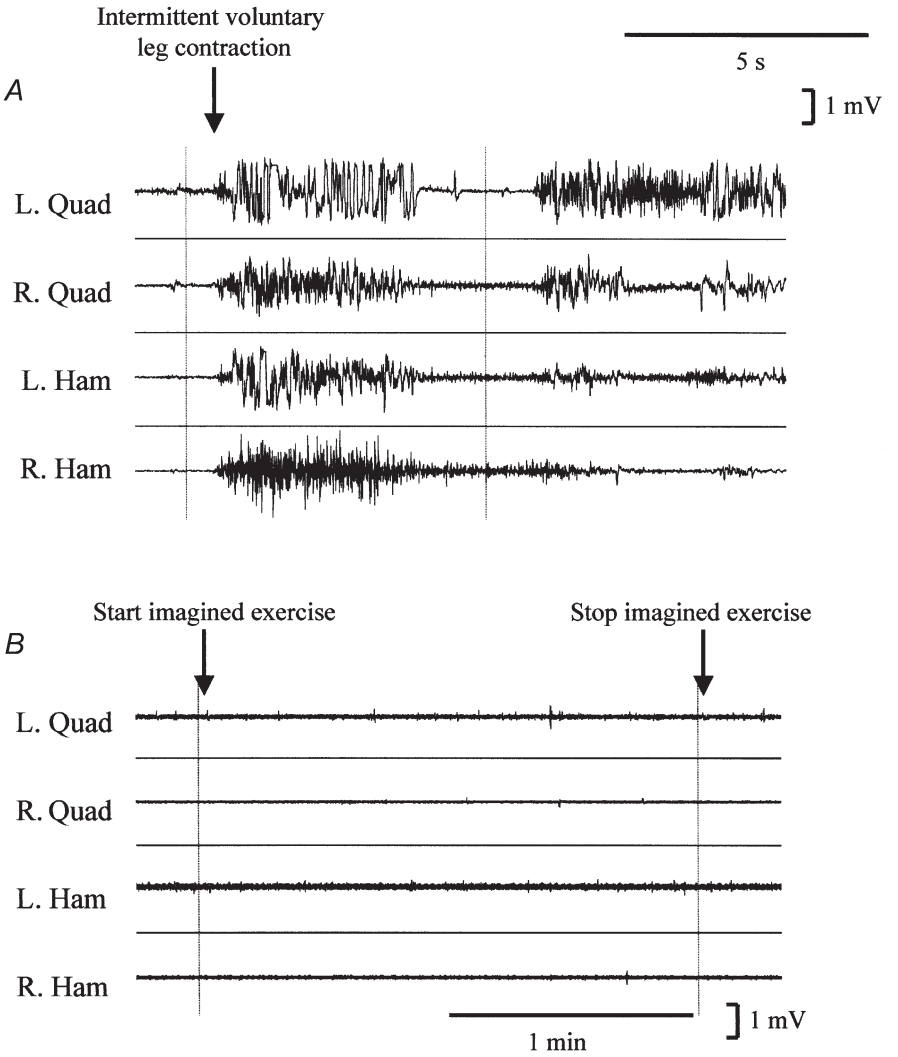

Figure 4. EMG activity during voluntary contraction and imagination of exercise

A comparison of voluntary leg movement (*A*) with the leg movement seen during imagination of exercise under hypnosis (*B*) in one subject. EMG recordings were made from left and right quadriceps and hamstrings. The vertical scale is the same in the two panels; the increase in EMG activity during imagination of exercise is minor.

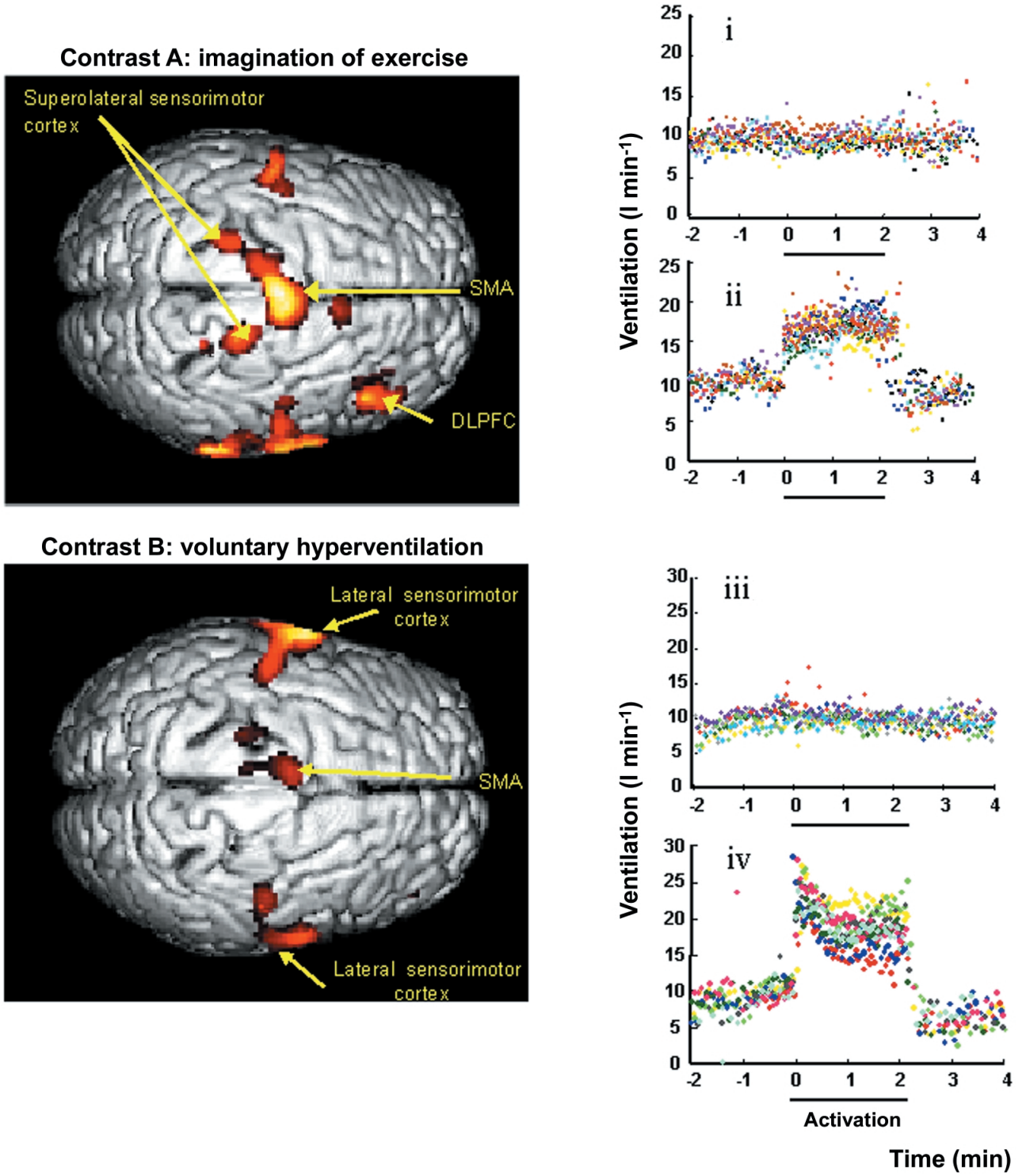

Figure 5. Activations during imagination of exercise and voluntary hyperventilation with associated respiratory responses

Left, 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. Only significant activations (Table 2) are labelled. Right, 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 absence of effect when imagining freewheeling downhill. Each point represents a single breath and the 8 colours represent each repeat of the protocol. Experimental periods of 2 min 10 s are marked by the filled bars when scan performed. SMA, supplementary motor area; DLPFC, dorso-lateral prefrontal cortex. Activations within 2 cm of the brain surface are represented.

right dorso-lateral prefrontal cortex and left postero-lateral cerebellum remain significant ($Z > 4.8$) after correction for multiple comparisons. In the absence of a prior hypothesis, the right parietal association area narrowly missed being significantly activated after correction for multiple comparsions (Pm = 0.07; $x = 62$, $y = -40$, $z = 19$, $Z = 4.6$). Of interest, there was a non-significant activation in the left insula cortex ($Z = 3.4$ Psmvc = 0.11). For contrast B (voluntary hyperventilation), Table 2 and Fig. 5 also show significant activations in the supplementary motor area and the lateral sensorimotor areas. There was no activation of the insula cortex.

Steady-state cardiorespiratory responses within the scanner during contrast A were as follows. Condition I caused no significant change in $\dot{V}_I$ or HR (Fig. 5i). Condition II increased $\dot{V}_I$ from 10.8 ± 0.5 to 19.3 ± 2 l min^{-1}, and HR from 64 ± 3 to 71 ± 5 beats min^{-1}; the dynamics of the increase in $\dot{V}_I$ and HR followed an exponential ($\dot{V}_I$: $t_{50\%} = 16$ s; HR: $t_{50\%} = 5$ s). For contrast B, condition I also caused no significant change in HR or $\dot{V}_I$ (Fig. 5iii). Condition III caused no change in HR (from 59 ± 5 to 60 ± 5 beats min^{-1}), but increased $\dot{V}_I$ from 8.8 ± 0.2 to 13.6 ± 1.5 l min^{-1} and f from 14 ± 2.2 to 26.2 ± 3.6 breaths min^{-1}; V_T decreased from 0.7 ± 0.1 to 0.6 ± 0.1 l and P_{ET,CO_2} decreased from 42.9 ± 1.4 to 41.8 ± 1.1 Torr.

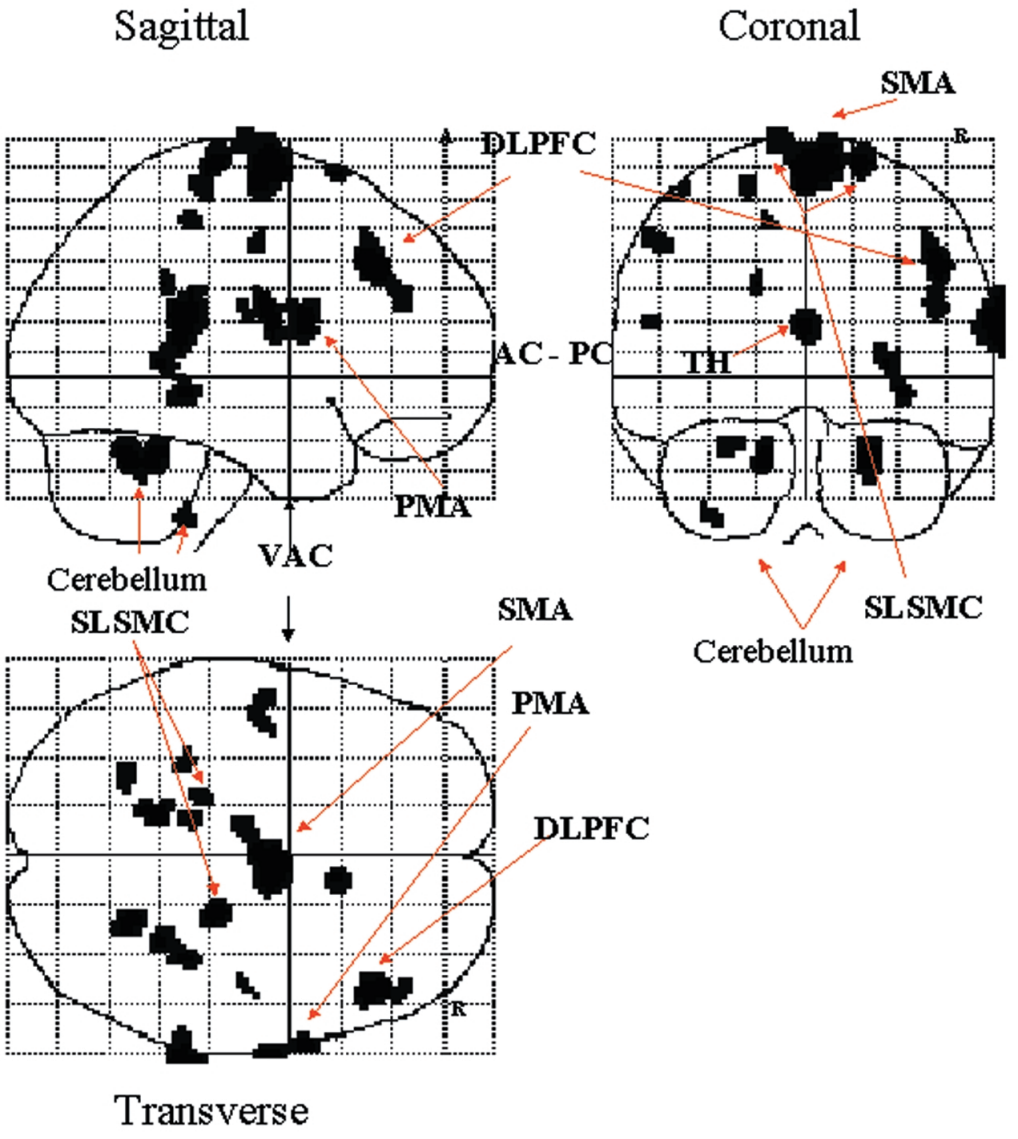

Figure 6. Areas of brain activated during imagination of exercise

Activations during imagination of exercise compared to imagination of freewheeling downhill (contrast A, $P < 0.001$, uncorrected for multiple comparisons) shown as through projections in standard stereotactic space (MNI). Only significant activations at $P < 0.05$ (Table 2) are labelled. R, right; A, anterior; AC–PC, commissural plane; VAC, vertical plane through anterior commissure; SMA, supplementary motor area; PMA, premotor area; DLPFC, dorso-lateral prefrontal cortex; TH, thalamus; SLSMC, superolateral sensorimotor cortex.

DISCUSSION

The imaging results of the present study have identified the neuroanatomical correlates likely to be responsible for a 'central command' mechanism underlying 'exercise' hyperpnoea without movement feedback.

The supplementary motor area (SMA) is activated both during single leg actual exercise (Fink *et al.* 1995) and in the present study of imagined exercise. It is well established that the SMA/PMA (both planning and programming areas; Roland *et al.* 1980; Eccles, 1982), cerebellum (Decety *et al.* 1988) and the dorso-lateral prefrontal cortex (Fuster, 1997), are concerned with volitional/motor control, including that of the respiratory muscles (Fink *et al.* 1995). Mental imagery of novel precise movements activates all these areas, except for the motor cortex (Ingvar & Philipson, 1977). Moreover imagination of exercise in athletes demonstrates that $\dot{V}_I$ (entirely in f) increases in proportion to the degree of imagined effort (Decety *et al.* 1993).

We interpret the activation of the dorso-lateral prefrontal cortex (seen in contrast A but not in contrast B) to reflect the task dictated by the experimental paradigm of imagining exercise without its execution, but at the same time evoking a cardiorespiratory response that mimics that seen in real exercise. The dorso-lateral prefrontal cortex is crucial in the self-generation of action or in actions generated on the basis of working memory (Frith *et al.* 1991). The output projections of the dorso-lateral prefrontal cortex are to the SMA and PMA but not to the motor cortex itself. If the movement is complex and novel, there is increased involvement of the prefrontal areas (Passingham, 1993), although it has not been established whether these areas are activated during task-familiar actual leg exercise (Fink *et al.* 1995). However, Pedersen *et al.* (1998) have shown activation of the left prefrontal cortex (middle frontal gyrus) during uncued movements of the right index finger, suggesting that Brodmann area 9 is directly related to motor command. The dorso-lateral prefrontal cortex receives information from the parietal association areas known to process information regarding perception of oneself in relation to the environment. This area narrowly missed significance in the present study. It is worth noting that the thalamus (significantly activated) has a projection to the parietal association areas.

In contrast B the SMA was significantly activated, but there were no activations in the superolateral sensorimotor cortices, which is a surprising finding given previous reports that have shown these areas to be activated during awake volitional inspiration (e.g. Gandevia & Rothwell, 1987; Colebatch *et al.* 1991). However, there was a strong activation in the lateral sensorimotor cortex that has been previously reported (but never explained) in volitional driven breathing, particular with the use of a face mask (Fink *et al.* 1996; Murphy *et al.* 1997). Activation of the lateral sensorimotor cortices presumably reflects sensorimotor changes in the face and/or upper airway (Penfield & Boldrey, 1937). The focus on changing breathing frequency as required in condition III of contrast B may have caused increased self-awareness of such anatomical structures.

We did not observe any significant activation in the sub-thalamic area (Fig. 7*A*; Eldridge *et al.* 1981). We also did not visualize any significant activation that we were confident of in the pontomedullary area. This latter observation could reflect limits of the scanner field of view down to the pontomedullary margin (Fig. 7*B*) together with 'edge' effects from activations of the medial cerebellum (Fig. 6, sagittal).

We observed a small increase in HR during imagination of exercise although there was only a non-significant activation in the left insula cortex. During volitionally driven breathing there was no change of HR or any activation in the left insula. Others (Williamson *et al.* 1997), however, have reported left insula activation during mild leg exercise with HR changes significantly greater than in the present study. There is evidence that this area projects to the ventrolateral medulla, lateral hypothalamus and nucleus tractus solitarius (Yasui *et al.* 1991). Electrical stimulation of the left insula cortex in the rat increases HR (Saper, 1982), suggesting that this area may be involved in the withdrawal of vagal tone to the sino-atrial node thereby allowing the rapid increase of HR at the onset of exercise. The lack of activation in our study may reflect the small change in HR and the limitation of small volume correction in a small area of brain.

Cardiorespiratory changes with imagination of exercise at rest

Imagination of exercise under hypnosis was associated with an increase in HR, $\dot{V}_I$ and hypocapnia. Whilst this has been observed previously (Daly & Overley, 1966; Wang & Morgan, 1992), we find this response to be robust and repeatable in experimentally naive subjects. This is not merely an increase in breathing in response to cognitive effort since imagining freewheeling downhill did not cause any cardiorespiratory changes (Table 1D). Neither is it an increase in breathing associated with the metabolic demands of movement. The onset dynamics of the cardiorespiratory response to imagined exercise followed an exponential, albeit somewhat faster than that described for real exercise (Whipp & Wasserman, 1991).

The increases in $\dot{V}_I$ seen during imagination of exercise under hypnosis in this study were via increases in f with no steady-state alterations in V_T. This is consistent with previous findings obtained in awake subjects imagining exercise (Decety *et al.* 1991; Wuyam *et al.* 1995) and in

hypnotized subjects (Agosti *et al.* 1965), although another previous study of imagined exercise under hypnosis reported hyperventilation with increases in both f and V_T (Arvidsson *et al.* 1970). We have no good explanation for the fact that V_T did not change during imagination of exercise in the present study, but we speculate that drives to breathe may act independently on f and V_T.

The use of hypnosis as a tool to modify the perception of exercise load was first reported by Nemtzova & Shatenstein (1936) and has been used by others (Morgan *et al.* 1973, 1976). Thornton *et al.* (1997) reported that subjects performing constant moderate exercise hyperventilated and become hypocapnic if told that the work rate had increased when in fact it had not changed. In this study

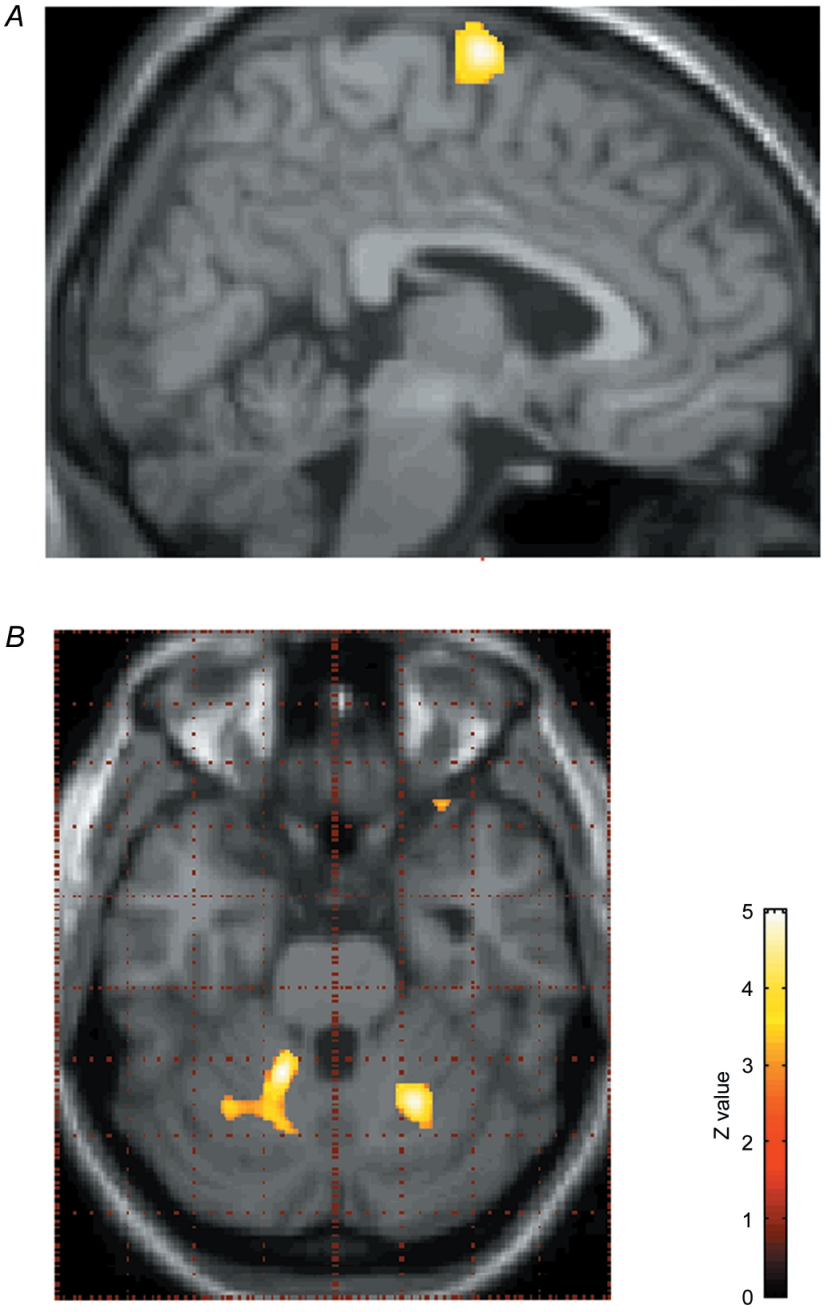

Figure 7. Transverse and sagittal activation during imagination of exercise

Two regions activated during imagination of exercise compared to imagination of freewheeling downhill, overlayed on a MRI. These areas are displayed at a level of $P < 0.001$ uncorrected for multiple comparisons. The Z statistic scale is shown in the lower right corner. The maximum activations in these areas, with $Z > 4$, are significant at $P < 0.05$ (Table 2). *A*, sagittal section ($x = 4$) showing activation of the SMA. *B*, transverse slice ($z = -28$) showing bilateral activation of the cerebellum.

the hyperventilation occurred via increases in f with no steady-state changes in V_T. The magnitude of the ventilatory response was similar to that expected from an actual increase in work rate. Krogh & Lindhard (1913) were the first to describe the effect of altered perception on ventilatory responses to exercise. 'In one experiment the subject J.L. was told to work at a rapid rate and with a heavy load (3 kg) but at the signal to begin, the current was not turned on to the magnets of the ergometer. The resulting respiration during the first few seconds was practically the same as if there had been a heavy load, though the actual work performed was insignificant . . .'

Limitations of the study

The neurophysiological basis underlying hypnosis is not understood; however, it has been used with neuroimaging to alter the perception of sensory information from a painful stimulus (Rainville *et al.* 1997, 1999). The hypnotic state allows isolation from the environment and a more directed imagination than is possible in the awake state (Coe *et al.* 1980), so we hypothesized that the cardiorespiratory response to imagination of exercise would be more robust if the imagination was performed under hypnosis. The use of a technique such as hypnosis to study cardiorespiratory variables raises the concern that we may be studying conformity in subjects who are eager to please. However, we believe that the responses we have observed are not merely volitional for a number of reasons. Subjects were experimentally naive with no medical or physiological training and no mention was made of cardiorespiratory variables in the presence of the subject during exercise suggestions. Whilst it is possible that studying volitional hyperventilation might alert subjects to our interest in breathing, this was always the final protocol performed. When specifically asked at the end of the study the subjects denied using their breathing as a cognitive strategy to aid imagination. If subjects attempted to mimic an exercise response we see no reason why they would choose to do this without altering their tidal volume. Moreover, both ventilatory and HR responses to imagination of exercise in this study were well fitted by an exponential and the time constant for the increase in HR was markedly faster than that for $\dot{V}_I$, as occurs in actual exercise (Whipp & Wasserman, 1991). It is unlikely that experimentally naive subjects could mimic such kinetics, particularly with the high degree of repeatability we observed when subjects performed multiple repeats of the same protocol. Moreover, there is no convincing evidence that HR is under voluntary control.

A problem related to the use of hypnosis is that there is no satisfactory objective measure of the depth of the hypnotic state. Given the behaviour of the subjects (immobility, automatic responding) and the vividness of the subjects' descriptions of hypnosis (partial amnesia, altered perception of the passage of time) our medical hypnotists were confident that the subjects were in a deep hypnotic state. There was also no evidence that the depth of hypnosis affected the magnitude of the results as the subjects exhibiting the largest cardiopulmonary responses were not necessarily those who were classed as being in the deepest hypnotic state.

A major limitation of PET studies is that the amount of radioactivity that can be given to any subject is clearly restricted. It was not possible therefore to have the same subject complete all three protocols in study 2 (PET). This necessitated two independent groups and prevented us from confidently studying a three-way interaction among conditions. As a consequence the validity of a statistical comparison between the results of contrasts A and B assumes that the two groups of subjects activate and deactivate the same areas and to the same degree when imagining the control state (freewheeling downhill). We cannot establish this point from our data. Nevertheless we have done a comparison of the results from contrasts A and B using a mixture of conjunction analysis and masking. Specifically, we have loaded up data from both contrasts into one design matrix and looked across the two protocols for commonalities or lack of commonalities in activation and deactivation areas. We found that many of the areas we were interested in behaved differently between the two protocols. However, it would be misleading to give the impression from these data that the behaviour in these areas was quantitatively different. The activations seen in contrast A (imagination of leg exercise, no movement feedback) are similar to those areas previously reported by Fink *et al.* (1995) during actual leg exercise. Moreover, for the same respiratory drive seen in contrast B (volitional hyperventilation), the dorso-lateral prefrontal cortex, PMA, superolateral sensorimotor cortex and cerebellum (activated in contrast A) were not activated in contrast B, highlighting a clear difference between the two cognitive conditions that resulted in the same behavioural end-point.

Implications for cardiorespiratory control in exercise

Positive and negative feedback loops based on 'error' signals have been thought to be fundamental in the control and regulation of many biological processes including the control of the cardiorespiratory response to exercise. However, it may be possible for control and regulation to occur in the absence of an error signal as has recently been suggested by Somjen (1992) for exercise and further elaborated by Blessing (1997) for other control systems. We provide evidence that a significant component of the respiratory response (all in f) to 'exercise' can be generated by what appears to be a behavioural response, given the neuroanatomical areas activated. These areas may encode a respiratory motor programme ('central command') that evolves as the motor task is learnt in development, interacting with classical error signals in real exercise.

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