Journal of Physiology (1991), **443**, *pp.* 91–103
With 3 figures
Printed in Great Britain

REGIONAL CEREBRAL BLOOD FLOW DURING VOLITIONAL BREATHING IN MAN

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(*Received 14 February 1991*)

SUMMARY

1. Positron emission tomographic imaging of brain blood flow was used to identify areas of motor activation associated with volitional inspiration in six normal male subjects.

2. Scans were performed using intravenous infusion of $H_2{}^{15}O$ during voluntary targeted breathing and positive pressure passive ventilation at the same level.

3. Regional increases in brain blood flow, due to active inspiration, were derived using a pixel by pixel comparison of images obtained during the voluntary and passive ventilation phases.

4. Pooling data from all subjects revealed statistically significant increases in blood flow bilaterally in the primary motor cortex (left, 5·4%; right, 4·3%), in the right pre-motor cortex (7·6%), in the supplementary motor area (SMA; 3·1%) and in the cerebellum (4·9%).

5. The site of increased neural activation in the motor cortex, associated with volitional inspiration, is consistent with an area which when stimulated, either directly during neurosurgery or transcranially with a magnetic stimulus, results in activation of the diaphragm.

6. The presence of additional sites of neural activation in the pre-motor cortex and SMA appears analogous to the results of studies on voluntary limb movement. The site of the increase in the SMA was posterior to that previously reported for arm movements. These areas are believed to have a role 'upstream' of the motor cortex in the planning and organization of movement.

7. This technique provides a means of studying the volitional motor control of respiratory related tasks in man.

INTRODUCTION

The automatic generation of a respiratory rhythm within pontomedullary structures and its projection to spinal motoneurones via the bulbospinal tract has

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been extensively investigated and reviewed (von Euler, 1986; Feldman, 1986). It is also recognized that the same spinal motoneurones can be activated from higher centres in the central nervous system (Aminoff & Sears, 1971; Hugelin, 1986) allowing modulation of breathing for behavioural purposes. In man, such non-automatic control of breathing is crucial for the performance of respiratory motor acts such as breath-holding as well as the production of speech. Even during quiet breathing, there is evidence that the level of arousal forms an important component of the overall respiratory drive (Fink, Katz, Rheinhold & Schoolman, 1962; Shea, Walter, Pelley, Murphy & Guz, 1987) and it has been suggested that some ventilatory responses, hitherto thought to be reflex in nature, may depend in part on a neural drive originating from above the brain stem (Eldridge, Milhorn & Waldrop, 1981; Murphy, Mier, Adams & Guz, 1990).

Studies in anaesthetized animals allow efferent projections from midbrain or forebrain areas to respiratory spinal motoneurones to be identified (Colle & Massion, 1958; Bassal & Bianchi, 1982; Lipski, Bektas & Porter, 1986) but tell us little about their role in the conscious state. Studies in conscious animals to address this question have only recently been attempted (Orem & Nettick, 1986) and are difficult to design and interpret. Consequently, much of what is known about the neurophysiological basis for respiratory control related to consciousness comes from observations in patients with defined neurological abnormalities (Plum & Leigh, 1981).

Despite the fact that humans clearly possess highly developed motor skills for volitional control of respiratory muscles, relatively little is known about the presumed areas in the cerebral cortex associated with this function. Foerster (1936) found an area in the primary motor cortex which, when stimulated electrically in conscious man during neurosurgery, resulted in contraction of the diaphragm (hiccough). More recently, Gandevia & Rothwell (1987) identified a short-latency electromyogram (EMG) response in the diaphragm following transcranial electrical stimulation at the vertex. Maskill, Murphy, Mier, Owen & Guz (1991), who used focal transcranial magnetic stimulation, reported the best site for activating the contralateral diaphragm to lie approximately 3 cm lateral to the vertex. Such studies support the existence of an oligosynaptic (probably corticospinal) excitatory projection between the cortex and the main inspiratory muscle in humans, but as in animal studies they permit only a limited interpretation in terms of the voluntary control of breathing.

Positron emission tomography (PET) allows the non-invasive measurement of regional cerebral blood flow (rCBF) and has been used to define areas of increased neural activity associated with specific motor or cognitive tasks in conscious man (Raichle, 1987). The aim of the present study was to use PET to identify those areas of the brain showing an increased blood flow (and hence neural activity) associated with volitional inspiration in normal subjects. The objective was to perform scans during 'active' inspiration and matched 'passive' inspiration with intermittent positive pressure ventilation (IPPV) against relaxed respiratory muscles. The reason for this approach was to control for, as far as possible, afferent feedback from the lungs and chest wall occurring during inspiration, thus only identifying sites dominated by 'centrally generated' neural activity.

This study has been presented in a preliminary form (Colebatch, Adams, Murphy, Martin, Lammertsma, Tochon-Danguy, Clark, Friston & Guz, 1991*a*).

METHODS

Six right-handed male subjects aged 24–60 years with no known respiratory or neurological abnormalities were studied. Local ethical committee approval was obtained and each subject gave informed consent. Three of the subjects were co-authors (L.A., K.M. and A.G.) and the remainder were respiratory physiologist colleagues not involved with this study.

Training

All the subjects were trained to perform the required tasks prior to scanning. Typically this required four to six sessions but no subject was unable to achieve satisfactory performance. For the 'active' respiratory task the subjects practised adopting a target respiratory volume and frequency, initially with auditory cues, and then maintaining this pattern without any external cues. For the 'passive' task, the subjects were taught to remain relaxed during IPPV. The adequacy of relaxation was judged from recordings of upper airway pressure (Datta, Shea, Horner & Guz, 1991) and initially this was displayed to the subjects on an oscilloscope.

Experimental protocol

Ventilation. The experimental arrangement is shown schematically in Fig. 1. The subjects inspired through a tightly-fitting nasal mask to a volume of 1·5–2 l with a frequency of 10–12 min^{-1}; expiration was passive. Inspiratory and expiratory airflows and volumes were measured with an ultrasonic flowmeter (Branta, UK) and tidal P_{CO_2} was monitored using an 'in-line' infra-red analyser (Hewlett Packard 47210A, USA). Sufficient additional deadspace, in the form of 2·5 cm i.d. anaesthetic tubing (approx. 1·5 m), was added to maintain end-tidal P_{CO_2} (P_{ET,CO_2}) at about 38 mmHg despite the voluntary over-ventilation. The pressure within the nasal mask was measured (Statham P23B, USA) as an index of upper airway pressure. Initially, subjects targeted their inspiratory and expiratory durations to the audible cycling of a mechanical ventilator and were given verbal feedback about the adequacy of their achieved tidal volume relative to the desired level. Subjects then maintained this pattern without any cues for the 4 min duration of each PET scan. For the 'passive' task, an intermittent positive pressure ventilator (Pneupac, UK) was connected to the terminal end of the dead space and set to deliver a similar inspiratory volume and frequency. While in the relaxed state, subjects were ventilated for the duration of the scan and were instructed not to sleep.

In order to assess the possible involvement of accessory muscles of respiration during voluntary breathing, three subjects performed the 'active' task, at a separate time (under exactly the same experimental conditions as described above), with EMG surface electrodes placed over the sternomastoid muscle; EMG signals were processed through an isolated differential amplifier of local design (bandwidth 10–1000 Hz).

PET scanning. Subjects were scanned six times consecutively in each session. Radiolabelled water ($H_2{}^{15}O$) was used as a tracer of cerebral blood flow. $H_2{}^{15}O$ was produced continuously by the catalytic reaction of $^{15}O_2$ and hydrogen and was infused intravenously in a concentration of approximately 8 mCi ml^{-1}. Preparation for scanning included insertion of cannulae into the left radial artery (under local anaesthesia; bupivacaine 1% s.c.) and also into the right antecubital vein. A polyurethane head mould was fitted to minimize head movement. Subjects lay supine in a quiet darkened room with eyes closed and ears unplugged and with the head placed in the scanner so that the lowermost plane was approximately parallel to, and 20 mm above, the orbitomeatal line.

Scanning was performed with an ECAT 931-08/12 (CTI Inc., Knoxville, USA) the physical characteristics of which have been described previously (Spinks, Jones, Gilardi & Heather, 1988). The scanner collects data in fifteen contiguous transverse planes, with a total axial field of view of 10·4 cm. Transmission data were collected first, over a period of 20 min, using an external ^{68}Ge ring source generating positrons. These data are required to correct subsequent emission scans for the effects of radiation attenuation by the tissues of the head. This period also served to accustom subjects to the environment.

For each measurement of rCBF, scans were collected sequentially over 3·5 min, with a 0·5 min background scan followed by twelve scans of 5 s duration and twelve of 10 s. The $H_2{}^{15}O$ infusion, at a rate of 10 ml min^{-1}, began immediately after the background scan and continued for 1 min. The scans collected in the 110 s following the start of the tracer infusion were added for calculation of the rCBF images. Arterial blood was drawn continuously during scanning at a rate of 5 ml min^{-1}

and radioactivity was measured every second. Corrections to the arterial radioactivity (input) curve for delay and dispersion in the brachial vessels and tubing were made and an average partition coefficient of 0·95 for the relative volume of distribution of $H_2{}^{15}O$ between brain 'tissue' and blood was assumed. The protocol and calculations were modified from those described by Lammertsma, Cunningham, Deiber, Heather, Bloomfield, Nutt, Frackowiak & Jones (1990) for $C^{15}O_2$ inhalation.

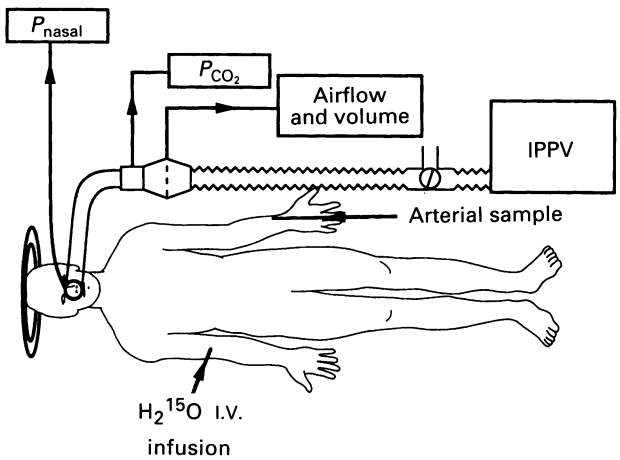

Fig. 1. Schematic representation of the experimental arrangement for measurement of changes in rCBF by PET scanning resulting from voluntary breathing. Subjects remained still, with the head positioned in the scanner and eyes and mouth closed, and breathed through a nasal mask via a deadspace (to maintain normocapnia), either volitionally from room air ('active' inspiration), or with relaxed respiratory muscles ('passive' inspiration) using 'matched' intermittent positive pressure ventilation (IPPV); expiration was always passive. Respiratory airflow (integrated to volume) and P_{CO_2} were measured continuously with appropriate 'in-line' transducers. Pressure within the nasal mask (P_{nasal}) provided an index of relaxation during IPPV. Radiolabelled water ($H_2{}^{15}O$) was infused over 1 min via the right antecubetal vein and blood was sampled continuously from the left radial artery to allow quantification of rCBF.

Six scans were collected for each subject, with rest periods of 10–12 min between scans to allow for decay of radioactivity from the previous measurement ($T_{\frac{1}{2}}$ for ^{15}O = 2·1 min). The scans were performed under 'active' and 'passive' conditions alternately and with the order reversed in half the subjects. A stable ventilatory pattern was established during the background scan of 30 s and maintained for a further 3·5 min until the last blood sample was collected. Scans were reconstructed using a Hanning filter with a cut-off frequency of 0·5 maximum resulting in an image resolution of 8·5 × 8·5 mm (at full width half maximum) and a slice thickness of 6·75 mm. The reconstructed images contained 128 × 128 picture elements (pixels) each 2·05 × 2·05 mm in size.

The images of CBF were automatically reorientated and resized in height, length and width to match best a reference set of images. This set of images had been aligned previously with respect to the intercommissural plane using the method of Friston, Passingham, Nutt, Heather, Sawle & Frackowiak (1989) and rescaled to correspond to the standard brain dimensions used by Talairach & Tournoux (1988) in their stereotaxic atlas. The final image consisted of twenty-six slices at 4 mm intervals with plane 8 being the intercommissural plane. Each image was smoothed with a Gaussian filter 10 pixels wide, to accommodate variations in functional and gyral anatomy.

Subjects differ in the level of overall CBF, but activation results in an additional component which is independent of the global flow. Differences in global flow were therefore accounted for pixel by pixel in each scan by normalizing to a standard mean CBF of 50 ml (100 ml brain volume)$^{-1}$ min^{-1}, using a method based on analysis of covariance with global flow as covariant (Friston, Frith, Liddle, Dolan, Lammertsma, & Frackowiak, 1990). For every pixel, this analysis generated an adjusted

mean rCBF for each of the two conditions ('active' and 'passive') and the error variance was used to compare the two conditions in a manner equivalent to a paired t test. In each of three subjects, one pair of scans was technically unsatisfactory and hence only fifteen individual pairs of scans contributed to each condition mean. The method of Friston, Frith, Liddle & Frackowiak (1991) was used to produce 'statistical images' of rCBF change with significance criteria set at $P < 0{\cdot}05$ and $P < 0{\cdot}01$. Only significant increases in rCBF in the 'active' compared to 'passive' condition were considered further. The most significant pixel within such regions of increased flow was used to determine anatomical location by reference to the corresponding locus in the atlas of Talairach & Tournoux (1988). Where foci occurred within the same anatomical structure (e.g. within the motor cortex) on multiple planes, 'weighted mean' co-ordinates were calculated (Colebatch, Deiber, Passingham, Friston & Frackowiak, 1991*b*). Average flow increases were quantified at the site of the most significant pixel using the images of normalized blood flow.

RESULTS

Subjects' comments

The subjects confirmed that during the scans they had remained awake with eyes closed and had experienced little or no discomfort. All subjects were confident that they had been able to maintain a fairly uniform pattern of breathing during the 'active' task and that they had kept their respiratory muscles relaxed during

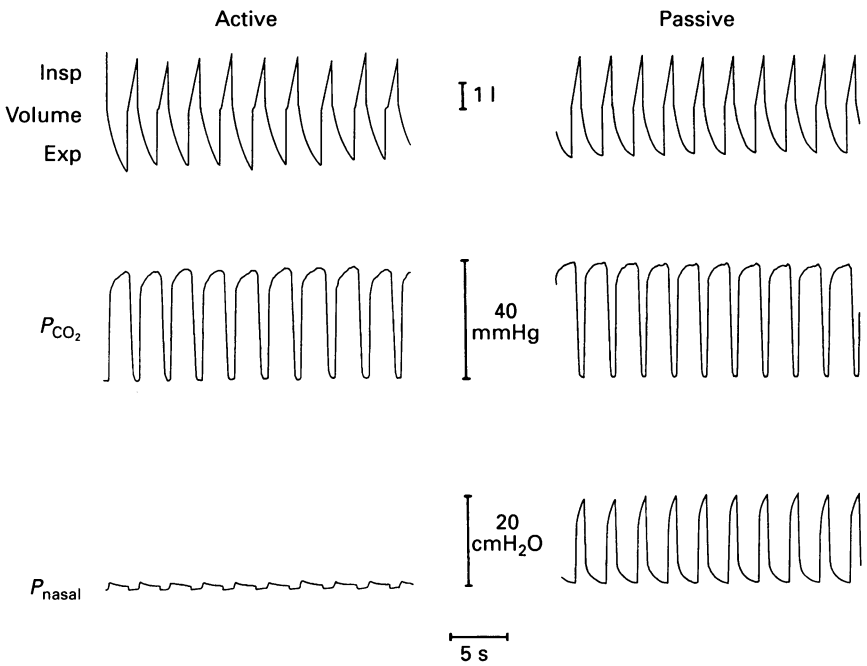

Fig. 2. Examples of original records of respiratory variables from one subject over 1 min infusion of $H_2{}^{15}O$ during volitional breathing (active) and 'matched' positive pressure ventilation (passive). Note similarity of: inspired volumes (Insp), respiratory frequency, expiratory volume profiles (Exp) and end-tidal P_{CO_2} levels in the two conditions. In Passive, smooth and repeatable pressure profiles within the nasal mask (P_{nasal}) indicate relaxed respiratory muscles.

positive pressure ventilation. Subjects did not report any particular concentration on their breathing during the 'passive' task other than being aware that they were being ventilated; by contrast, the 'active' task did require continuous attention to the rate and depth of breathing.

Pattern of breathing

A record of the breathing pattern, tidal P_{CO_2} and pressure recorded within the nasal mask (P_{nasal}) during the 'active' and matched 'passive' breathing tasks is

TABLE 1. Mean ventilatory variables during PET scans

Subject (scan no.)	T_I (s)		T_E (s)		V_T (l)		P_{ET,CO_2} (mmHg)	
	Act	Pas	Act	Pas	Act	Pas	Act	Pas
AG (1)	2·1	1·7	4·0	3·4	1·83	1·60	34·9	36·5
AG (2)	2·1	1·8	3·9	3·7	1·62	1·70	35·5	37·0
RL (1)	2·0	1·6	3·3	3·4	1·72	1·63	37·0	38·1
RL (2)	1·9	1·8	3·6	3·5	1·41	1·42	36·6	37·8
KM (1)	1·8	1·6	2·9	2·9	1·32	1·50	39·4	37·1
KM (2)	2·2	2·0	3·9	3·3	1·81	1·65	37·3	38·3
LA (1)	1·9	1·5	3·4	3·0	1·72	1·82	38·0	39·0
LA (2)	1·9	1·5	3·5	3·2	1·74	1·70	37·2	38·1
LA (3)	1·6	1·5	3·1	3·2	1·51	1·55	40·6	39·4
AI (1)	1·4	1·4	3·2	3·1	1·32	1·40	43·0	41·0
AI (2)	1·4	1·4	3·2	3·1	1·45	1·45	38·5	38·0
AI (3)	1·6	1·6	3·6	3·1	1·71	1·70	35·5	36·5
RH (1)	1·6	1·6	4·8	3·4	1·60	1·45	35·0	36·5
RH (2)	2·5	1·6	4·7	3·4	1·83	1·54	33·0	33·5
RH (3)	1·6	1·6	3·9	4·2	1·70	1·55	32·2	33·2
$\bar{x}$	1·84	1·61	3·67	3·33	1·62	1·58	36·9	37·3
S.D.	0·31	0·16	0·55	0·32	0·18	0·12	2·8	2·0
P	0·004		0·02		0·16		0·23	

Mean values, for each of six subjects, of inspiratory time (T_I), expiratory time (T_E), tidal volume (V_T) and end-tidal P_{CO_2} (P_{ET,CO_2}) over the 1 min of $H_2{}^{15}O$ infusion (9–14 breaths) during a PET scan. Each subject underwent two or three pairs of scans during 'active' voluntary inspiration (Act) and 'passive' positive pressure ventilation (Pas). The mean ($\bar{x}$) and standard deviation (S.D.) of these average values for the fifteen paired scans comprising the rCBF analysis are shown. P gives the level of statistical significance for differences in the means of each variable for Active *vs.* Passive (paired t test).

shown for one subject in Fig. 2. A breath by breath analysis of inspiratory time (T_I), expiratory time (T_E), tidal volume (V_T) and P_{ET,CO_2} corresponding to the 1 min of $H_2{}^{15}O$ infusion (taken as representative of the scan period), was performed for each of the 'active' and 'passive' runs; the number of breaths taken during this period ranged from nine to fourteen between subjects but never differed by more than three between a matched pair of runs. The mean values of these ventilatory variables are given in Table 1. Paired t test analysis on each variable for the 'active' *vs.* 'passive' conditions in the fifteen matched runs revealed significantly lower values for both T_I (1·61 *vs.* 1·84 s) and T_E (3·33 *vs.* 3·67 s) in 'passive' compared with 'active' breathing but V_T and P_{ET,CO_2} were not significantly different between the two conditions.

All subjects showed a smooth and repeatable P_{nasal} trace during 'passive' inspiration (Fig. 2) for virtually all breaths occurring during scanning. Over the 1 min of $H_2{}^{15}O$ infusion, the mean peak P_{nasal} ranged between 14·1 and 30·8 cmH_2O for different subjects, and for individual scans the coefficient of variation of P_{nasal} in

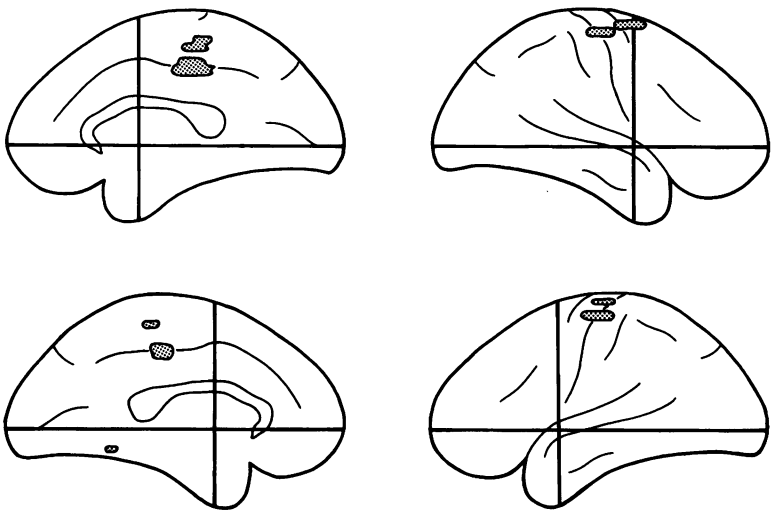

Fig. 3. Diagram summarizing the sites of significantly increased rCBF occurring with active inspiration in pooled data from 6 subjects. Medial (left-hand) and lateral (right-hand) views of the right (upper-half) and left (lower-half) hemispheres are shown. The horizontal lines indicate the position of the intercommissural (AC–PC) plane and the vertical line the location of Vca, a line passing through the anterior commissure (Talairach & Tournoux, 1988). The shaded areas indicate the regions, projected onto these views, at which significant ($P < 0·05$) increases in rCBF occurred during the 'active' task. The right medial view shows two regions (comprising four foci) and the left medial view two regions (three foci) of increased flow within the SMA, which, due to their proximity to the mid-line, could not be allocated to either hemisphere with certainty. The medial view of the left hemisphere also shows, below the AC–PC plane, the focus of increased rCBF occurring within the cerebellum which overlay the cerebral cortex at this level. The lateral projections, show, on the right, a focus within the motor cortex and, anteriorly, one within the pre-motor cortex. On the lateral view of the left hemisphere are 2 foci of increased flow within the motor cortex. The brain outlines were copied from a drawing by R. Passingham taken from the atlas of Talairach & Tournoux (1988).

nine to fourteen successive breaths ranged between 0·9% and 6·5% (median 1·9%). During 'active' inspiration, peak P_{nasal} never exceeded $-2·5$ cmH_2O, consistent with the relatively low resistance of the external breathing circuit (Fig. 1).

Minimal or no EMG activity was recorded in the sternomastoid muscles in the three subjects studied.

Regional cerebral blood flow

The brain volume successfully imaged in all subjects extended from the vertex to the upper cerebellum. Global cerebral blood flow was not significantly different ($P =$ 0·4, paired t test) between the 'active' and 'passive' conditions. Significantly

increased flows ($P < 0.05$) in association with the 'active' state occurred within five brain regions: the right pre-motor cortex, the supplementary motor area (SMA), the cerebellum and both the right and left motor cortices (Fig. 3). Given that the peri-Rolandic foci were located anterior to the fissure and that our experiment was designed to subtract out any change due to afferent activity, we felt justified in using

TABLE 2. Sites of significantly increased blood flow in active inspiration

Region	Average flow increase (%)	Co-ordinates (mm)
Left Motor (2)	5·4	−18, −23, 65
Right Motor	4·3	+18, −18, 60
Right Pre-motor	7·6	+18, −2, 64
SMA (4)	3·1	+4, −29, 48
Cerebellum	4·9	−6, −52, −8

Degree of flow increase and co-ordinates for sites of significantly ($P < 0.05$) increased blood flow in the 'active' compared to the 'passive' task. The flow changes represent the average values from the six subjects. Co-ordinates are given in order of sagittal, coronal and vertical locations and refer to the stereotaxic atlas of Talairach & Tournoux (1988). The sagittal reference is the mid-line (displacements to the right are positive), the coronal reference is a plane vertical to the intercommissural plane, passing through the anterior commissure with distances anterior being positive; the vertical is the distance above the intercommissural plane. The figures given in brackets indicate the number of foci (on different transverse planes) lying within the same anatomical region. All the regions except the cerebellum included some foci which were also significant at the $P < 0.01$ level.

the term 'motor' rather than 'sensorimotor' cortex. All but the cerebellar region included foci which remained significant at the $P < 0.01$ level. Foci of significantly increased flow occurred in four transverse planes within the SMA (two at the $P < 0.01$ level). Within the left motor cortex, foci of significantly increased flow occurred in two transverse planes (one at the $P < 0.01$ level). Average flow increases ranged from 3·1 to 7·6% within the different regions and are given with their co-ordinates in Table 2. The laterality of the cerebellar and SMA sites of activation is uncertain because of the proximity of the sagittal coordinates to the mid-line.

DISCUSSION

Respiratory motor control is characterized by the presence of rhythmical motor outflow that proceeds in the absence of conscious awareness, as well as by the capacity for a high degree of volitional modification of this basic rhythm. Physiological observations, as well as the effects of disease in man in which the automatic and 'voluntary' aspects of breathing can sometimes be dissociated (Plum & Leigh, 1981), suggest that these two functions reflect differences in the relative contribution from cortical and brain stem structures.

The present study was designed to examine the neural control of breathing in its 'most voluntary' form. The subjects were required to generate accurately a specific inspiratory volume and respiratory frequency, a task that could not be achieved without training. Anxiety, a potential influence on breathing (Howell, 1990) was minimized by training sessions, and by explanation and reassurance during the study. The target tidal volume was roughly three times normal and end-tidal P_{CO_2}

was kept at low normal levels to ensure that chemical drives to breathe were minimized. The level of P_{CO_2}, however, was not low enough to cause a significant alteration in overall cerebral blood flow (Kety & Schmidt, 1948).

The 'passive' task was used as a control for the afferent activity evoked in the 'active' task. Inflation of the lungs excites afferents within the lung and airways, as well as in the skin and muscles of the chest wall, and there is direct evidence that afferents within intercostal nerves at least, project to the cerebral cortex (Gandevia & Macefield, 1989). In order that any cortical activation resulting from the 'passive' task reflect only the effects of peripheral afferent discharge, it was clearly necessary that the subjects' inspiratory muscles did indeed remain relaxed during this control condition; the recordings of pressure from within the nasal mask indicated that this was so. Although end-tidal P_{CO_2} levels showed that the overall levels of ventilation were well matched, there were small differences in the duration of the inspiratory and expiratory phases in the 'active' and 'passive' tasks. Furthermore, although afferent activity from all sources should have been very similar in the expiratory phases of both tasks, the afferent discharge generated during the inspiratory phases would not have been perfectly matched. While intrathoracic, cutaneous and joint receptor discharge should have been similar in the two conditions throughout the respiratory cycle, extrathoracic airway pressure receptors, facial afferents innervating skin within the mask and respiratory muscle afferents would have been expected to discharge differently during the inspiratory phase of the two tasks. Indeed perfect matching of afferent activity is probably impossible for this and most motor tasks.

Previous measurements of rCBF during movements of the eyes and limbs (Roland, Larsen, Lassen & Skinhøj, 1980; Fox, Fox, Raichle & Burde, 1985*a*; Colebatch *et al.* 1991*b*) have measured increases against a resting state. Due to the limited temporal resolution possible with PET, the problem arises of whether the increases seen are the cause, or the result of the movement. It has been shown, for example, that both muscle and cutaneous afferents project to the pre- and post-central gyri, the SMA and the pre-motor cortex (Powell & Mountcastle, 1959; Lemon & Porter, 1976; Hummelsheim, Bianchetti, Wiesendanger & Wiesendanger, 1988) and could have contributed towards the increased blood flow recorded for these regions. By subtracting out the effects of a 'passive' control state, it is likely that the sites identified represent cortical areas dominated by 'centrally generated' neural activity in association with the volitional inspiratory task.

The size of the flow increases reported here are modest in comparison with increases seen in association with limb movements. Repetitive contraction of a single digit, for example, has been reported to result in a 13% increase in rCBF within the sensorimotor cortex (Colebatch *et al.* 1991*b*). Several factors could have contributed towards the modest blood flow increases found in the present study. Firstly, the experiment was designed to remove flow increases associated with the 'passive' task. Such peripheral afferent activity may have contributed significantly to increases in rCBF seen with limb movements; Colebatch, Findley, Frackowiak, Marsden & Brooks (1990) reported increases of 15% in sensorimotor cortex blood flow in response to passive wrist movements. Secondly, only about one-third of the 'active' task scan time was actually spent in generating inspiratory airflow, the remainder being spent in expiration which occurred passively in both tasks. Finally, the

repetition rate used here (12 breaths min^{-1}) was much slower than that used in some studies of limb movement (e.g. 40 movements min^{-1}, Colebatch *et al.* 1991*b*). Although the dynamic sensitivity of rCBF to different rates of movement is not known, Fox & Raichle (1984, 1985), who studied occipital cortex rCBF responses to visual stimuli, found a linear increase in flow with increasing repetition rates between 1 s^{-1} and 8 s^{-1}.

The motor cortex, SMA, pre-motor cortex and cerebellum, activated in this study, have also been reported to be active in association with simple, repetitive arm and hand movements (Fox *et al.* 1985*a*; Fox, Raichle & Thach, 1985*b*; Colebatch *et al.* 1991*b*). This suggests that these regions participate in the generation of all voluntary movements with clearly defined targets and disagrees with the claim by Roland *et al.* (1980) that only complex motor tasks require SMA and pre-motor activation. Furthermore, there would appear to be a fundamental similarity in the mechanism by which voluntary movements of both the limbs and respiratory muscles are generated. Anatomically, the motor and non-primary motor areas are closely interrelated (e.g. Ghosh, Brinkman & Porter, 1987) and, for different movements of the arm, the activation within sensorimotor cortex, SMA and premotor cortex change roughly in parallel (Colebatch *et al.* 1991*b*). In unilateral movement, increases in flow in the pre-motor cortex may occur either bilaterally or just contralateral to the limb moved (Roland, Meyer, Shibasaki, Yamamoto & Thompson, 1982). In the present study, where a symmetrical bilateral movement was performed, the unilateral premotor activation seen raises the possibility of hemispheric specialization for the 'active' task; this may be related to a greater degree of attention associated with this manoeuvre (Pardo, Fox & Raichle, 1991).

The present study outlines the motor cortical areas involved in the inspiratory 'active' task but cannot define exactly which inspiratory muscles are 'represented' by these areas. Although inspiratory intercostal muscles could certainly have been activated during the 'active' task, the diaphragm would have been the principal muscle of inspiration. The locations in the motor cortical foci in each hemisphere correspond well to an earlier report of an optimal site for direct stimulation of the cortex to activate the diaphragm in man (Foerster, 1936). The use of transcranial magnetic stimulation in man (Maskill *et al.* 1991) has indicated an optimal site for activating the contralateral diaphragm, approximately 3 cm lateral to the vertex. With the assumption of a skull thickness of 0·8 mm, it is possible to calculate that the motor cortical sites identified in the present study correspond to locations approximately 2·5 cm lateral to the vertex.

The SMA, which in monkeys has been shown to have its own projection to the spinal cord (Macpherson, Marangoz, Miles & Wiesendanger, 1982) is nevertheless generally believed to have a role in planning movement 'upstream' of the motor cortex (Roland *et al.* 1980). Our results indicate a role for the SMA in voluntary respiratory movements and complement recent evidence for the presence of a Bereitschaftspotential (Deecke, 1987) preceding similar respiratory manoeuvres (Macefield & Gandevia, 1991). The location of the SMA focus in the present study lay at a similar vertical height above the intercommissural plane as reported in association with shoulder movements (Colebatch *et al.* 1991*b*) but 15 mm more posterior. Rostrocaudal somatotopy within the SMA has been reported for man, with

areas active in vocalization and eye movements lying progressively more rostral to that for arm movement (Talairach, Szlika, Tournoux, Prossalentis, Bordas-Ferrer, Corello, Iacob & Mempel, 1967; Fox *et al.* 1985*a*). Our data suggest that the SMA region, active in association with the inspiratory task used here, lies posterior to that for arm movement and is thus separated by it from the region involved in vocalization.

This study, using rCBF as an indicator of local neural activation (Raichle, 1987), has provided, for the first time, direct evidence for a functional role of specific cortical structures in the generation of a voluntary inspiratory task. The present methodology is potentially capable of enabling the study of respiratory motor control under a variety of different behavioural conditions in both normal volunteers and patients with defined deficits. Careful choice of experimental paradigms should allow conclusions to be drawn about the control of breathing not only in other overtly volitional tasks but also, for example, during speech and in states of anxiety. Such everyday examples of behavioural influences on breathing have, in the past, been extremely difficult to study in a rigorous fashion.

This work forms part of a Wellcome Trust Programme Grant to A.G. The Wellcome Trust independently supported J.G.C. and K.J.F. We thank Ms C. Taylor and Mr G. Lewington of the MRC Cyclotron Unit for their invaluable assistance. We are indebted to Dr K. Gibson, Dr T. Jones and Professor R. Frackowiak for their support, advice and encouragement. We greatly appreciate the assistance given by Dr D. Brown and Dr R. Wise, without which the study could not have been completed.

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