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MOTOR CORTICAL REPRESENTATION OF THE DIAPHRAGM IN MAN

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SUMMARY

1. Transcranial magnetic stimulation was performed using a figure-of-eight-shaped coil over the right motor cortex with the aim of identifying those areas involved with activation of the diaphragm.
2. The response of the right and left hemi-diaphragms was recorded using surface electrodes in either the 7th or 8th intercostal spaces 3 cm lateral to the anterior costal margin on either side.
3. The compound muscle action potentials recorded over the left diaphragm in response to transcranial magnetic stimulation were maximal when the centre of the figure-of-eight coil was placed approximately 3 cm to the right of the mid-line and 2–3 cm anterior to the auricular plane.
4. The amplitude of the response recorded from the diaphragm depended upon the angulation of the figure-of-eight coil and hence the direction of the stimulating current.
5. The response of the inspiratory muscles to magnetic stimulation of one side of the brain was predominately contralateral but a small response was seen on the ipsilateral side. Ultrasonic techniques confirmed that the diaphragm was responding contralaterally and not ipsilaterally.

INTRODUCTION

The muscles of breathing can be activated behaviourally or automatically; phrenic motorneurones can be controlled by both bulbo- and corticospinal pathways (Aminoff & Sears, 1971). Rapidly conducting oligosynaptic pathways from motor cortex to the diaphragm were first demonstrated in man by Gandevia & Rothwell (1987) using transcranial electrical stimulation (Merton & Morton, 1980) with an anode at the vertex and a cathode 6–7 cm anterior to the vertex. This optimal site was confirmed by Murphy, Mier, Adams & Guz (1990) using transcranial magnetic stimulation (Barker, Freeston, Jalinous, Merton & Morton, 1985) with a circular coil centred on average 1 cm behind the vertex in the mid-sagittal line.

These results suggested that the cortical representation of inspiratory muscles may lie close to the vertex but the methods for stimulation used did not have much

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focusing ability. The finding of Foerster (1936), who had mapped the human cortex during neurosurgery under local anaesthesia, was of great relevance since a focal cortical site was identified (Fig. 1) anterior to the thoracic muscle site of representation, which when stimulated gave rise to hiccough; this site was close to the vertex. No information was given concerning the frequency with which such a site was identified, the reproducibility of the results of stimulation or whether ipsilateral, contralateral, or both diaphragms contracted.

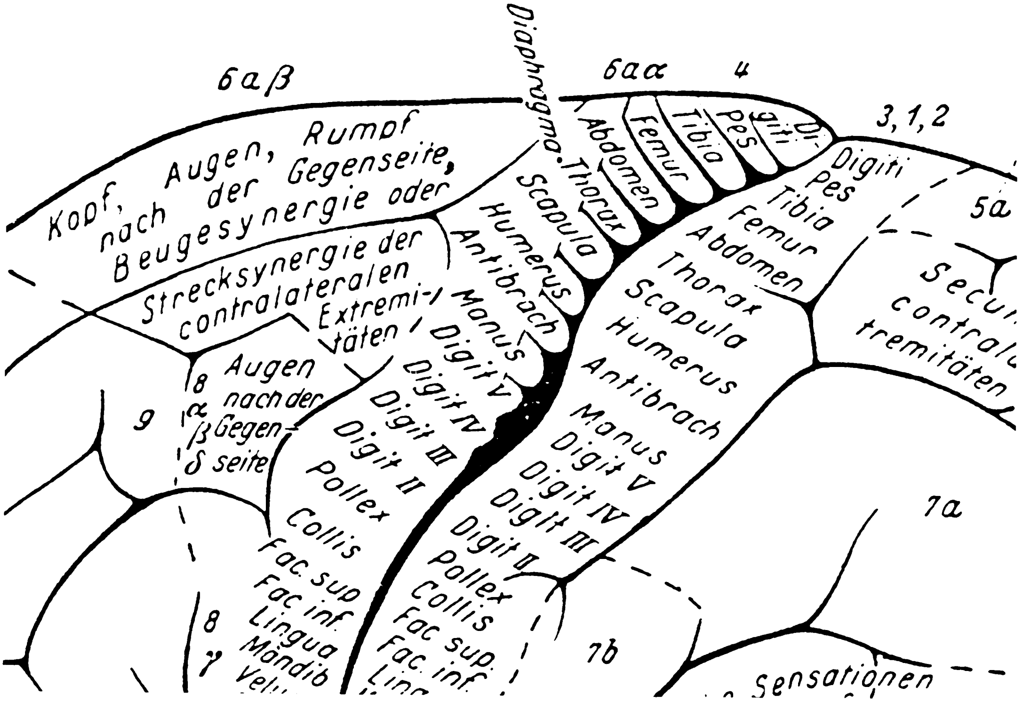

Fig. 1. Section of the functional map of the motor cortex derived from the results of electrical stimulation of the exposed brain during neurosurgery in man. This map shows a site, near the vertex, marked vertically as 'Diaphragma' which when stimulated produced a loud 'hiccough'. Taken from Foerster (1936) Fig. 69a, p. 50 with permission of the publishers, Springer–Verlag.

The object of the present study was to examine whether transcranial magnetic stimulation could be used with an improved coil design to increase the ability to focally stimulate a unilateral cortical representation of the inspiratory muscles and also to establish what this activation did to diaphragmatic contraction.

The finding that a figure-of-eight coil was superior at exciting a specific motor area and a demonstration that the orientation of the principal current vector was the most critical stimulation parameter (Rösler, Hess, Heckmann & Ludin, 1990) suggested that we should use such a coil. These findings were confirmed by the experimental work of Boniface, Mills & Schubert (1990) and by the elegant experimental and theoretical work of Cohen, Roth, Nilsson, Dang, Panizza, Bandinelli, Friauf & Hallett (1990*b*).

Preliminary results have been presented in abstract form (Maskill, Murphy, Mier & Guz, 1991).

METHODS

The method described by Murphy *et al.* (1990) was modified to allow mapping of the cortical site(s) responsible for activation of the inspiratory muscles, especially the diaphragm. The studies were performed in five male subjects aged 32–61 years. Full mapping as described below was carried out in each subject and then the reproducibility of any optimal site found was reassessed. In two of these subjects, the response of the diaphragm to cortical stimulation was visualized using an ultrasonic technique. A limited further study was performed in one female subject aged 21 years whose left phrenic nerve had been unavoidably transected during intrathoracic surgery to remove a benign mediastinal mass 3 weeks previously; the left diaphragm was not elevated on chest radiography.

All subjects gave their informed consent to these procedures which had local ethical approval.

Physiological measurement systems

The compound muscle action potentials (CMAP) evoked in the diaphragm and perhaps lower inspiratory intercostal muscles were recorded using pairs of surface electrodes (Ag–AgCl; MEDI-TRACE, Graphic Controls) placed in the 7th or 8th intercostal spaces bilaterally, 3 cm lateral to the anterior costal margin approximately in the anterior axillary line. The precise position chosen was thought to be optimal for diaphragmatic recording, particularly when a lower frequency 'rumbling' sound could be heard through an audio amplifier with inspiration (Lansing & Saville, 1989). The electrode sites were optimized on the basis of the amplitude of the CMAP evoked by stimulation of the phrenic nerve near the posterior border of the sternomastoid muscle at the level of the cricoid cartilage (Newsom-Davis, 1967). Surface bipolar stimulating electrodes (Medelec 53054) with felt tips, 5 mm in diameter, were used to deliver square-wave impulses 0·1 ms in duration at a frequency of 1 Hz from a Digitimer 3072 stimulator. Voltages used were supramaximal and ranged from 100 to 140 V for each nerve.

A further pair of electrodes were located over the left rectus abdominus muscle to record any possible interfering activation during inspiration by a conventional expiratory muscle.

The electromyogram (EMG) signals were processed through isolated differential amplifiers of local design (bandwidth of 10–1000 Hz), displayed on an oscilloscope (SEM 121, SE Laboratories Ltd) and then passed to a computer-based data capture/averaging system (Cambridge Electronic Design 1401 and Tandon PCA20 computer) triggered by the discharge of the stimulator. The sample rate was such that each 'bin' was equivalent to 0·2 ms.

Diaphragmatic movement was recorded by ultrasound using a 3·5 MHz, curvilinear probe on a SIEMENS AC machine.

Magnetic stimulation

Transcranial stimulation was performed using a magnetic stimulator (Magstim 200, Novametrix Medical Systems), which can discharge a high voltage very quickly through a coil placed tangentially on the head, thus creating a brief high-intensity magnetic field which induced a monophasic pulse (Claus, Murray, Spitzer & Flügel, 1990; 2·1 Tesla at full power with a duration of approximately 150 μs). The coil used was a figure-of-eight design (inset in Fig. 2) wired so that the current in the central axis had twice the magnitude of the current flowing in the two arms of the coil; the direction of current flow in the central axis is towards the handle. The advantage in such a coil is greater focality of the stimulation-induced current vector and the ability to change the direction of that vector (Rösler *et al.* 1990). To improve the accuracy of coil placement on the head a point in the centre of the intersection of the two halves was clearly marked (X in Figs 2 and 7). A circular coil (o.d. 12 cm, i.d 4·5 cm) was separately used in preliminary studies (Murphy *et al.* 1990).

The magnetic stimulator required triggering at a constant level of inspiratory drive in view of the dependence of the diaphragmatic CMAP on the magnitude of this drive (Murphy *et al.* 1990). It was thought that the mapping procedure would benefit from the increased size and clarity of the CMAP obtained with increased inspiratory drive above the resting level, due to the phenomenon of facilitation i.e. the increase in the effectiveness of the stimulus when the muscles are already activated volitionally (Merton & Morton, 1980; Murphy *et al.* 1990). To this end the magnetic stimulator was triggered automatically at a fixed level of integrated EMG activity (equivalent to a tidal volume of approximately 1–2 l) from one of the inspiratory muscle recording sites, whilst the subject inspired through a restricted airway with peak mouth pressure ranging from -10 to $-20\ \mathrm{cmH_2O}$.

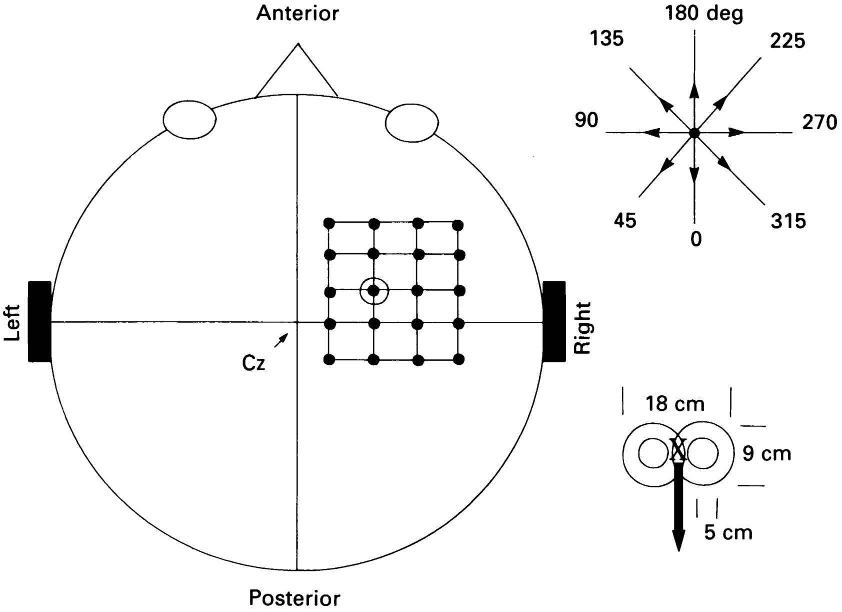

Fig. 2. Schematic representation of the top of the head marked with a line from left to right ear intersecting a line from the inion to the nasion at the point Cz (international 10–20 electroencephalogram electrode placement system). The grid marks, 2 cm apart, used during stimulation are shown with reference to a circled point; this point had previously been chosen as one which gave an approximate maximum compound muscle action potential response in the recording site on the contralateral side. Above and to the right is a 'star' showing the different angles at which stimulation was performed; the arrow-head shows the direction of the current flowing in the central axis. The lower symbol represents the stimulation coil and is marked with an X to indicate that part of the coil which was aligned over the grid points; the arrow shows the direction of the current in the central axis.

Recording system

All EMG signals together with the 'integral' used for triggering and a mark coincident with stimulator triggering were recorded on a strip chart-recorder (Brush Gould Inc.) at a speed of 2 mm/s. The ultrasonic echo signals were recorded on videotape (U-matic), together with an audio signal marking the moment of stimulation.

Protocols

1. Mapping

(*a*) *Principal.* Subjects were seated comfortably in a high-backed chair which allowed the head to be supported throughout the whole study; the electrodes were than applied for EMG recording. A mid-sagittal and a transverse line between the ears was then drawn on a tightly fitting rubber swimming cap to define the vertex (Cz, see Fig. 2). Pilot studies had suggested that a focal point, which particularly activated the contralateral inspiratory muscles, existed at a position approximately 3 cm lateral and 2 cm anterior to Cz. This point was first defined in each of the subjects studies (circled grid point in Fig. 2) on the right side of the head, after which a grid of 2 cm steps was drawn on the cap to permit mapping. The point marked at the intersection of the coil halves was placed over each grid point and stimuli applied (90 % of maximum power output) twice at each 45 deg angle of the coil handle and therefore direction of the current vector through this point (X). During these studies the EMG activity in the rectus abdominus during the loaded inspiration was required to be absent or minimal; this was usually the case, but if activity was persistently seen, the subject was given feedback and encouraged to inspire without such abdominal muscle activity.

Mapping studies were confined to the right cortex.

(*b*) *Diaphragmatic movement visualization.* In two of the subjects, studied supine, diaphragmatic movement was visualized using the echo system. The ultrasonic probe was stabilized on a stand to prevent spurious movement. The right diaphragm was scanned in a sagittal plane through the liver; the left diaphragm was scanned in an oblique coronal plane through the spleen. Both diaphragms could be scanned together in an oblique axial plane from just below the xiphisternum (Cosgrove & McCready, 1982). The adequacy of the visualization was first tested during unilateral phrenic nerve stimulation in the neck. Scans of left, right and both diaphragms were recorded during cortical stimulation using (a) the figure-of-eight coil at the optimal site to the left of the mid-line or (b) the circular coil, its centre 1 cm posterior to Cz. All stimuli were given during inspirations of approximately 1–2 l.

(*c*) *Focusing ability of circular and figure-of-eight coils.* During inspiration (1–2 l) cortical stimulation was performed while the CMAP amplitude was exclusively recorded on the left. The centre of the circular coil and the point marked 'X' on the figure-of-eight coil, were moved transversely across a line through Cz from 9 cm to the left up to 9 cm to the right of Cz in 3 cm steps; five stimuli were given at each step.

2. *Diaphragmatic contribution to surface EMG*

In the one subject with interrupted conduction of the left phrenic nerve, the response to (a) phrenic nerve stimulation in the neck on both sides at functional residual capacity (FRC) and (b) cortical stimulation, at the optimal spot, on both sides of the head, was measured during inspiration (1–2 l) using the figure-of-eight coil.

Analysis

Each stimulation triggered the computer system to record a sweep of 100 ms (0·2 ms bin width); if there were any ECG artifacts on the signal it was rejected. The CMAPs, at an appropriate latency (Gandevia & Rothwell, 1987; Murphy *et al.* 1990), evoked from repeated stimuli in any given condition were averaged and the peak-to-peak amplitude measured.

RESULTS

General observations

Mapping required 350–400 transcranial magnetic stimuli over a period of approximately 2 h. The stimulus intensity ranged from 90 to 95 % of maximum output. Subjects did not report any untoward effects during or after the stimulation other than the discomfort in the head produced by the tight-fitting swimming cap. In addition, as stated previously by Murphy *et al.* (1990), no subject reported any unexpected changes in behaviour, mood or intellectual performance.

Protocol 1a

The effect of varying the angle of the principal stimulating current vector in the figure-of-eight coil around an optimal site (see below) over the right cortex is shown for one subject in Fig. 3; the CMAPs evoked were recorded from the contralateral site optimal for recording the diaphragm. The striking effect of varying the angle was apparent at the optimal sites in all subjects, the most effective angle being between 270 and 0 deg. A similar dependence with angle was seen over sites that were not necessarily optimal.

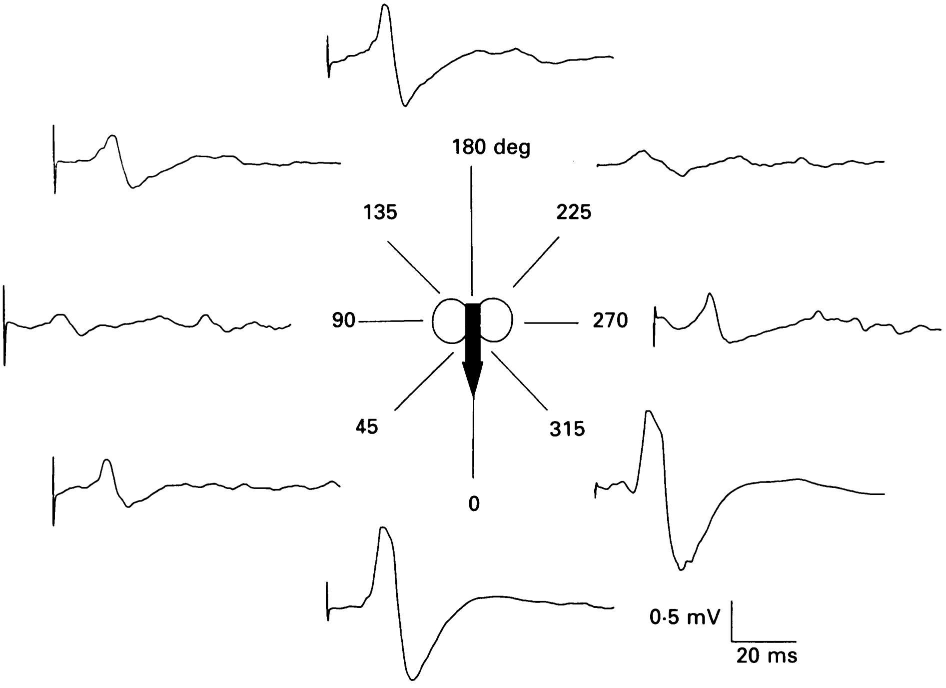

Fig. 3. Compound muscle action potentials obtained at the optimal recording site in the left 7th intercostal space in one subject in response to transcranial magnetic stimulation over the optimal site in the right cortex during inspiration (1–2 l). The responses from two stimuli given at each stimulation angle have been averaged and plotted at their appropriate position to show the variation in response as a function of the coil orientation and hence direction of stimulation current flow as shown by the direction of the arrow. The optimal coil orientation is between 315 and 0 deg.

This dependence of the amplitude of CMAP evoked on the direction of the principal stimulating current, meant that the most effective coil angles had to be established in the mapping procedure. The results are shown for four subjects in Fig. 4 (contralateral response) and for one subject in Fig. 5 (contralateral and ipsilateral response). These maps show that a focal cortical area for stimulating the contralateral inspiratory muscles can be demonstrated. The positions of these 'foci' are shown in Table 1; they correspond with the surface projection of the upper end of the human motor cortex (Hamilton, 1976; Fig. 321). Effective cortical stimulation could be obtained over distances at least 2–3 cm from the optimal site; the amplitude of the CMAP fell with increasing distance from this site. The angle of stimulating current at the optimal site for each subject is also shown in Table 1.

A small ipsilateral response was seen in all subjects and is demonstrated in Fig. 5. There was no apparent optimal point for this response. Furthermore, the ipsilateral response seen when the centre of the figure-of-eight coil was near the mid-line (where the left-hand edge of the stimulating coil could possibly be directly stimulating the other side of the cortex) could be contrasted with that obtained from a site 6·5 cm lateral from the mid-line where direct stimulation of the other side of the head would be highly unlikely (Fig. 6). The ipsilateral response remained essentially the same with the coil in either position; this was found in all subjects.

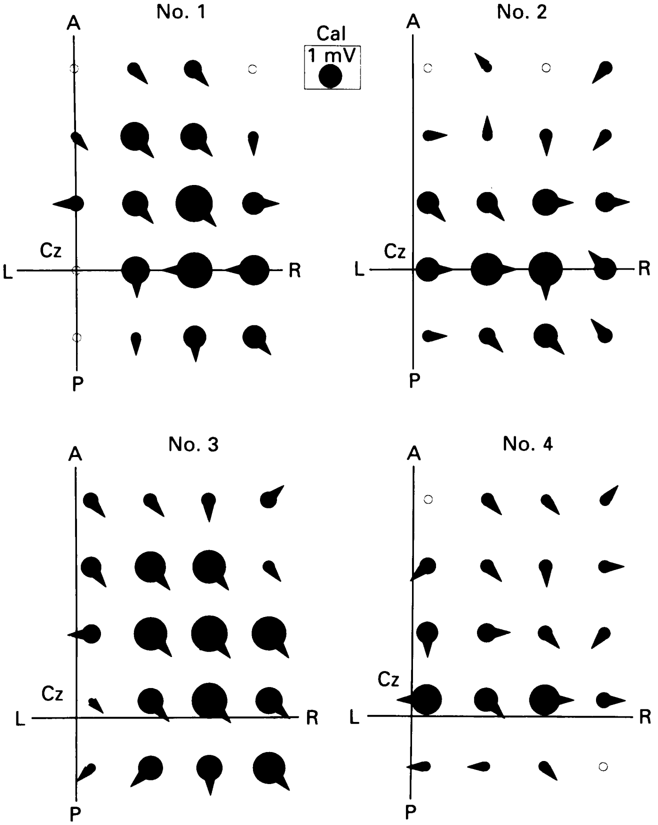

Fig. 4. The 2 cm stimulation grid (as shown in Fig. 2) enlarged in four subjects (Nos. 1, 2, 3, 4) showing the anterior–posterior (A–P) and inter-aural (L–R) lines intersecting at Cz. The area of the filled circles at each point is proportional to the maximum amplitude of the compound muscle action potential recorded (calibration (Cal) is for area representing 1mV) on the left-hand side of the body in response to transcranial magnetic stimulation of the right side of the brain during inspiration (1–2 l). The arrow-heads indicate the direction of the current flow at which this maximum response was seen. Small open circles indicate that no response was recorded at any angle at this point. These results show an approximate 'stimulation focus' for each subject.

The conduction times for the contralateral and especially the small ipsilateral responses could not, in general, be measured with any accuracy in view of the signal-

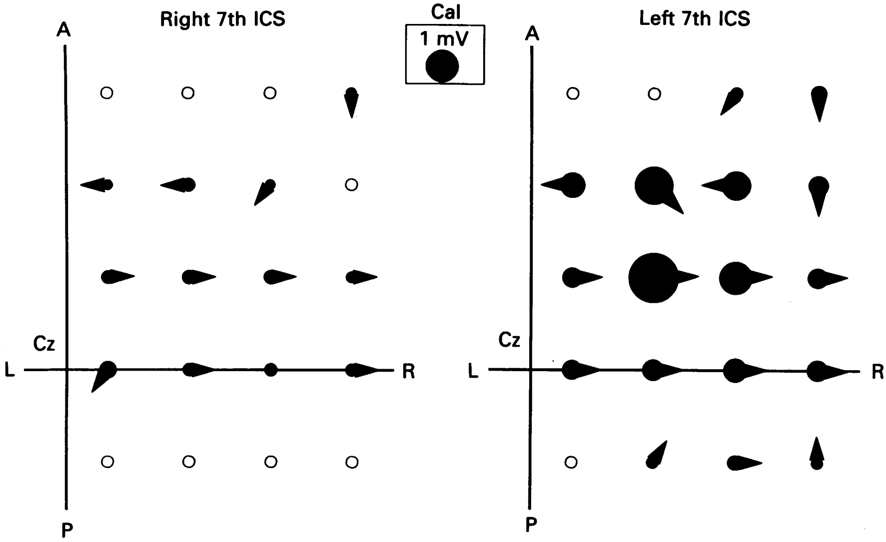

Fig. 5. The figure is constructed in a manner similar to Fig. 4. These results, in further subject (No. 5), are from simultaneous recordings from the left and right optimal recording sites in the 7th intercostal space (ICS) in response to transcranial magnetic stimulation of the right side of the brain during inspiration (1–2 l). These results show the 'stimulation focus' in the right cortex causing contralateral activation; in addition there is a small but significant activation on the side ipsilateral to the stimulation.

TABLE 1. Co-ordinates of 'foci', on the right side of the head, optimal for stimulating contralateral inspiratory muscles, together with the optimal angle of the principal stimulation current vector at these co-ordinates.

Subject no.	Distance lateral to mid-sagittal plane (cm)	Distance anterior to auricular plane (cm)	Optimal angle (deg)
1	4·0	2·0	312
2	4·5	0·0	270
3	4·5	2·5	315
4	4·5	0·5	270
5	3·0	2·0	27

to-noise ratio accepted without averaging multiple stimuli (Murphy *et al.* 1990). However, the ipsilateral response, where measurement was possible, was of a similar or smaller magnitude than found with the contralateral response; the findings in Fig. 6*A* are typical.

Protocol 1b

The images obtained using ultrasound techniques (Fig. 7) show that the contralateral diaphragm was activated in response to transcranial magnetic stimulation at the optimal spot but the ipsilateral diaphragm showed no visible movement. If the figure-of-eight coil was replaced with a circular coil sited 1 cm posterior to the vertex (a site which stimulates both sides of the diaphragm; Murphy *et al.* 1990), then both diaphragms contracted in response to the stimulus.

Protocol 1c

In four of the subjects, CMAPs from the left recording site could be obtained with the centre of the circular coil anywhere from 9 cm to the right of Cz through to 3 cm on the left of Cz; the amplitude fell progressively from right to left. By contrast, the CMAPs recorded with the figure-of-eight coil showed a peak at 3 cm to the right of Cz which fell to zero at Cz and close to zero 6 cm to the right of Cz. This finding is illustrated in one subject (No. 5) in a preliminary report by Maskill *et al.* (1991; Fig. 1*A*).

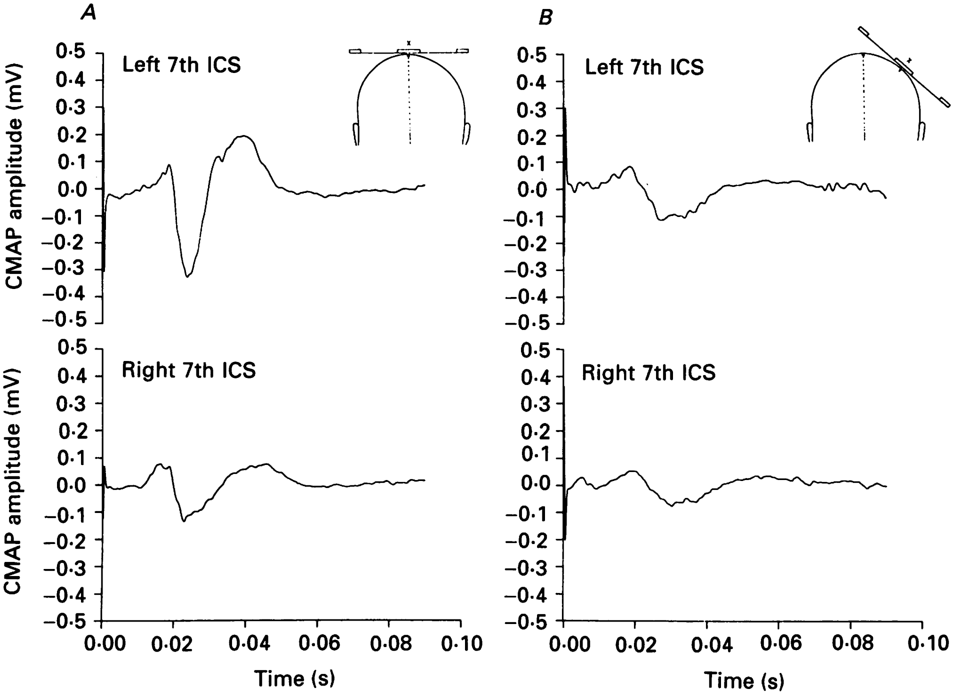

Fig. 6. Recordings from the optimal sites in the left and right 7th intercostal spaces (ICS), in one subject (No. 4), in response to transcranial magnetic stimulation during inspiration (1–2 l) with the coil centre (X) placed 0·5 cm to the right of the mid-line (*A*) and 6·5 cm to the right of the mid-line (*B*). The small diagrams show the coil arrangement as viewed from the back of the subject. In addition to the contralateral response, an ipsilateral response is clearly seen in *A* and even *B* where direct stimulation of the left cortex is unlikely.

Protocol 2

Percutaneous stimulation of the phrenic nerve in the neck of the subject with the cut phrenic nerve showed no response on the left (cut) side but a normal response on the right (Fig. 8). Transcranial magnetic stimulation of the left side of the head, using the figure-of-eight coil at the optimal site, evoked a normal CMAP response recorded from the electrodes placed on the right side of the thorax. When the coil was placed on the right side of the head, at a position which mirrored the optimal site on the left

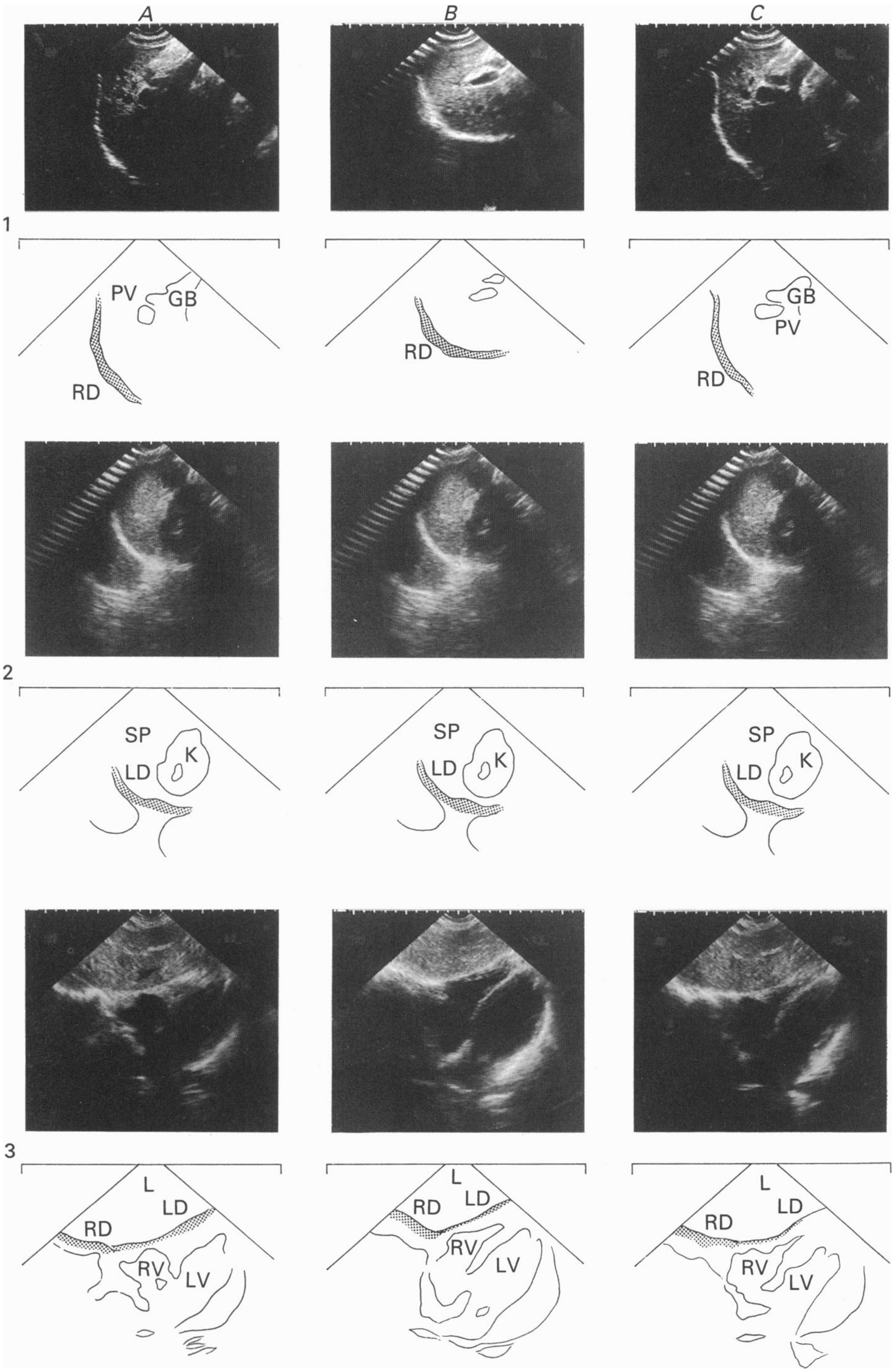

Fig. 7. Ultrasound recordings, together with a representation of the relevant anatomy, during inspiration in subject No. 5 lying supine. The sequences shown in 1 and 2 are the effect of stimulating the optimal site in the left cortex using a figure-of-eight coil with 1 illustrating the movement of the contralateral right diaphragm and 2 the lack of

side of the head, stimulation did not evoke any CMAP response on the left side of the chest, even though the underlying intercostal muscles were normally innervated and active during deep inspiration (Fig. 8); searching around this presumed optimal site on the right side of the head still did not induce any response on the left side of the thorax.

DISCUSSION

The results described in this paper show that with the use of transcranial magnetic stimulation it is possible to define a site of cortical representation of the inspiratory musculature in man unilaterally and that stimulation of this site activates predominantly the contralateral diaphragm.

The experimental protocol only mapped the right cortex. This restriction was imposed by the investigators in view of the very large number of stimuli required over a comparatively short period of time. Although a consensus exists that no untoward effects occur as a result of the use of this technique (Cohen & Hallett, 1987; Bridgers & Delaney, 1989; Krain, Kimura, Yamada, Cadwell & Sakamaki, 1990) and this was found in the present study, some reports have suggested that the subtle effects can be detected objectively. Amassian, Cracco, Cracco, Eberle, Maccabee & Rudell (1988) have reported transient suppression of visual perception occurring maximally 80–100 ms after transcranial magnetic stimulation of the occipital cortex. Ammon & Gandevia (1990) have shown that subthreshold magnetic stimuli affected the selection of motor programmes in hand movement over a period of 2–5 s after stimulation, while Saltuari, Marosi, Kofler, Karamat, Schmidhuber, Kemmler & Jeschow (1991) detected small but significant changes in concentration, attention, fatiguability and visual memory, following magnetic cortical stimulation, which were all back to normal 24 h later. Although this cautious approach seemed justifiable, pilot studies in some of the subjects from this present study had shown that exploration of the left cortex gave similar results in terms of site and predominant effect on the contralateral side i.e. right diaphragm.

A further consequence of this cautious approach was that time-bin averaging with multiple stimuli could not be used to reduce signal-to-noise ratio adequately to make reliable estimates of conduction times; this was particularly true for the much smaller ipsilateral responses.

Ability to focus stimulation, together with the ability to change the direction of the inducing current, were absolute requirements for mapping; in the absence of these factors mapping was as poor as demonstrated using the circular coil (Maskill *et al.* 1991). Amassian, Cadwell, Cracco & Maccabee (1987), and subsequently Cohen, Hallett & Lelli (1990*a*), showed that it was possible to stimulate movement of

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movement of the ipsilateral left diaphragm, before (*A*), during (*B*) and after (*C*) the stimulus. Sequence 3 shows the response in both diaphragms to the use of a circular coil whose centre had been placed 1 cm posterior to the vertex; *A*, *B* and *C* as above. Both diaphragms respond to stimulation with the circular coil (3*B*) but only the contralateral diaphragm (1*B* cf. 2*B*) responds to the figure-of-eight coil centred at the optimal site. Over the time scale portrayed (< 2 s), the normal inspiratory diaphragmatic movements are minimal and can just be detected in 2*B* cf. 2*A*. SP, spleen; K, kidney; GB, gall bladder; PV, portal vein; L, liver; RV, right ventricle; LV, left ventricle; LD, left diaphragm; RD, right diaphragm.

different individual fingers and therefore achieve some degree of focal stimulation, even with a circular coil, if varying orientations of the coil over the scalp were utilized. However, reproducible results in the same and different subjects could not be obtained. Cohen *et al.* (1990*b*) have measured the relative ability to produce focal stimulation of both circular and figure-of-eight coils by studying the magnetic field produced in air. Peak voltage proportional to the time derivative of the magnetic field were recorded with a search coil 1 cm in diameter and this allowed the magnetic field distribution to be mapped; the induced electric field, difficult to measure, could then be computed using a validated mathematical model based on simple physical principles and the assumption of a homogeneous medium. The figure-of-eight coil, with current flowing clockwise in one loop and anti-clockwise in the other loop, induced an electric field that was both maximal and focused at the centre of the

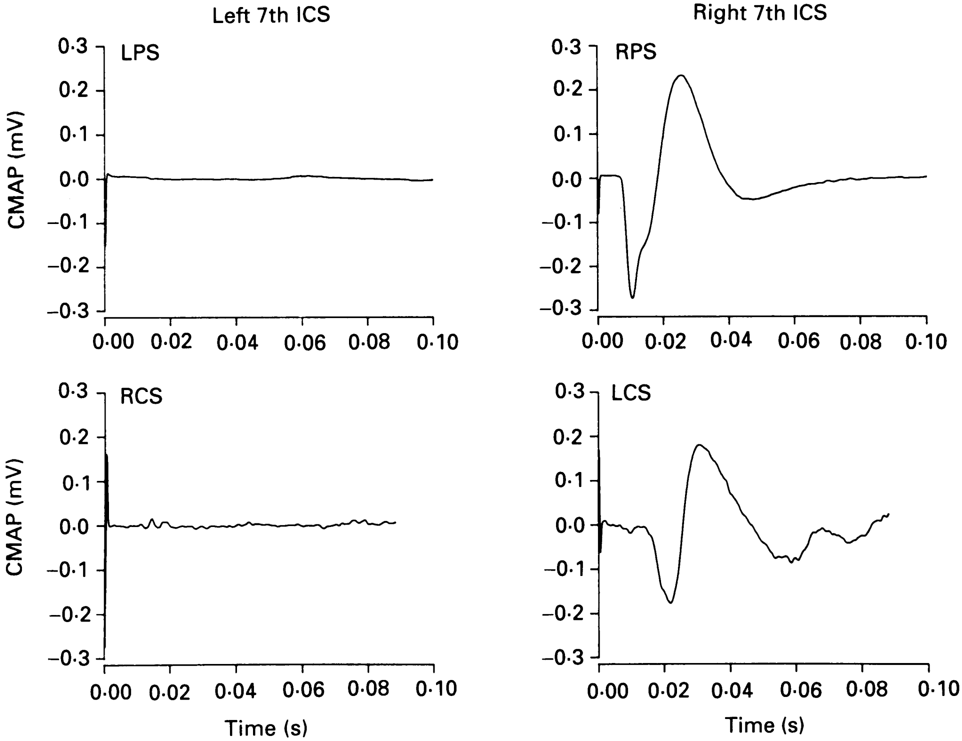

Fig. 8. Results from the subject with loss of phrenic nerve conduction within the chest on the left side. Recordings are from the left and right 7th intercostal space (ICS) in response to (a) upper panel: transcutaneous phrenic nerve stimulation at functional residual capacity, on the left (LPS) and right (RPS) confirming the loss of conduction on the left and (b) lower panels: transcranial magnetic stimulation, during inspiration (1–2 l), on the left (LCS) and right (RCS) optimal cortical sites, showing a normal response only on the side with an intact phrenic nerve and a minimal response on the other side. These results confirm that the surface recordings are predominantly from the underlying diaphragm with minimal contribution from the intercostal muscles. Inspiratory EMG activity can be seen during the deep inspiration in the lower two records (by contrast with the absence of activity at FRC in the upper two records).

double coil and which fell to 50, 27 and 16% at 2, 3 and 4 cm respectively relative to the value at 1 cm under the centre (Cohen *et al.* 1990*b*; Figs 5 and 6). By contrast, the computed electric field from the circular coils was maximal under the circumference and minimal at the centre of the coil

These advantages of a figure-of-eight coil are enhanced by practical aspects of the design. Thus with the coil centre over the scalp location chosen and the plane of the coil tangential to the curvature of the scalp, the outer edge of the loops are furthest from neural tissue (Fig. 6) and therefore less effective; this factor combined with the decrease in induced electric field with distance from the centre ensures that neural structures close to the centre are the ones that are predominately activated. It seems unlikely, however, that only central 'point' stimulation is being achieved.

A further advantage of the figure-of-eight coil is that the orientation of its central axis can be changed about a point (X in Fig. 2); this means that the principal stimulation-induced current can have its direction changed. Our results confirm the major significance of this stimulation parameter as described by Rösler *et al.* (1989) in their study of optimal circular and figure-of-eight coil positions in exciting the cortical representations of abductor digiti minimi and tibialis anterior. Similar confirmatory findings have been made by Boniface *et al.* (1990) when activating the first dorsal interosseous muscle by stimulating over the left cortex; these authors raised the possibility that optimal angulation may reflect the prevailing direction of 'horizontal neural elements' that are being stimulated since the most effective stimulation of a neurone occurs when the current flow is parallel to the axis of that neurone (Rushton, 1927). If this explanation is correct, then it may explain the modest variation in optimal angulation found in the present study, presumably based on anatomical variability. Mapping of the area of interest in the present study would have been impossible to interpret without knowledge of the significance of coil orientation.

The requirement for a signal-to-noise ratio as large as possible and the observation in pilot studies that the signal obtained with unimpeded inspiration of 1–2 l magnitude was often small, even with the stimulator set at 90–95% of full power, led to the use of a restricted airway to increase volitional facilitation. Facilitation was originally described by Merton & Morton (1980) and was demonstrated for the diaphragm by Gandevia & Rothwell (1987) and Murphy *et al.* (1990); the response to cortical stimulation increases with increased volitional drive. It is possible that such volitional facilitation increases the size of the cortical area involved in the response, but it is unlikely that the site of the central focal 'point' would be altered by the strength of inspiratory drive. There is no information on this problem in studies of motor cortical sites that are easier to activate with the present available technology. The area of the motor cortical site for the deltoid muscle activated by transcranial magnetic stimulation has been shown to be larger in two patients with long-standing quadriplegia than is found in the normal (Amassian, Cadwell, Levy & Traad, 1990).

The question of whether lower thoracic surface EMG electrodes were predominantly recording from a unilateral contracting diaphragm was of some concern, particularly because of the 1–2 l inspiratory volumes and the use of an inspiratory resistance, both of which might have been expected to recruit inspiratory intercostal muscles. During quiet tidal breathing, at least in the supine posture, the inspiratory intercostals in the area of interest remained electrically silent when probed with needle electrodes in quiet breathing and also during deep breathing (Taylor, 1960), while the surface electrodes in the same area recorded diaphragmatic activity in inspiration and also, during deep breathing, expiratory intercostal activity. Because of the contrary findings of Campbell (1955) with surface electrodes, suggesting that inspiratory lower intercostals were activated with deep inspiration, and also because of the fact that the sitting posture was used in the present studies, a degree of uncertainty remained. The study on the patient with one cut phrenic nerve demonstrated only minimal involvement of intercostal muscles in the phenomena recorded. It is possible that inspiratory *movements* are what is represented in the human motor cortex and therefore it may not matter whether the compound muscle action potential recorded from surface electrodes is purely diaphragmatic or whether it contains a contribution from the inspiratory intercostal muscles.

The ultrasound studies confirmed the findings of electromyography and showed that *movement* of a single leaf of the diaphragm can be elicited from focal stimulation of the contralateral cortex at an appropriate site; this occurs without any downward movement of the diaphragm on the side ipsilateral to that stimulated.

The findings of the present study amplify the observations of Foerster (1936) confirming the site of diaphragmatic cortical representation. The area of this site in the present studies seems too large but this presumably results from a relative inability to focus stimulation even with the improved figure-of-eight coil design. Foerster (1936) merely described a 'spot' in the exposed human motor cortex where electrical stimulation was effective in generating a hiccough; this 'spot' apparently required a careful search. Penfield & Rasmussen (1950) in later studies did not mention the cortical representation of the diaphragm or other respiratory muscles; this also suggests that the relevant site is small.

The findings of the present study are in keeping with the observations of Colebatch, Adams, Murphy, Martin, Lammertsma, Tochon-Danguy, Clark, Friston & Guz (1991) using positron emission tomography (PET) in normal man to highlight those areas of the cortex involved in the volitional act of inspiring 1·5–2 l. The protocol ensured that any increase in regional blood flow due to associated afferent feedback was subtracted out with passive ventilation, so that images obtained represented areas dominated by centrally generated neural activity in association with the volitional task. Focal statistically significant increases in blood flow were seen bilaterally in the primary motor cortex approximately 2·5 cm either side of the mid-line. This study also showed significant increases in blood flow in the right pre-motor cortex (PMA) and also in the supplementary motor cortex (SMA) and the cerebellum (sides uncertain). The cortical site being stimulated in the present study presumably corresponds to the right motor cortical site demonstrated in the PET study (Colebatch *et al.* 1991); however, we cannot exclude simultaneous stimulation of the sites in the PMA and SMA. It would seem unlikely that the SMA is being stimulated given the very rapid fall-off in the calculated electric field with depth (Cohen *et al.* 1990*b*; Fig. 6).

The finding of two separate motor cortical foci on the right and left in the study using PET (Colebatch *et al.* 1991), together with the demonstration in the present study of a predominant contralateral effect of stimulating what is likely to be one of these foci, raises the question of how both diaphragms act together in a volitional inspiration. There is no evidence of any major cross-innervation at the level of the diaphragm (Hammond, Gordon, Fisher & Richmond, 1989). Integration between right and left sides during an inspiration is unlikely to be achieved utilizing the small ipsilateral activation demonstrated in the present study; no downward movement of a diaphragm was seen on the ipsilateral side in response to unilateral stimulation (Fig. 7). Integration during an inspiration could be achieved via the corpus callosum; it would be of great interest to know whether patients whose corpus callosum has been cut show no integration of right and left diaphragm movements. The cervical spinal cord remains a very obvious candidate as a site of integration of descending inspiratory drive on the two sides and there is experimental evidence to support this (Janczewski & Karczewski, 1990). Finally it is entirely possible that cortical activation of the diaphragm is transmitted via the respiratory-related neuronal complex ('respiratory centre') in the medulla; a great deal of evidence exists on 'cross-over' from side to side within this neuronal complex (Merrill, 1974; Karczewski & Gromysz, 1981). Experimental evidence exists in the cat (Colle & Massion, 1958; Planche, 1972) that direct stimulation of cortical areas in the frontal lobe on one side elicited long-latency bilaterally symmetrical excitatory and inhibitory responses of phrenic motoneurones; this was thought to result from transmission to the cord indirectly over cortico-bulbospinal pathways. By contrast, short-latency responses compatible with direct corticospinal activation could be recorded only from the contralateral phrenic motoneurone (Planche, 1972) and this seems compatible with the results in man presented above.

Similowski, Catala, Orcel, Willer & Derenne (1991) have recently studied patients with hemiplegia due to a lesion in the internal capsule using transcranial magnetic stimulation and estimating the cortex-to-diaphragm conduction time; other neurological patients without motor dysfunction and healthy subjects were used as controls. Only in the patients with a capsular hemiplegia was a significant difference found between the conduction times on the right and left side; the prolongation occurred on the hemiplegic side contralateral to the site of the lesion. The authors concluded that a single leaf of the diaphragm had a unilateral, contralateral cortical representation.

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