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RESEARCH NOTE

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Diaphragmatic silent period to transcranial magnetic cortical stimulation for assessing cortical motor control of the diaphragm

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Abstract This study was designed to determine whether a silent period could be elicited in the diaphragm electromyographic (EMG) activity by transcranial magnetic stimulation (TMS) of the motor cortex and, if so, to assess the influence of reflex or voluntary control of breathing on diaphragmatic cortical silent period (cSP). Diaphragmatic EMG activity was recorded in six healthy volunteers after motor cortex TMS triggered by the inspiratory flow peak and applied during forced inspiration (FI), voluntary hyperventilation (vHV) and reflex hyperventilation (rHV) to a CO_2 stimulus. Electrophysiological and respiratory parameters were studied, including diaphragmatic cSP duration and transdiaphragmatic pressure swing (ΔPdi). A diaphragmatic cSP was found and correlated with ΔPdi values. ΔPdi and cSP duration were similar in the vHV and rHV conditions but were significantly increased during FI. This study established for the first time the existence of a diaphragmatic cSP to motor cortex TMS. The diaphragmatic cSP duration depended on the magnitude of the respiratory effort, as assessed by ΔPdi, but not on the mechanism (volitional or reflex) of diaphragm activation.

Keywords Clinical neurophysiology · Diaphragm · Electromyographic silent period · Respiration physiology · Transcranial magnetic stimulation

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Introduction

Respiratory muscle activity during spontaneous respiration is under involuntary control related to gas exchanges and to a complex neurohumoral regulation system. This regulation is ensured by various pontomedullary oscillators and other neuronal centers located in the brainstem (Guz 1997; Gallego and Gaultier 2000). In these centers, interacting populations of excitatory and inhibitory interneurons are driven in parallel by the pacemaker neurons of the pre-Bötzinger complex. These pacemaker neurons can be temporarily inhibited by inhibitory interneurons, thereby sculpting the pattern of breathing (Smith et al. 2000). Then, the respiratory rhythm is transmitted to cervical and thoracic spinal motoneurons at the origin of the phrenic and intercostal nerves.

Cortical centers can act directly on spinal motoneurons by way of the pyramidal tracts, bypassing the brainstem centers. Besides, an indirect cortical control of respiratory muscle activity through synaptic relay within the brainstem may exist. Thus, voluntary motor control plays an important role in breathing, even if the interactions between brainstem and cortical respiratory centers remain to be delineated (Guz 1997; Gallego and Gaultier 2000). In a recent study using transcranial magnetic stimulation (TMS) of the motor cortex, the amplitude of the motor evoked potentials (MEPs) recorded in the diaphragm did not differ between normocapnia and hypocapnia, suggesting that the level of demand on brainstem respiratory oscillators did not interfere with the cortical control of the diaphragm (Corfield et al. 1998).

Since the introduction of TMS in 1985 (Barker et al. 1985), this technique of stimulation has gained widespread acceptance not only for studying pyramidal tract conduction by recording MEPs but also for testing motor cortex excitability. For this last purpose, various methods have been proposed, using single or paired pulses, but one of the most reliable tests consists of recording the cortical silent period (cSP). A silent period is an interruption of the electromyographic (EMG) signal following a stimulus applied during a sustained voluntary contraction and

results from the recruitment of motor inhibitory interneurons. A silent period in the EMG activity of a muscle can be elicited by stimulating at a supramaximal intensity the peripheral nerve that innervates this muscle (cutaneous or peripheral silent period, pSP) or by stimulating the motor cortex (cSP).

The pSP was first observed by Hoffmann (1919) at the beginning of the century, was characterized 30 years later (Merton 1951) and at present is attributed to intraspinal inhibitory mechanisms (Leis 1998; Manconi et al. 1998; Logigian et al. 1999). The cSP is a more recent finding. Following the first report of post-TMS inhibitory phenomena (Calancie et al. 1987), the cSP was characterized in 1990–1991 (Holmgren et al. 1990; Fuhr et al. 1991). In contrast to pSP, an intracortical inhibitory control causes the cSP, at least in its second part (Fuhr et al. 1991; Cantello et al. 1992; Wilson et al. 1993; Haug and Kukowski 1994; Brasil-Neto et al. 1995). Whereas pSP is considered as a nociceptive defense reflex (Inghilleri et al. 1997), cSP assesses GABAergic pathways (Inghilleri et al. 1996; Ziemann et al. 1996), which are involved in voluntary motor control, as shown by numerous observations made in patients with movement disorders. The cSP was found shortened in patients with Parkinson's disease (Cantello et al. 1991; Haug et al. 1992; Priori et al. 1994a) and prolonged in patients with Huntington's disease (Priori et al. 1994b; Tegenthoff et al. 1996; Modugno et al. 2001). The cSP was also altered in various motor disorders related to vascular disease (Uozumi et al. 1992; Schnitzler and Benecke 1994; Braun and Fritz 1995; Catano et al. 1997; Ahonen et al. 1998) or to degenerative disease (amyotrophic lateral sclerosis) (Prout and Eisen 1994; Desiato and Caramia 1997; Triggs et al. 1999).

A diaphragmatic pSP using phrenic nerve stimulation was described in a single previous study (Delhez 1975), but a diaphragmatic cSP following cortical stimulation was never reported. The goals of this study were to look for the existence of a diaphragmatic cSP, and if this cSP was found, to evaluate the respective influence of reflex and voluntary activation of breathing on the diaphragmatic cSP. To this end, we recorded diaphragmatic EMG activity following motor cortex TMS during forced inspiration, reflex and voluntary hyperventilation.

Materials and methods

Six healthy volunteers gave their informed consent for this study, which was approved by the local ethics committee. They were free from any pulmonary, neurological or psychological diseases. None was taking medication. There were five men and one woman, aged from 34 to 44 years.

Measurements

The subjects were comfortably seated and the experiments took place in a quiet room. They wore a nose-clip and breathed via a mouthpiece. Flow was measured using a pneumotachograph (Fleisch no. 2, Lausanne, Switzerland) connected to a differential pressure transducer (Validyne MP 45±5 cmH_2O, Northridge, USA). End-tidal CO_2 partial pressure was measured in the breathing tube close to the lips (PET_{CO2} infrared analyzer, Gould, USA). Esophageal pressure (Pes) and gastric pressure (Pga) were recorded using a catheter-mounted transducer (Gaeltec, Dunvegan, Isle of Skye, UK). The validity of the Pes measurements was checked by analyzing the shape of the Pes curve during water drinking and by the occlusion technique (Baydur et al. 1982). All respiratory signals were computerized after being sampled and digitalized at 128 Hz, using an analog/digital system (MP100, Biopac System, Goleta, USA).

TMS was performed using a Magstim 200 (Magstim, Whitland, Carmarthenshire, Wales) with a 90-mm circular coil placed over the vertex. The coil was secured to the scalp by a device that ensured a fixed and accurate positioning throughout the session. Diaphragmatic motor responses were recorded through a band-pass of 20–2,000 Hz, using a DISA 13K63 bipolar esophageal electrode (DISA, Copenhagen, Denmark) taped to the nose and a standard EMG machine (Phasis II, EsaOte Biomedica, Florence, Italy).

Experimental protocol

In preliminary experiments, we look for the existence of a diaphragmatic cSP in various subjects during basal spontaneous breathing. But, in these conditions, a cSP was never observed. Even at maximal facilitation during forced inspiration, the cSP was barely detectable at TMS intensities lower than 100% of the maximal output of the TMS machine. Then, we recorded diaphragmatic responses to TMS at 100% intensity under three experimental conditions, described as follows, and applied in random order.

First, reflex hyperventilation (rHV) was obtained by asking the subject to breathe for 15 min through an external dead-space tube. This tube had an inner diameter of 5.2 cm and a length sufficient to obtain a volume greater than 1 l as measured by water displacement. This condition was designed to assess the reflex activation of breathing at the level of brainstem respiratory centers following the stimulation of chemoreceptors by CO_2 increase (Fenner et al. 1968).

Second, to study the volitional respiratory activation, a condition of voluntary hyperventilation (vHV) was performed, the subject being asked to actively hyperventilate for 15 min. In terms of respiratory effort, the requested degree of hyperventilation was similar between vHV and rHV conditions.

Third, a forced inspiration (FI) condition was designed and consisted of asking the subject to perform ten FIs within a 5-min period, each FI corresponding to a maximal voluntary inspiratory effort.

A series of ten TMSs was performed during the 5 min of the FI condition and during the last 5 min of the rHV and vHV conditions. To standardize cSP recordings, the stimulations were performed at a constant TMS intensity of 100% and were triggered by the inspiratory flow peak. Fatigue was avoided by allowing the subjects to have a rest between each of the three experiments.

Data analysis

Two items of electrophysiological data were analyzed from the trans-esophageal recordings of diaphragm EMG activity: the peak-to-peak amplitude of the diaphragmatic MEPs and the duration of the diaphragmatic cSP. The onset of the cSP was taken at MEP end (when the post-MEP EMG signal returned to baseline) and the end of the cSP was taken at EMG activity recovery (when the amplitude of the raw EMG signal exceeded 50 μV). For each subject, ten MEPs and ten post-MEP cSPs have been analyzed in each condition.

In addition, the following respiratory variables were determined in each condition on at least 30 breath cycles, before any TMS application. The PET_{CO2} was measured as the peak of airway CO_2 at each breath. The tidal volume (VT) was measured from the calibrated integrated flow signal. The inspiratory time (TI) was the

time from the inspiratory flow onset to the expiratory flow onset, the remainder of the breath cycle duration being the expiratory time (TE). Additional parameters have been calculated from these data: the respiratory rate [RR=1/(TI+TE)], the total ventilation ($\dot{V}_E$=VT×RR) and the mean inspiratory flow rate (VT/TI). Finally, the respiratory effort was assessed by ΔPdi, which was the swing of transdiaphragmatic pressures (Pga–Pes) (peak value at each inspiration using end-expiration value as reference). For analysis, a mean value was calculated for all these parameters, in each condition. For the FI condition, only VT, TI, and ΔPdi were determined.

Statistical analysis

The ANOVA test was used to analyze the electrophysiological values or the respiratory data obtained in the three conditions and a post hoc Tukey-Kramer's test or a Welch *t*-test was used to compare the two conditions. The relationship between the electrophysiological data and ΔPdi (including basal spontaneous breathing data) was assessed by linear regression analysis. The level of significance was set at 5%.

Results

Electrophysiological results

In FI and both HV conditions, each attempt of motor cortex TMS at 100% intensity was allowed to elicit a diaphragmatic MEP followed by a cSP (Fig. 1). The mean amplitude of the diaphragmatic MEPs did not differ significantly between the three conditions (Table 1). In contrast, the diaphragmatic cSP duration was significantly longer in the FI condition than in the vHV or rHV conditions (Table 1). Similar results were obtained whatever the gender of the subject.

Respiratory parameters

The respiratory parameters did not differ between the vHV and the rHV conditions, except for the PET_{CO2}, which was higher in the rHV than in the vHV condition (Table 1). Compared to the FI condition, TI was prolonged and VT/TI and ΔPdi were reduced in the vHV or rHV condition.

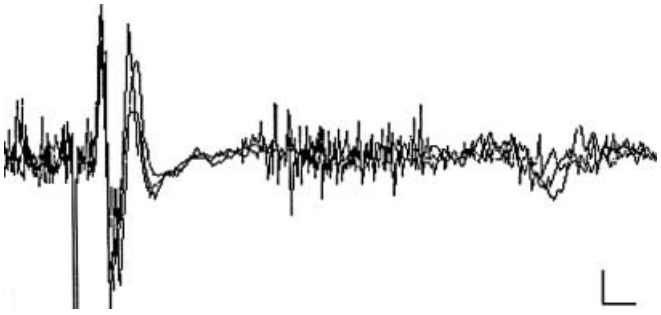

Fig. 1 Example of the silent period in diaphragm electromyographic activity following a motor evoked potential in response to motor cortex stimulation during voluntary hyperventilation. Three traces are superimposed (*horizontal bar* 10 ms, *vertical bar* 25 μV)

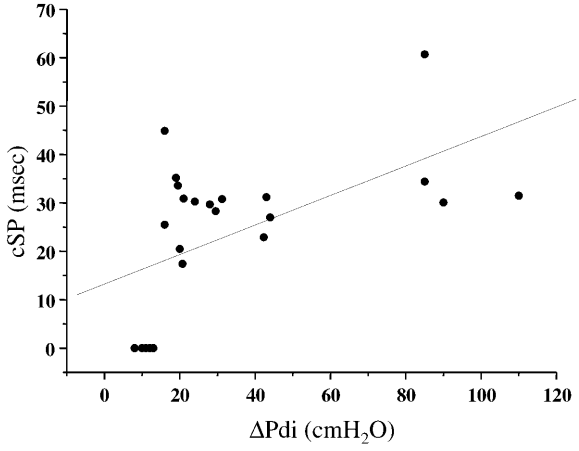

Fig. 2 Correlation between the swing of the transdiaphragmatic pressure (Δ*Pdi*) and the duration of the diaphragmatic cortical silent period (*cSP*). The *straight line* is the regression line (*r* 0.55, *P* 0.006)

Table 1 Means ± standard error of the mean (SEM) of the amplitude of diaphragmatic motor evoked potentials (MEPs), duration of the diaphragmatic cortical silent period (cSP), end-tidal partial pressure of CO_2 (PET_{CO2}), total ventilation ($\dot{V}_E$), tidal volume (*VT*), respiratory rate (*RR*), inspiratory time (*TI*), mean inspiratory flow rate (*VT/TI*) and transdiaphragmatic pressure swing (Δ*Pdi*) in three experimental conditions: forced inspiration (*FI*), voluntary hyperventilation (*vHV*) and reflex hyperventilation (*rHV*). Statistical analysis used ANOVA for data obtained in the three conditions and the post hoc Tukey-Kramer's test or the Welch *t*-test for comparisons between the two conditions (*NA* not available, *ns* not significant, the level of significance being set at 5%)

	FI	vHV	rHV	ANOVA	FI vs vHV	vHV vs rHV
MEP amplitude (mV)	243.1±20.6	272.9±36.6	257.5±30.1	NS	NS	NS
SP duration (ms)	38.5±1.6	27.4±0.6	27.9±0.7	*P*<0.0001	*P*<0.001	NS
PET_{CO2} (mmHg)	NA	25.2±3.1	42.3±1.7			*P*=0.02
$\dot{V}_E$ (l/min)	NA	30.9± 3.2	26.7±4.4			NS
RR (per min)	NA	16.3±1.7	16.3±1.4			NS
VT (l)	2.5±0.5	1.9±0.2	1.6±0.2	NS	NS	NS
TI (s)	0.8±0.1	1.4±0.2	1.5±0.2	*P*=0.01	*P*=0.02	NS
VT/TI (l/s)	3.6±0.8	1.6±0.2	1.2±0.2	*P*=0.008	*P*=0.03	NS
ΔPdi (cmH_2O)	68.3±15.8	30.8±4.3	24.9±4.1	*P*=0.02	*P*=0.04	NS

Regression analysis

The diaphragmatic cSP duration correlated with the respiratory effort assessed by ΔPdi (r=0.55, P=0.006) (Fig. 2). In contrast, the amplitude of diaphragmatic MEPs did not correlate with ΔPdi (r=0.06, P=0.82).

Discussion

This study is the first to establish that a cSP to motor cortex TMS exists for the diaphragm as for any skeletal limb muscles. In addition, we found that cSP duration correlated to the magnitude of the diaphragmatic effort as assessed by ΔPdi, but did not seem to differ between volitional and reflex control of the diaphragm activity.

In respiratory application, TMS was first used to stimulate the phrenic nerves at the neck (Similowski et al. 1989). Later, motor cortex TMS was performed to investigate the cortical representation of the diaphragm and to measure the pyramidal tract conduction time corresponding to this muscle (Murphy et al. 1990; Maskill et al. 1991; Gea et al. 1993; Lissens 1994; Zifko et al. 1996). But the existence of a diaphragmatic cSP to TMS has not yet been reported. The cSP is usually recorded in hand muscles but has also been observed in lower limb muscles (Wilson et al. 1993; Ziemann et al. 1993) and in facial muscles (Werhahn et al. 1995; Cruccu et al. 1997). As stated previously, a pSP to phrenic nerve electrical stimulation was found in the diaphragm EMG activity (Delhez 1975), indicating that spinal inhibitory mechanisms are able to influence this muscle, like any limb muscles. The present study gave evidence that the diaphragm can also be subjected to intracortical inhibitory control.

We found a positive correlation between cSP duration and ΔPdi value. ΔPdi, which is about 12 cmH_2O during spontaneous breathing (Macklem 1985), increased 2.5-fold during vHV and almost 6-fold during FI. The fact that diaphragmatic cSP was not observed for spontaneous inspiration but was present in the vHV or rHV condition and more prolonged in the FI condition supported the correlation found between the cSP duration and the inspiratory effort. This observation is in contrast with the results reported for hand muscles, in which cSP depends on TMS intensity but not on the strength of voluntary contraction (Cantello et al. 1992; Haug et al. 1992; Uozumi et al. 1992). Nevertheless, TMS intensity probably influences diaphragmatic cSP duration, given that cSP was barely detectable using TMS intensities lower than 100% of maximal output, even during FI.

In contrast to cSP duration, diaphragmatic MEP amplitude did not correlate with ΔPdi and showed similar values for the FI and HV conditions. This finding was unexpected since MEPs are classically facilitated by increasing muscle contraction force (Hess et al. 1987; Mills and Kimiskidis 1996). However, for high stimulation intensities, MEP amplitude facilitation by voluntary muscle contraction is almost maximal at 10% of the maximum contraction force (Hauptmann and Hummelsheim 1996). Then, a possible explanation for the present result is that facilitation was already maximal when TMS was applied during the HV condition and could not be enhanced in the FI condition. Besides, it has already been reported that MEP facilitation by voluntary contraction was less marked for the diaphragm than for hand muscles (Zifko et al. 1996).

The cSP is thought to result, at least in part, from the stimulation of intracortical inhibitory pathways by TMS. Therefore, one goal of this study was to compare the influence of volitional and reflex respiratory activation on the cortical inhibitory control of diaphragm contraction. No difference was found in cSP duration between vHV and rHV conditions, which use the two different mechanisms of diaphragm activation, involving either the motor cortex or the brainstem respiratory centers. Taking into account the correlation between cSP duration and ΔPdi, the cortical inhibitory regulation of diaphragm activity assessed by cSP seemed to be associated with the feedback control of the force exerted by the diaphragm rather than with the site of its activation.

However, the PET_{CO2} was significantly reduced in the vHV condition compared to the rHV condition and hypocapnia could have a depressant effect on intracortical inhibitory pathways, as reported for hand muscles, in which cSP was shown to be reduced after 5 min of vHV (Priori et al. 1995). If this is true, then at normo/hypercapnia the cSP during vHV may have been larger than the cSP during rHV, suggesting an influence of the central site of activation of the diaphragm on its cortical inhibitory control. However, to maintain eucapnia during vHV, CO_2 should be inhaled, resulting in the reflex activation of brainstem respiratory centers. In these conditions, it could be impossible to appraise the respective influence of hypocapnia and of voluntary versus reflex activation on diaphragm cSP. In contrast, we confirmed that the amplitude of the diaphragmatic MEPs did not differ between normo/hypercapnia (rHV) and hypocapnia (vHV), suggesting, as previously stated (Corfield et al. 1998), that the demand on brainstem respiratory centers did not interfere with the motor cortical command of the diaphragm.

In summary, we showed that a cSP was following the diaphragmatic MEP elicited by motor cortex TMS at high stimulation intensity. Diaphragmatic cSP duration, but not MEP amplitude, was found to be primarily associated with contraction force. Thus, the phenomena of cortical inhibition and facilitation of muscle contraction, as assessed by TMS, may differ between diaphragm and skeletal limb muscles. In the present study, these tests did not help to distinguish between a voluntary and a reflex activation of the respiration. Nevertheless, motor cortex TMS could be used to assess not only the pyramidal tract conduction time but also some intracortical regulatory mechanisms corresponding to diaphragm activity. This opens new perspectives for the neurophysiological testing of the respiratory muscles in pathological conditions, such as the problem of weaning from mechanical ventilation in

the intensive care unit, respiratory failure in advanced amyotrophic lateral sclerosis, or impairment of central diaphragmatic control in stroke.

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References

Ahonen JP, Jehkonen M, Dastidar P, Molnar G, Hakkinen V (1998) Cortical silent period evoked by transcranial magnetic stimulation in ischemic stroke. Electroencephalogr Clin Neurophysiol 109:224–229

Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of the human motor cortex. Lancet i:1106–1107

Baydur A, Behrakis PK, Zin WA, Jaeger MJ, Milic-Emili J (1982) A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 126:788–791

Brasil-Neto JP, Cammarota A, Valls-Sole J, Pascual-Leone A, Hallett M, Cohen LG (1995) Role of intracortical mechanisms in the late part of the silent period to transcranial stimulation of the human motor cortex. Acta Neurol Scand 92:383–386

Braun HJ, Fritz C (1995) Transcranial magnetic stimulation-evoked inhibition of voluntary muscle activity (silent period) is impaired in patients with ischemic hemispheric lesion. Stroke 26:550–553

Calancie B, Nordin M, Wallin U, Hagbarth KE (1987) Motor-unit responses in human wrist flexor and extensor muscles to transcranial cortical stimuli. J Neurophysiol 58:1168–1185

Cantello R, Gianelli M, Bettucci D, Civardi C, De Angelis MS, Mutani R (1991) Parkinson's disease rigidity: magnetic motor evoked potentials in a small hand muscle. Neurology 41:1449–1456

Cantello R, Gianelli M, Civardi C, Mutani R (1992) Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 42:1951–1959

Catano A, Houa M, Noel P (1997) Magnetic transcranial stimulation: clinical interest of the silent period in acute and chronic stages of stroke. Electroencephalogr Clin Neurophysiol 105:290–296

Corfield DR, Murphy K, Guz A (1998) Does the motor cortical control of the diaphragm 'bypass' the brain stem respiratory centres in man? Respir Physiol 114:109–117

Cruccu G, Inghilleri M, Berardelli A, Romaniello A, Manfredi M (1997) Cortical mechanisms mediating the inhibitory period after magnetic stimulation of the facial motor area. Muscle Nerve 20:418–424

Delhez L (1975) Electrical responses of the human diaphragm to the electrical stimulation of the phrenic nerves. Electromyogr Clin Neurophysiol 15:359–372

Desiato MT, Caramia MD (1997) Towards a neurophysiological marker of amyotrophic lateral sclerosis as revealed by changes in cortical excitability. Electroencephalogr Clin Neurophysiol 105:1–7

Fenner A, Jansson EH, Avery ME (1968) Enhancement of ventilatory response to carbon dioxide by tube breathing. Respir Physiol 4:91–100

Fuhr P, Agostino R, Hallett M (1991) Spinal motor neuron excitability during the silent period after cortical stimulation. Electroencephalogr Clin Neurophysiol 81:257–262

Gallego J, Gaultier C (2000) Comportement respiratoire. Rev Mal Respir 17:41–49

Gea J, Espadaler JM, Guiu R, Aran X, Seoane L, Broquetas JM (1993) Diaphragmatic activity induced by cortical stimulation: surface versus esophageal electrodes. J Appl Physiol 74:655–658

Guz A (1997) Brain, breathing and breathlessness. Respir Physiol 109:197–204

Haug BA, Kukowski B (1994) Latency and duration of the muscle silent period following transcranial magnetic stimulation in multiple sclerosis, cerebral ischemia, and other upper motoneuron lesions. Neurology 44:936–940

Haug BA, Schonle PW, Knobloch C, Kohne M (1992) Silent period measurement revives as a valuable diagnostic tool with transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 85:158–160

Hauptmann B, Hummelsheim H (1996) Facilitation of motor evoked potentials in hand extensor muscles of stroke patients: correlation to the level of voluntary contraction. Electroencephalogr Clin Neurophysiol 101:387–394

Hess CW, Mills KR, Murray NMF (1987) Responses in small hand muscles from magnetic stimulation of the human brain. J Physiol (Lond) 388:397–419

Hoffmann P (1919) Demonstration eines Hemmungsreflexes im menschlichen Ruckenmark. Z Biol 70:515–524

Holmgren H, Larsson LE, Pedersen S (1990) Late muscular responses to transcranial cortical stimulation in man. Electroencephalogr Clin Neurophysiol 75:161–172

Inghilleri M, Berardelli A, Marchetti P, Manfredi M (1996) Effects of diazepam, baclofen and thiopental on the silent period evoked by transcranial magnetic stimulation in humans. Exp Brain Res 109:467–472

Inghilleri M, Cruccu G, Argenta M, Polidori L, Manfredi M (1997) Silent period in upper limb muscles after noxious cutaneous stimulation in man. Electroencephalogr Clin Neurophysiol 105:109–115

Leis AA (1998) Cutaneous silent period. Muscle Nerve 21:1243–1245

Lissens MA (1994) Motor evoked potentials of the human diaphragm elicited through magnetic transcranial brain stimulation. J Neurol Sci 124:204–207

Logigian EL, Plotkin GM, Shefner JM (1999) The cutaneous silent period is mediated by spinal inhibitory reflex. Muscle Nerve 22:467–472

Macklem P (1985) Inferring the actions of the respiratory muscles. In: Roussos C, Macklem P (eds) The thorax. Marcel Dekker, New York, pp 531–538

Manconi FM, Syed NA, Floeter MK (1998) Mechanisms underlying spinal motor neuron excitability during the cutaneous silent period in humans. Muscle Nerve 21:1256–1264

Maskill D, Murphy K, Mier A, Owen M, Guz A (1991) Motor cortical representation of the diaphragm in man. J Physiol (Lond) 443:105–121

Merton PA (1951) The silent period in a muscle of the human hand. J Physiol (Lond) 114:183–198

Mills KR, Kimiskidis V (1996) Cortical and spinal mechanisms of facilitation to brain stimulation. Muscle Nerve 19:953–958

Modugno N, Curra A, Giovannelli M, Priori A, Squitieri F, Ruggieri S, Manfredi M, Berardelli A (2001) The prolonged cortical silent period in patients with Huntington's disease. Clin Neurophysiol 112:1470–1474

Murphy K, Mier A, Adams L, Guz A (1990) Putative cerebral cortical involvement in the ventilatory response to inhaled CO_2 in conscious man. J Physiol (Lond) 420:1–18

Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M (1994a) Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. Brain 117:317–323

Priori A, Berardelli A, Inghilleri M, Polidori L, Manfredi M (1994b) Electromyographic silent period after transcranial brain stimulation in Huntington's disease. Mov Disord 9:178–182

Priori A, Berardelli A, Mercuri B, Inghilleri M, Manfredi M (1995) The effect of hyperventilation on motor cortical inhibition in humans: a study of the electromyographic silent period evoked by transcranial brain stimulation. Electroencephalogr Clin Neurophysiol 97:69–72

Prout AJ, Eisen AA (1994) The cortical silent period and amyotrophic lateral sclerosis. Muscle Nerve 17:217–223

Schnitzler A, Benecke R (1994) The silent period after transcranial magnetic stimulation is of exclusive cortical origin: evidence from isolated cortical ischemic lesions in man. Neurosci Lett 180:41–45

Similowski T, Fleury B, Launois S, Cathala HP, Bouche P, Derenne JP (1989) Cervical magnetic stimulation: a new painless method for bilateral phrenic nerve stimulation in conscious humans. J Appl Physiol 67:1311–1318

Smith J, Butera R, Koshiya N, Del Negro C, Wilson C, Johnson S (2000) Respiratory rhythm generation in neonatal and adult mammals: the hybrid pacemaker-network model. Respir Physiol 122:131–147

Tegenthoff M, Vorgerd M, Juskowiak F, Roos V, Malin JP (1996) Postexcitatory inhibition after transcranial magnetic single and double brain stimulation in Huntington's disease. Electroencephalogr Clin Neurophysiol 101:298–303

Triggs WJ, Menkes D, Onorato J, Yan RS, Young MS, Newell K, Sander HW, Soto O, Chiappa KH, Cros D (1999) Transcranial magnetic stimulation identifies upper motor neuron involvement in motor neuron disease. Neurology 53:605–611

Uozumi T, Ito Y, Tsuji S, Murai Y (1992) Inhibitory period following motor potentials evoked by magnetic cortical stimulation. Electroencephalogr Clin Neurophysiol 85:273–279

Werhahn KJ, Classen J, Benecke R (1995) The silent period induced by transcranial magnetic stimulation in muscles supplied by cranial nerves: normal data and changes in patients. J Neurol Neurosurg Psychiatry 59:586–596

Wilson SA, Thickbroom GW, Mastaglia FL (1993) Topography of excitatory and inhibitory muscle responses evoked by transcranial magnetic stimulation in the human motor cortex. Neurosci Lett 154:52–56

Ziemann U, Netz J, Szelenyi A, Homberg V (1993) Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex. Neurosci Lett 156:167–171

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996) The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 109:127–135

Zifko U, Remtulla H, Power K, Harker L, Bolton CF (1996) Transcortical and cervical magnetic stimulation with recording of the diaphragm. Muscle Nerve 19:614–620