Electroencephalography and clinical Neurophysiology, 81 (1991) 257–262

ADONIS 0924980X91000828

ELMOCO 90078

Spinal motor neuron excitability during the silent period after cortical stimulation

Peter Fuhr *, Rocco Agostino and Mark Hallett

Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892 (U.S.A.)

(Accepted for publication: 23 November 1990)

Summary During tonic voluntary muscle contraction, a period of electromyographic silence follows the motor evoked potential produced by transcranial stimulation of the contralateral motor cortex. We studied the silent period in the wrist flexors of 3 normal volunteers and a deafferented patient during 20% of maximal contraction. To test the excitability of the spinal motor neuron pool during the period of silence, the H-reflex was evoked in the normal subjects at different intervals after cortical stimulation. The amplitude of the H-reflex in the silent period was expressed as a percentage of the amplitude during complete muscle relaxation. The H-reflex was profoundly depressed at the beginning of the silent period (13.5–27% of the control measurement), but showed a clear tendency to recover toward the end of the silent period despite continued absence of muscle activation (71–84% of the control). Moreover, the silent period in the deafferented patient was of longer duration than can be accounted for by segmental mechanisms. These findings imply, at least in the late part of the silent period, that a reduction in the excitability of the spinal motor neuron pool plays only a minor role in determining the phenomenon and that it is probably caused by lack of cortical drive.

Key words: Silent period; Magnetic stimulation; Cortical stimulation; H-reflex; Inhibition; Sensory neuropathy

Recent reports have shown that cortical stimulation during voluntary muscle activity evokes a pause in electromyographic (EMG) activity following the motor evoked potential (MEP; Calancie et al. 1987; Lüders et al. 1987). With low amplitude stimuli, there might even be a pause without an evident MEP (Calancie et al. 1987). Although the mechanism of activation of the motoneuron pool after both electrical and magnetic cortical stimulation has been studied extensively (Patton and Amassian 1954; Kernell and Wu 1967; Day et al. 1987a,b, 1989a; Hess et al. 1987; Amassian et al. 1989; Cohen et al. 1990; Fuhr et al. 1991), the cause of the silent period after cortical stimulation is unknown. One possible mechanism is the inexcitability of the spinal motor neuron pool. Since the amplitude of the H-reflex gives a quantitative measure of the excitability of the spinal motor neurons (Schieppati 1987), we measured the H-reflex amplitude during the silent period after magnetic stimulation of the contralateral motor cortex.

* Supported by the Swiss National Science Foundation.

Correspondence to: Dr. Mark Hallett, Building 10, Room 5N226, NINDS, NIH, Bethesda, MD 20892 (U.S.A.).

Subjects and methods

We studied 3 normal volunteers (2 men and 1 woman), aged 35, 48 and 51 years, and a 67-year-old man with extreme sensory neuropathy. His neuropathy started to develop when he was age 40 and gradually progressed from the lower extremities to involve all extremities, as well as the trunk and face. In 1970, he had a diagnosis of chronic sensory neuropathy with Immunoglobulin M gammopathy. This same patient was described earlier as showing an absence of enhanced physiological tremor related to fatigue and a heavy dependence on visual input in postural and fine motor control (Sanes 1985; Sanes et al. 1985). At the time of this study, he had absent reflexes, absent sensory potentials, slow motor nerve conduction velocities, profound loss of position sense in all extremities, and no sensation of light touch or vibration. Some sensation of pressure was preserved, and the sensation of heat was intact. He had decreased general coordination and mild distal atrophy and was confined to a wheelchair. His general health was good. He had some difficulty in producing maximal force in the wrist flexors because of pain caused by a frozen shoulder syndrome. All subjects gave written informed consent for the study, which was approved by the institute's clinical research review committee.

The subject's right forearm was strapped to a metal plate on which was mounted a frame carrying a force transducer (Myometer, Penny and Giles Transducers, Christchurch, U.K.). The force produced was displayed digitally to both the subject and the experimenter. The subject activated the wrist flexor with 20% of the maximal force and held this level of force steady until told to relax.

The left motor cortex was stimulated with a Cadwell MES-10 magnetic stimulator using 80% of its maximal output. A butterfly-shaped coil was used to obtain a focal stimulus (Cohen et al. 1990). With the subject at rest, the scalp position from which a MEP of maximal amplitude could be elicited was determined by moving the center of the coil centimeter by centimeter along a coronal line through the vertex until the best position was identified. From there, it was moved on a parasagittal line anteriorly and posteriorly in search of a position from which a MEP of still larger amplitude could be generated. This scalp position was chosen for evoking the silent period.

EMG recording was done with surface electrodes from the right flexor carpi radialis (FCR) muscle. A DISA 15C01 amplifier was used, with low filters set at 100 Hz and high filters at 2 kHz. The recordings were printed and analyzed off-line. Muscle relaxation was controlled by auditory monitoring of EMG activity.

The H-reflex was elicited by delivering a 1 msec stimulus from a constant-current stimulator (DISA 15E25) to the median nerve at the elbow. The stimulus intensity chosen produced a maximal H-reflex without an M response. This was 3% to 38% of the maximal M. The amplitude of the H-reflex was measured peak to peak, and the average of 10 measurements obtained during the silent period was compared with the average amplitude of 10 control H-reflexes obtained at each delay between the cortical and the median nerve stimulation. The interval between median nerve stimulations was 10 sec.

H-reflexes of the FCR were evoked alternately during muscle relaxation (control condition) and at different delays (40, 60, 80, 100, 120, 140, 160 and 180 msec) after magnetic stimulation of the contralateral motor cortex so that they would appear at different times during the silent period.

In each subject, ANOVA for repeated measures, applying Scheffé's test, was used to compare the amplitudes of the H-reflex during muscle relaxation and after cortical stimulation. A significance level of $P \leq 0.01$ was applied.

Results

The duration of the silent period was estimated by measuring the time from the beginning of the MEP to the recovery of voluntary activity, because the MEP gradually decays after its last peak, making the exact determination of its end impossible. This period lasted between 110 and 115 msec.

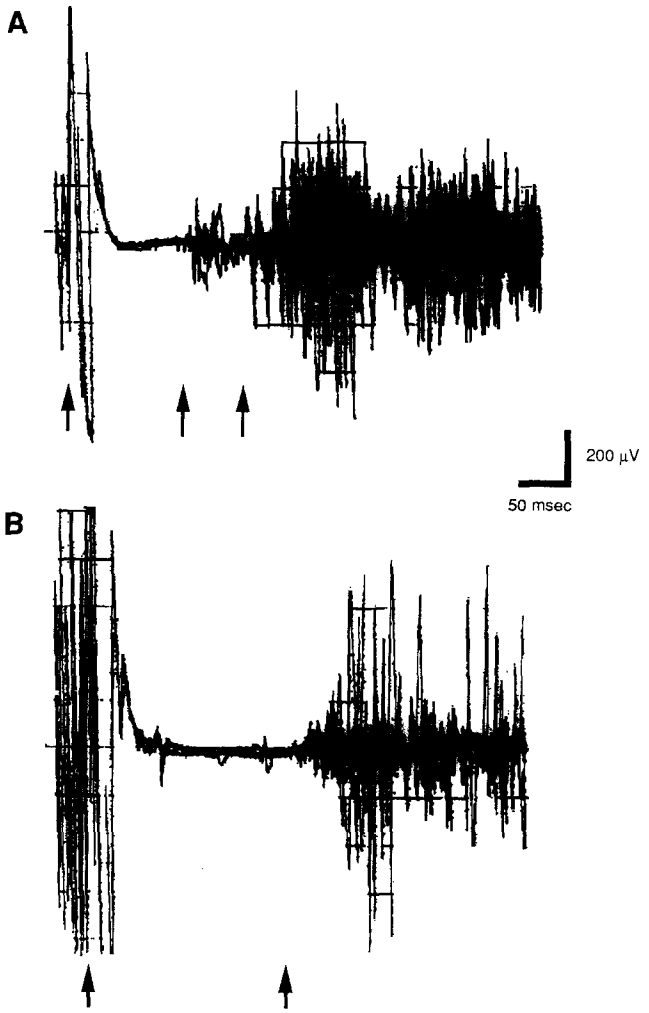

Fig. 1. Silent period in the FCR muscle after magnetic stimulation of the contralateral motor cortex. A: 4 superimposed recordings from a normal subject. Stimulation was given at the beginning of the trace. The first arrow indicates the onset of the MEP; the second arrow, the end of the complete silent period; the third arrow, the end of the partial silent period. B: 4 superimposed recordings from a 67-year-old man with severe sensory neuropathy. The arrows indicate onset of the MEP and the end of the silent period.

The period of complete EMG silence was followed by partial recovery lasting another 50–80 msec. The beginning of steadily increasing EMG activity thereafter was taken as the end of the partial silent period. It occurred 160–190 msec after the onset of the MEP. Maximal EMG activity during the partial silent period in the three normal subjects was about 25%, 50% and 60% of the EMG activity before cortical stimulation (Fig. 1A).

The latency of the MEP was 15 msec in all 3 normal subjects, and the latency of the H-reflex was 17–22 msec.

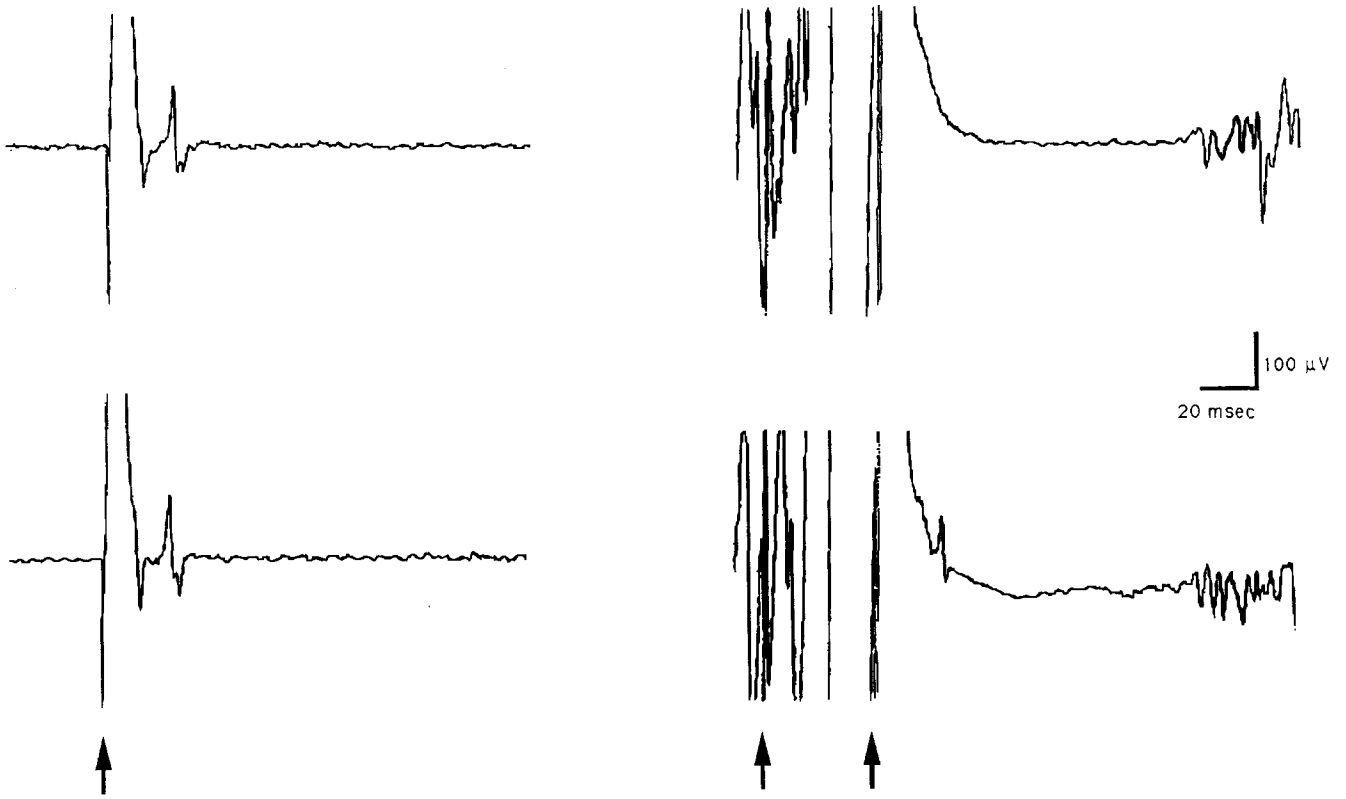

Fig. 2. Inhibition of the H-reflex during the silent period. Left: H-reflexes during muscle relaxation. The arrow indicates the time of median nerve stimulation. Right: H-reflexes after magnetic stimulation of the contralateral motor cortex. The first arrow indicates cortical stimulation, the second, median nerve stimulation. The delay between them was 40 msec. The upper traces show complete suppression of the H-reflex; the lower traces, a reduction of H-reflex amplitude to 64%.

The amplitudes of the H-reflexes were profoundly depressed at the beginning of the complete silent period (values obtained < 50 msec after the onset of the MEP were 13.5–27% of the amplitudes during muscle relaxation; $P \leq 0.01$; Fig. 2). Their mean value remained under 50% of the control value for at least 63, 87 and 62 msec for subjects 1, 2 and 3, respectively. The H-reflex recovered toward the end of the complete silent period, when its amplitudes reached 71–84% of the value during muscle relaxation, and no significant difference between the two conditions could be detected ($P > 0.2$).

At the beginning of the partial silent period, the H-reflex amplitudes were not significantly different from the control values or from the last value obtained during the complete silent period ($P > 0.2$). Thereafter, they behaved differently in the 3 normal subjects: in 2 subjects they were more or less in the range of the control values, while in the third subject they showed facilitation (Fig. 3).

A silent period occurred after cortical magnetic stimulation in the deafferented patient. Due to the slow peripheral motor conduction, the MEP had an onset latency of 30 msec; it was followed by an almost complete silent period that lasted until 170–215 msec after onset of the MEP, when EMG activity gradually returned (Fig. 1B).

Discussion

Several mechanisms can conceivably account for the silent period that occurs after cortical stimulation. On the suprasegmental level, it could be generated by a pause in the emission of excitatory waves by the motor cortex due to elicitation of a 'negative' response (Lüders et al. 1987), refractoriness, or interruption of the voluntary activation (Day et al. 1989b). On the segmental level, the highly synchronized discharge of the spinal motor neuron pool (Day et al. 1987a) is likely to activate the Renshaw cells. Another mechanism of segmental inexcitability would be the activation of inhibitory Ia interneurons, which probably receive input from the motor cortex (Cowan et al. 1986). It also is likely that the additional muscle shortening produced by the magnetic stimulation generates a pause in the Ia afferent activity and elicits a Ib afferent volley from the Golgi tendon organs, which in turn inhibit the alpha motoneurons; these mechanisms are known to play a role in generating the silent period after peripheral

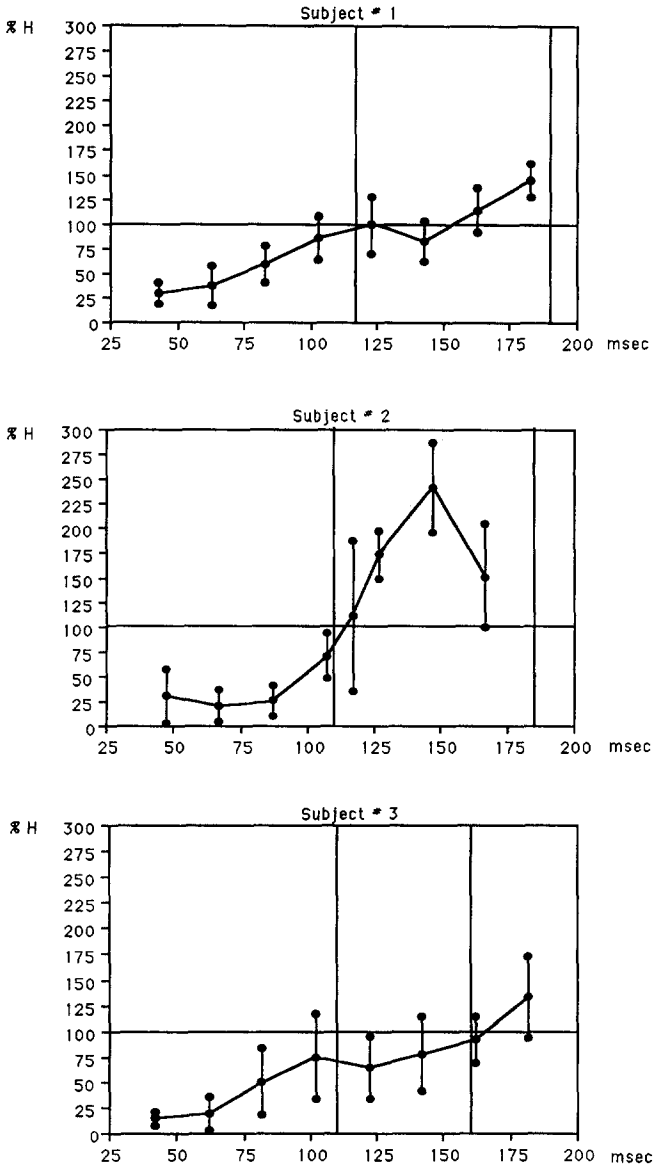

Fig. 3. Relative amplitude of the H-reflex (mean ± S.D.) during the complete and partial silent period. 100% corresponds to the amplitude of the H-reflex during muscle relaxation. The delay between the onset of the MEP and the H-reflex is given on the horizontal axis. From left to right, the first vertical line indicates the end of the complete silent period; the second vertical line, the end of the partial silent period.

nerve stimulation (Shahani and Young 1973). However, their effects are less clear in the silent period after cortical stimulation than in the silent period after peripheral nerve stimulation, because stimulation of the motor cortex activates many muscles simultaneously, among them antagonists that influence each other reciprocally. Refractoriness of the alpha motoneurons is unlikely to play a role, since in human soleus motoneurons it lasts only about 4–8 msec (Pierrot-Deseilligny et al. 1976).

We addressed the possibility of segmental inexcitability by measuring the amplitude of the H-reflex during the silent period after cortical stimulation. The tested H-reflexes were of considerably lower amplitude than the maximal M response in all 3 normal subjects. According to the size principle of recruitment of motor units (Henneman et al. 1965; Henneman and Mendell 1981), the H-reflex elicits small motor units, as does a weak voluntary contraction. This assumption also has recently been proved true in humans (Cros et al. 1989). The H-reflex is, therefore, a test of the same part of the motor neuron pool that falls silent after cortical stimulation during a weak tonic contraction.

The results of the present study show a deep depression of the excitability of the alpha motoneurons at the beginning of the complete silent period. However, an impressive recovery of the motoneuronal excitability was observed toward its end despite continued absence of muscle activation. Therefore, suprasegmental mechanisms seem to become more important with the elapse of time from the appearance of the MEP.

At the beginning of the partial silent period, the H-reflex was similar to the last value in the complete silent period and to the baseline value for all 3 normal subjects. It is conceivable that the return of EMG activity in the partial silent period is caused mainly by segmental mechanisms like enhanced Ia or decreased Ib input due to stretching of the muscle (Calancie et al. 1987). However, if this were true, the H-reflex would be expected to be facilitated as compared with either the control value or the last value in the complete silent period. Since this is not the case, the return of EMG activity seems to be due to a breakthrough of the suprasegmental input. It also suggests that the suprasegmental drive would be sufficiently powerful to evoke EMG activity, if it were present during the late part of the complete silent period.

A silent period occurred after magnetic stimulation of the brain in the deafferented patient. Since the MEP does not generate peripheral inhibitory input to the alpha motoneurons (Ia pause and Ib afferent volley from the wrist flexors and reciprocal inhibitory input from the wrist extensors), the only mechanisms remaining active are located in the central nervous system. Segmental inhibitory mechanisms, driven by the Renshaw cells and Ia interneurons, are likely to play a role in the early part of the silent period. This is supported by the finding that stimulation of a mixed nerve in deafferented muscles also generates a silent period that lasts longer than can be accounted for by the collision of impulses in the motor axons (Shahani and Young 1973). However, while the silent period lasts only 50 msec after peripheral stimulation in this condition, its duration is clearly longer after cortical stimulation. This further supports the hypothesis that the mechanism responsible for the later part of the silent period must be located on a suprasegmental level.

We conclude that while segmental inhibitory mecha-

nisms may play a role in the origin of the first part of the complete silent period, they do not determine the later part. Rather, the later part is caused by a suprasegmental mechanism, probably by interruption of the voluntary drive at the cortical level. This is supported by recent evidence from an experiment (Day et al. 1989b) with double cortical stimulation: a magnetic stimulus followed 50 msec later by an electrical stimulus. The electical stimulus, which acts in part by direct activation of descending corticomotoneuronal axons, was able to produce an MEP. This finding demonstrates that the spinal motoneurons and the corticospinal axons are no longer refractory after a delay of 50 msec.

The silent period after cortical stimulation described in the present study is quite different from the silent period after peripheral nerve stimulation. It is a newly discovered inhibitory phenomenon generated at least in part by a mechanism located on a suprasegmental level, probably within the cortex. The interest in inhibitory mechanisms of the central nervous system is generated by recent reports on their role in motor control (Day et al. 1983, 1984, 1989b; Tanaka 1983) and on their failure in patients with movement disorders (Tanaka 1983; Hughes and McLellan 1985; Dick et al. 1987; Cohen and Hallett 1988; Delwaide and Olivier 1988; Nakashima et al. 1989; Panizza et al. 1989, 1990; Fuhr and Hallett 1990). Investigation of this phenomenon in patients with movement disorders might provide new insights into their pathophysiology.

The authors thank Ms. B.J. Hessie for editorial assistance and Ms. N. Dang for technical help.

References

Amassian, V.E., Cracco, R.Q. and Maccabee, P.J. Focal stimulation of human cerebral cortex with magnetic coil: a comparison with electrical stimulation. Electroenceph. clin. Neurophysiol., 1989, 74: 401–416.

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

Cohen, L.G. and Hallett, M. Hand cramps: clinical features and electromyographic patterns in focal dystonia. Neurology, 1988, 38: 1005–1012.

Cohen, L.G., Roth, B.J., Nilsson, J., Dang, N., Panizza, M., Bandinelli, S., Friauf, W. and Hallett, M. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. Electroenceph. clin. Neurophysiol., 1990, 75: 350–357.

Cowan, J.M.A., Day, B.L., Marsden, C. and Rothwell, J.C. The effect of percutaneous motor cortex stimulation on H-reflexes in muscles of the arm and leg in intact man. J. Physiol. (Lond.), 1986, 377: 333–347.

Cros, D., Day, B. and Shahani, B.T. Single motor unit analysis of the H-reflex. Neurology, 1989, 39: 415 (abstract).

Day, B.L., Rothwell, J.C. and Marsden, C.D. Transmission in the spinal reciprocal Ia inhibitory pathway preceding willed movements of the human wrist. Neurosci. Lett., 1983, 37: 245–250.

Day, B.L., Marsden, C.D., Obeso, J.A. and Rothwell, J.C. Reciprocal inhibition between the muscles of the human forearm. J. Physiol. (Lond.), 1984, 349: 519–534.

Day, B.L., Rothwell, J.C., Thompson, P.D., Dick, J.P.R., Cowan, J.M.A., Berardelli, A. and Marsden, C.D. Motor cortex stimulation in intact man. 2. Multiple descending volleys. Brain, 1987a, 110: 1191–1209.

Day, B.L., Thompson, P.D., Dick, J.P., Nakashima, K. and Marsden, C.D. Different sites of action of electric and magnetic stimulation of the human brain. Neurosci. Lett., 1987b, 75: 101–106.

Day, B.L., Dressler, D., Maertens de Noordhout, A., Marsden, C.D., Nakashima, K., Rothwell, J.C. and Thompson, P.D. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J. Physiol. (Lond.), 1989a, 412: 449–473.

Day, B.J., Rothwell, J.C., Thompson, P.D., Maertens de Noordhout, A., Nakashima, K., Shannon, K. and Marsden, C.D. Delay in the execution of voluntary movement by electrical or magnetic brain stimulation in intact man. Brain, 1989b, 112: 649–663.

Delwaide, P.J. and Olivier, E. Motor cortex excitability modulations in parkinsonian patients. An explanation for rigidity? Paper presented at the Congress of the International Medical Society of Movement Disorders (ISMD), Rome, Italy, June 2–4, 1988.

Dick, J.P.R., Rothwell, J.C., Day, B.L., Wise, R.S.J., Benecke, R. and Marsden, C.D. Modulation of the long-latency reflex to stretch by the supplementary motor area in humans. Neurosci. Lett., 1987, 75: 349–354.

Fuhr, P. and Hallett, M. Cutaneous reflexes in hand muscles in Parkinson's disease. Muscle Nerve, 1990, 13: 876 (abstract).

Fuhr, P., Cohen, L.G., Roth, B.and Hallett, M. Latency of motor evoked potentials to focal transcranial stimulation varies as a function of scalp positions stimulated. Electroenceph. clin. Neurophysiol., 1991, 81: 81–89.

Henneman, E. and Mendell, L.E. Functional organization of motoneuron pool and its input. In: Handbook of Physiology, Vol. II. Part 1. American Physiological Society, Bethesda, MD, 1981: 448–452.

Henneman, E., Somjen, G. and Carpenter, D.O. Excitability and inhibitability of motoneurones of different sizes. J. Neurophysiol., 1965, 28: 599–620.

Hess, C.W., Mills, K.R. and Murray, N.M.F. Responses in small hand muscles from magnetic stimulation of the human brain. J. Physiol. (Lond.), 1987, 388: 397–419.

Hughes, M. and McLellan, D.L. Increased co-activation of the upper limb muscles in writer's cramp. J. Neurol. Neurosurg. Psychiat., 1985, 48: 782–787.

Kernell, D. and Wu, C.-P. Responses of the pyramidal tract to stimulation of the baboon's motor cortex. J. Physiol. (Lond.), 1967, 191: 653–672.

Lüders, H.J., Lesser, R.P., Dinner, D.S., Morris, H.H., Hahn, J.F., Friedman, L., Skipper, G., Wyllie, E. and Friedman, D. Commentary: chronic intracranial recording and stimulation with subdural electrodes. In: J. Engel, Jr. (Ed.), Surgical Treatment of the Epilepsies. Raven Press, New York, 1987.

Nakashima, K., Rothwell, J.C., Day, B.L., Thompson, P.D., Shannon, K. and Marsden, C.D. Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. Brain, 1989, 112: 681–697.

Panizza, M.E., Hallett, M. and Nilsson, J. Reciprocal inhibition in patients with hand cramps. Neurology, 1989, 39: 85–89.

Panizza, M., Lelli, S., Nilsson, J. and Hallett, M. H-reflex recovery curve and reciprocal inhibition of H-reflex in different kinds of dystonia. Neurology, 1990, 40: 824–828.

Patton, H.D. and Amassian, V.E. Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. J. Neurophysiol., 1954, 17: 345–363.

Pierrot-Deseilligny, E., Bussel, B., Held, J.P. and Katz, R. Excitability of human motoneurones after discharge in a conditioning reflex. Electroenceph. clin. Neurophysiol., 1976, 40: 279–287.

Sanes, J.N. Absence of enhanced physiological tremor in patients without muscle or cutaneous afferents. J. Neurol. Neurosurg. Psychiat., 1985, 48: 645–649.

Sanes, J.N., Mauritz, K.-H., Dalakas, M.C. and Evarts, E.V. Motor control in humans with large-fiber sensory neuropathy. Hum. Neurobiol., 1985, 4: 101–114.

Schieppati, M. The Hoffman reflex: a means of assessing spinal reflex excitability and its descending control in man. Progr. Neurobiol., 1987, 28: 345–376.

Shahani, B.T. and Young, R.R. Studies of the normal human silent period. In: J. Desmedt (Ed.), New Developments in Electromyography and Clinical Neurophysiology. Karger, Basel, 1973.

Tanaka, R. Reciprocal Ia inhibitory pathway in normal man and in patients with motor disorders. In: J.E. Desmedt (Ed.), Motor Control Mechanisms in Health and Disease. Raven Press, New York, 1983.