ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 1998, 58: 69-77

Cortical excitability threshold for distal limb muscles in transcranial magnetic stimulation. Method - normative values

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Technical communication

Abstract. Transcranial magnetic stimulation was carried out in 30 healthy subjects , aged 20 to 55 and 156 to 180 cm tall, in whom cortical excitability threshold was determined for musculus (m.) abductor digiti minimi (ADM) and m. extensor digitorum brevis (EDB). The lowest stimulus intensity causing in the muscle a reproducible potential of an amplitude of 0.1 mV was adopted as the threshold value. The intensity of the stimulus was noted as a percentage of maximum stimulator output, defined as 100% (Magstim 200). In the stimulation of cortical areas for ADM, a circular coil (2.0T-530 V/m) was used while the in case of EBD, a double-cone coil (1.4T - 660 V/m) was used. The threshold was noted while the muscle was relaxed and during weak voluntary contraction. The application of the double-cone coil allowed us to obtain for foot muscles similar threshold values as for hand muscles with a circular coil. It was confirmed that the threshold declines with voluntary contraction of the muscles under investigation. Normative values were prepared , with the norm, limits of the norm, outlier values and pathological markers being distinguished.

Key words: transcranial magnetic stimulation, cortical threshold, distal muscles, normative values

INTRODUCTION

The cortical threshold in transcranial magnetic stimulation is a measure of excitation of the corticomotoneuron (Eisen 1992b). The determination of the cortical threshold is usually used in routine clinical practice to establish the value of maximal stimulus intensity for motor potentials evoked by magnetic stimulation in different muscles (Eisen 1992a, Furby et al. 1992). However, recent evidence has shown that cortical excitability threshold can become a parameter in itself, allowing evaluation of the function of the pyramidal system (Hufnagel et al. 1990, Caramia et al. 1991, Hömberg et al. 1991, Eisen 1992b, Meyer et al. 1992, Mavroudakis et al. 1994, Di Lazzaro et al. 1995, Perreti et al. 1996).The cortical threshold has been investigated in many patients with central nervous system disease. It has generally been assumed that an increased threshold reflects pyramidal tract involvement. An increased threshold was found in a high percentage of patients with clinical and subclinical motor pathway dysfunction. (Caramia et al. 1991, Meyer et al. 1992, Perretti et al. 1996). Eisen (1992b) revealed that cortical threshold in amyotrophic lateral sclerosis (motor neuron disease) is a function of excitable corticomotoneurons. He postulated that measuring the cortical threshold might be a way of monitoring progress of the disease and response to therapy. Hufnagel et al. (1990) and Mavroudakis et al. (1994) have shown reversible effects of antiepileptic medication on magnetic motor-evoked potentials, including elevation of the cortical threshold during treatment.

The normative values of thresholds are based mainly on data from stimulation of the cortex with flat coils (Caramia et al. 1991, Macdonell et al. 1991, Eisen 1992, Furby et al. 1992). These are most effective in the stimulation of the motor cortical areas for hand muscles located at the convex of the hemispheres. Stimulation with a flat coil fails to stimulate lower limb muscles in approximately 20% of healthy subjects (Caramia et al. 1991), which largely undermines the usefulness of the normative values for these muscles. The use of the double-cone coil, specially adjusted to stimulate cortical areas controlling lower limb muscles situated inside the interhemispheric fissure, significantly improves the stimulation conditions (Jalinous 1992).

It therefore seemed advisable to prepare normative values of cortical excitability thresholds with the use of a double cone coil for lower limb muscles and a circular coil for upper limb muscles and then to compare them.

METHODS

Thirty healthy, paid volunteers (24 women and 6 men), aged 20 to 55, 156 to 180 cm tall, were examined. The subjects were matched according to age at 5-year age intervals. None of the subjects had a history of neurological diseases and all gave written consent to the investigations. The study was approved by the local Ethics Commission.

A Magstim 200 stimulator (Magstim Ltd. Co.) was used for magnetic stimulation of the cortex. Motor evoked potentials were observed on the monitor of an electromyograph (Mystro by MS 25 by Medelec Ltd. Co.) applying a sensitivity of 200 uV/div, sweep speed of 5 ms/div for ADM and 10 ms/div for EBD as well as a system of filters of 100 Hz-10 Khz. Surface electrodes (Ag - AgCl) were applied to record the potentials evoked in muscles . M. abductor digiti minimi (ADM) and m.extensor digitorum brevis (EBD) were examined bilat-

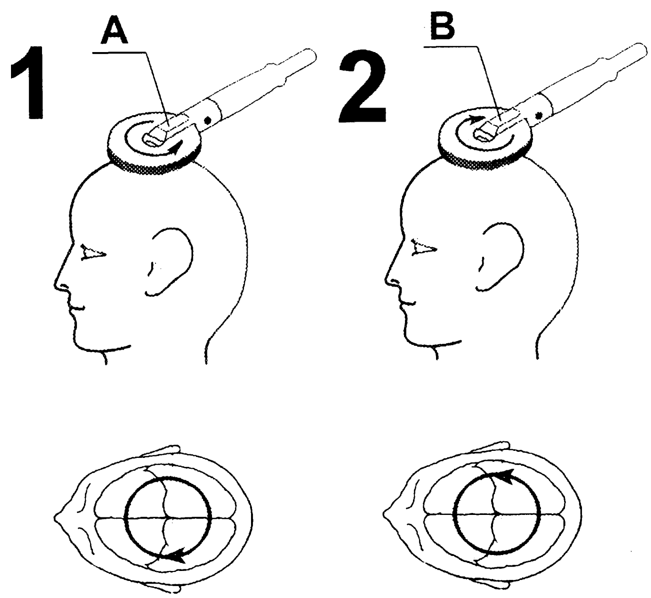

Fig. 1. Diagram of the orientation of a circular flat coil (2.0T-530V/m) during transcranial magnetic stimulation over the hand areas. The coil centered over the vertex (Cz). Position 1 - Side A of the coil visible, counterclockwise current flow in the coil produces a clockwise current flow in the brain. The induced current predominantly stimulates motor cortex of the left hemisphere because the direction of the induced current, from posterior to anterior, appears to be most effective. Position 2 - Side B of the coil visible, clockwise current flow in the coil, counterclockwise direction of the induced current in tissue. The motor cortex of the right hemisphere is predominantly stimulated.

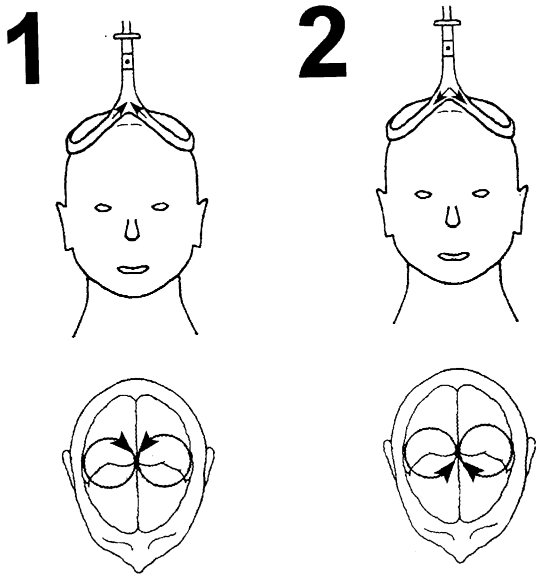

Fig. 2. Diagram of the orientation of a double - cone coil (1.4T-660V/m) during transcranial magnetic stimulation over the foot muscle areas. The coil is centered over the vertex (Cz) with a common longitudinal part of the coil along the interhemispheric fissure. Position 1 - The forehead to the occiput current flow in the central longitudinal part of the coil produces the occiput to the forehead flow in the brain, significantly high in the interhemispheric fissure. Position 2 - The occiput to the forehead current flow in the central longitudinal part of the coil, reverse direction of the induced current in tissue. The double - cone coil is especially useful to stimulate cortical areas for lower limb muscles situated on the medial surface of hemispheres - inside the interhemispheric fissure. The current stimulates both hemispheres with the same effect. Hence, one direction of the stimulation may be chosen.

erally. An active electrode was positioned on the belly of the muscle while a reference electrode was positioned in a distant place (base of the fifth finger). Cortical areas for the hand were stimulated with a high power circular coil, with an external diameter of 90 mm (2.0 T - 530 V/m), the centre of which was applied to the cranium at the vertex (Cz). Side A of the coil (A visible) and side B of the coil (B visible) were used for stimulation. Upon stimulation with side A the current in the coil flowed in a counterclockwise direction, while upon stimulation with side B in a clockwise direction. The direction of the current induced in tissues is always reverse (Fig. 1). For stimulation of cortical areas for the foot muscles, a double-cone coil (1.4 T - 660 V/m) was used. Its central part was applied to the cranium at the vertex and the common longitudinal part along the saggital line. Stimulation was performed twice, once in the direction of the current passing in the central longitudinal part of the coil from the occiput to the forehead, and the second time from the forehead to the occiput (reverse direction of the induced current; Fig. 2). The lowest stimulus intensity which evoked in the muscle a reproducible potential of an amplitude of 0.1 m V was adopted as the value of the threshold. The intensity of the stimulus was given as a percentage of maximum stimulator output which was defined as 100 %. Stimulation was initiated at 30% output, and the intensity of the stimulus was increased by 5% intervals until a proper, reproducible response was obtained (Fig. 3). This procedure was repeated during slight voluntary contraction of the muscles under investigation. The amplitude of the emg was maintained at a level of approximately 20-50 μV (Fig. 4).

Statgraphics v. 5 program (Statistical Graphics Corporation) was used for statistical evaluation. Mean values ± standard deviations were calculated, the significance of differences between groups of measurements was estimated (Student *t*-test, Mann-Whitney U Test), and correlations with height and age were examined. Standard ranges as well as standard limits were defined by separating outlier values, sporadically encountered in the material studied. In the estimation of separated normative ranges the principle of 95% confidence interval was applied. Sometimes, however,the distribution of values was abnormal and then the ranges were determined arbitrarily. The normal values contained 70% (42 out of 60) measurements closest to the mean. The remaining 15% (9 out of 60) lowest and 15% highest measurements was defined as normal limit. If the extremely low or high values, clearly distinct from the other measurements, were found in the material there were excluded from the normal limit as outliers. A number of outliers could not exceed 5% (1-3 out of 60) measurements. Therefore, the entire normal limits contained at least 95% of measurements (or 100% when there were no outliers). Analogous rules were used to define normal limits in those groups where a number of measurements was 30 (Johnson and Bhattacharyya 1987).

RESULTS

Mean values of the intensity of threshold stimuli obtained for the muscles studied are presented in Table I. The table shows that in the case of the hand muscles (ADM) , the lowest thresholds were obtained with the use of induced current stimulation of brain tissue with the current running from the back to the front of the cere-

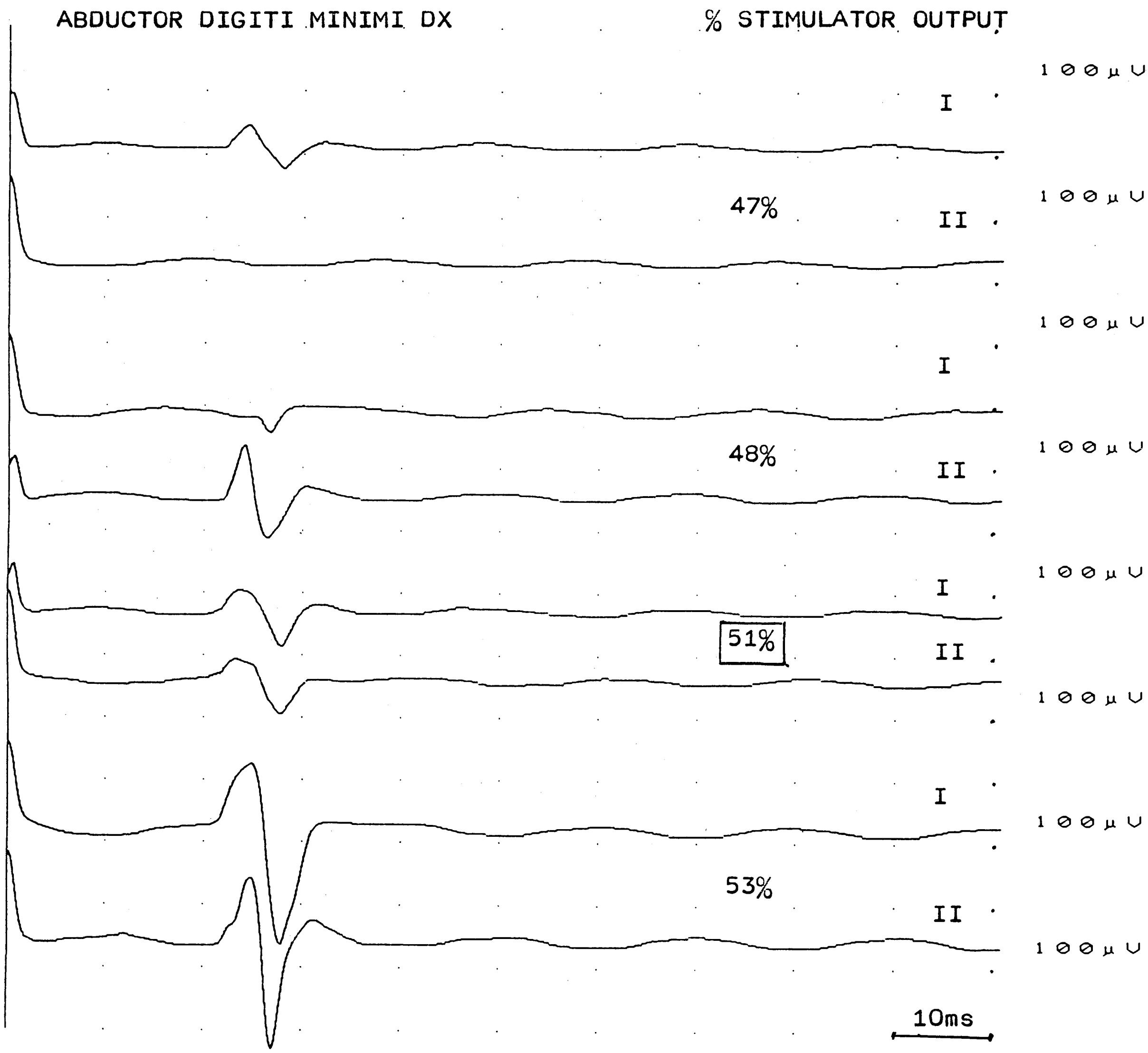

Fig. 3. An example of the determination of the cortical threshold value in relaxed muscle in a normal subject. Stimulus intensity of 51% of the maximum stimulator output evoked a proper, reproducible 100uV muscle potential (threshold value).

brum. For the right-hand muscles this was stimulation by side A of the circular coil while for the left-hand muscles by side B of the coil.(Fig. 1) This was found to be true for both relaxed muscles (at rest) and during their slight voluntary contraction (activation). The mean normal values obtained for the right hand muscles with side A of the coil visible and for the left hand muscles with side B of the coil visible did not differ significantly in statistical terms both at rest and upon activation. Activation significantly lowered the threshold for both muscles (Fig. 3 and Fig. 4). Due to the need to apply separate stimulation when determining thresholds for the right and left hand muscles, the proposed ranges of normative values for these muscles are presented separately (Table II).

For foot muscles (EDB), the effectiveness of the stimulating current with the use of the double-cone coil was the same for both directions of stimulation (insignificant differences - Table I). During activation , the stimulating current running from the front to the back of the cranium was more effective for the left hand muscles (t_{29} = 2.33, P<0.026). Upon stimulation with a reverse direction current , the thresholds for the left hand and right hand muscles did not differ significantly. The normative values were therefore prepared only for the thre-

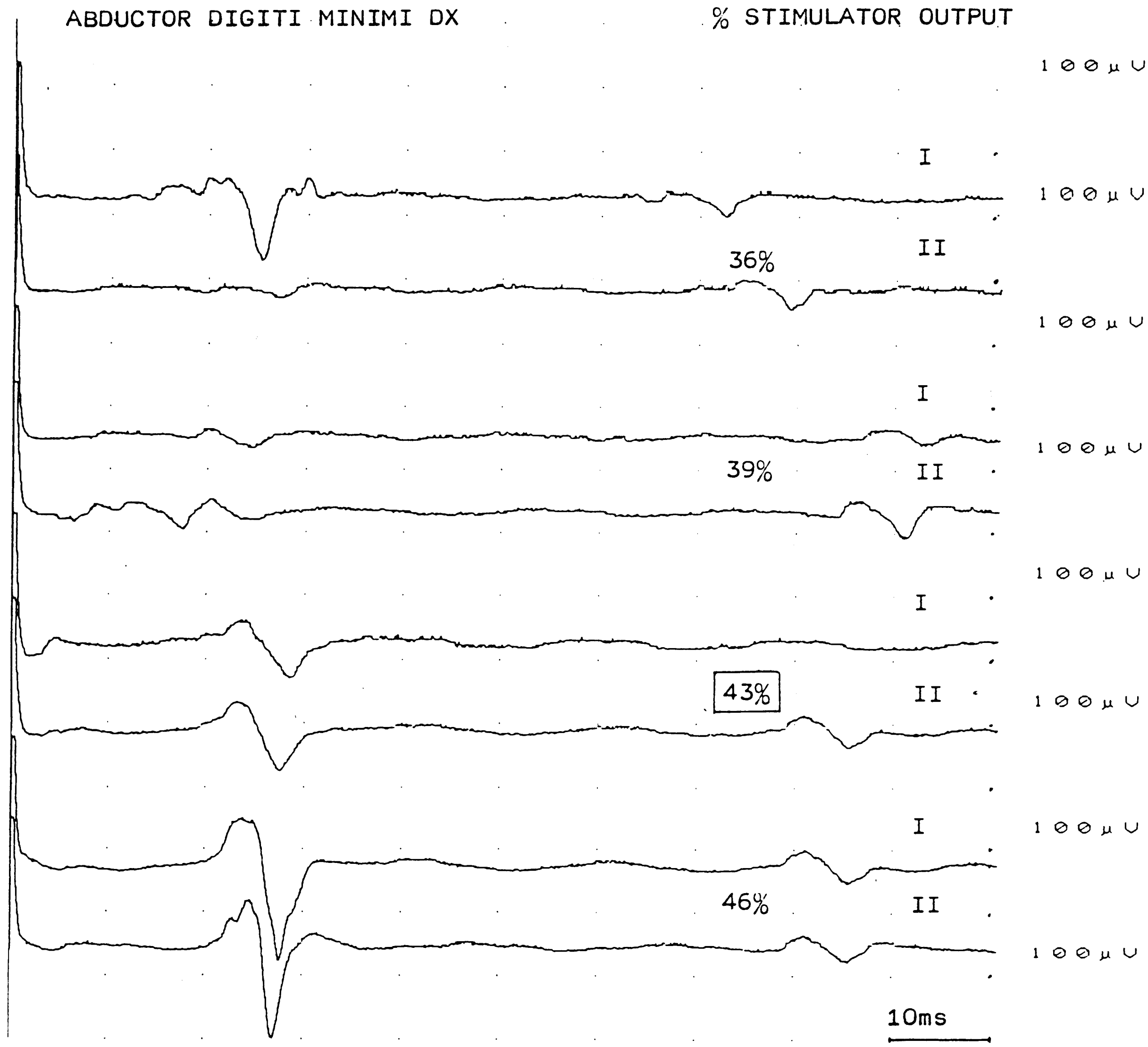

Fig. 4. The determination of the cortical threshold in the same subject and muscle as in Fig. 3 but the tested muscle was slighty contracted (see the sporadic low voltage emg activity). Notice that muscle contraction lowered the cortical threshold value. The proper, reproducible muscle response was obtained at this condition with only 43% of the maximum stimulator output.

sholds determined with this direction of stimulation (Position 1 in Fig. 2). Lack of statistically significant differences between the intensity of the threshold stimulus for the right and left hand muscles, at rest as well as during activation, allowed us to arrive at control values for EDB on the basis of 60 measurements. The data can be seen in Table I. As in the case of ADM, activation lowered EDB thresholds in a statistically significant way (t_{59} = 6.35, P<0.000). The range of normative values is given in Table II. Individual, absolute differences between the sides were also evaluated (Table III). Side differences are on average 1% lower for the foot muscles than for the hand muscles.

In the studied group of healthy subjects a number of outlier values did not exceed 3% of measurements (Tables II - III). The analysis of Tables II and III shows also that mean values of thresholds presented in Table I fail to characterize well the material evaluated. Values within the range of the so called lower norm prevail, hence the range of standards has to be wide.

There was no correlation between threshold values and height or age of the subjects studied.

TABLE I

Transcranial magnetic stimulation. Mean treshold for abductor digiti minimi - ADM and extensor digitorum brevis - EDB (% of maximal stimulator output). Comparison of results in right and left muscles and of effectiveness two directions of induced, stimulating current

Hand muscles, circular coil (2.0T, 530 v/m)

ADM		Clockwise direction (A visible)					Counterclokwise direction (B visible)			
		n	mean	SD	min-max		*n*	mean	SD	min-max
	Right	30	44.0	9.4	30.0-65.0	t_{29} = -8,63	30	58.0	13.9	38.0-85.0
Rest*		t_{29} = -7.52, $P<0.000$				$P<0.006$	t_{29} = 5.5, $P<0.000$			
	Left	30	55.0	10.6	30.0-73.0	t_{29} = -8,11	30	46.0	12.2	32.0-85.0
						$P<0.002$				
	Right	30	41.0	9.7	20.0-68.0	t_{29} = 5.6	30	53.0	13.6	30.0-85.0
Activation		t_{29} = -6.11, $P<0.000$				$P<0.002$	t_{29} = 7.58, $P<0.000$			
	Left	30	52.0	12.1	32.0-93.0	t_{29} = 9.27	30	40.0	11.5	27.0-85.0
						$P<0.0001$				

Foot muscles, double cone coil (1.4T, 660 v/m)

EDB		From nose to occiput direction					From occiput to nose direction			
		n	mean	SD	min-max		*n*	mean	SD	min-max
	Right	30	41.0	7.5	25.0-55.0	no	30	42.0	9.2	30.0-70.0
Rest			no					no		
	Left	30	39.0	9.8	25.0-65.0	no	30	43.0	10.3	28.0-70.0
	Right	30	40.0	8.4	25.0-65.0	no	30	38.0	8.4	25.0-60.0
Activation		t_{29} = 2.33, $P<0.026$						no		
	Left	30	36.0	7.5	25.0-53.0	no	30	39.0	9.7	22.0-65
					Rest*	Right + Left	60	42.4 ± 9.6		28.0-70.0
					Activation	Right + Left	60	38.6 ± 8.9		22.0-65.0

*Rest, activation threshold difference for right ADM t_{29} = 2.13, $P<0.04$, for left ADM t_{29} = 4.34, $P<0.000$, for EDB t_{59} = 6.35, $P<0.000$; no, nonsignificant.

DISCUSSION

Our study confirmed the known fact that in the case of hand muscles, both at rest and during activation, stimulation with induced current penetrating into the brain hemispheres from the posterior pole was most effective. For the right side muscles, stimulation with a circular coil with side A visible proved most effective, while for the left side stimulation with side B visible was most effective (Day et al. 1989, Macdonell et al. 1991, Furby et.al. 1992). However, assurance of proper direction of induced stimulation current (using circular coil) requires separate stimulation for right (A side visible) and for left hand muscles (B side visible).

The same effects were obtained in the case of foot muscles using the double-cone coil. Moreover, stimulating current flowing from the back of the cranium to its front was equally effective for the left and right muscles. Hence, in the case of foot muscles the double cone coil allows testing of the threshold for both side foot muscles simultaneously. The special shape of the double cone coil enables generation in the interhemispheric fissure an induced current of significant intensity (70 % higher than with a circular coil) which contributes to the particular

TABLE II

Transcranial magnetic stimulation. Ranges and distribution of the threshold values (% of maximal stimulator output) for abductor digiti minimi - ADM and extensor digitorum brevis - EDB

		Ranges of	Normal values	Normal limits	Outlier values	Pathology
Right ADM	Rest	upper	44-54 (7)	55-65 (5)	66-70 (-)	>70 (-)
(circular coil		lower	43-35 (15)	34-30 (3)	29-20 (-)	<20 (-)
A side visible)	Activation	upper	41-51 (10)	52-61 (3)	62-70 (1)	>70 (-)
n - 30		lower	40-32 (12)	31-22 (3)	21-12 (1)	<12 (-)
Left ADM	Rest	upper	46-58 (3)	59-70 (4)	71-85 (1)	>85 (-)
(circular coil		lower	45-35 (21)	32-21 (1)	20-15 (-)	<15 (-)
B side visible)	Activation	upper	40-49 (8)	50-65 (3)	66-85 (1)	>85 (-)
n - 30		lower	39-28 (17)	27-17 (1)	16-11 (-)	<11 (-)
Right + Left	Rest	upper	42-52 (20)	53-66 (6)	67-70 (2)	>70 (-)
EDB		lower	41-33 (25)	32-28 (7)	27-20 (-)	<20 (-)
(double cone coil*)	Activation	upper	39-49 (20)	50-60 (6)	61-65 (1)	>65 (-)
n - 60		lower	38-30 (25)	29-22 (8)	21-15 (-)	<15 (-)

*Direction of induced, stimulating current from occiput to nose; ( ), number of measurements.

usefulness of the double cone coil in the stimulation of more deeply situated cortical areas for lower limb muscles (Jalinous 1992).

This seems to explain why the threshold values for EDB obtained in this study are lower than was described upon stimulation with a circular coil. When the flat coil only was used, it was believed that the cortical sensitivity threshold is much lower for hand muscles than for foot muscles (Eisen 1992a, Furby et al. 1992). Values of thresholds for ADM designated with relaxed muscles are slightly lower though comparable to the data found by other authors (Hufnagel et al. 1990, Eisen 1992a, Furby et al. 1992, Mavroudakis et al. 1994, Perretti et al. 1996).

It is believed that transcranial magnetic stimulation with a typical position of the center of the coil in the region of the vertex and flow of the induced current from the back to the front stimulates cortical motoneurons transsynaptically. Stimulation used by some investigators, with a latero-medial direction flow of induced current like anodal electrical stimulation, activates corticospinal axons directly in the white matter and hence the shorter latencies of muscular response in this case (Day et al. 1989, Amassian et al. 1990, Mazzocchio et al. 1994, Werhahn 1994, Di Lazzaro et al. 1995). The muscle contraction lowers the excitability threshold of cortical motoneurons stimulated indirectly (transsynaptically) without affecting their excitability upon direct stimulation of their long axons (Di Lazzaro et al. 1995, Mazzocchio et al. 1994). This seems to indicate that the value of the threshold in the transcranial magnetic stimulation method with a typical position of the stimulating coil depends on the state of excitability of cortical motoneurons in the period preceding the appearance of the stimulus (Mazzocchio et al. 1994) and should well reflect any changes of cortical excitability. The cortical threshold determined at rest is of greater diagnostic significance than that determined during activation (Eisen 1992a) which causes individual differentiation of the conditions of cortex stimulation in an unmeasurable way. Examination during activation should thus be applied exclusively in the case of a lack of response in relaxed muscles which was not observed in any healthy subjects covered by this study. On the other hand, it should be borne in mind that the evaluation of the cortical excitability threshold as an evaluation of the functional state of the cortex at the time of the investigation is likely to be largely dependent also on the conditions of the examination. In our case we always performed stimulation in the same room, largely isolated from external stimuli. Prior to the beginning of the stimulation we explained the character of the

TABLE III

Transcranial magnetic stimulation. Side to side differences between right and left hemisphere stimulation for motor evoked potential thresholds in hand (ADM) and foot (EDB) muscles (absolute differences in percentage of maximal stimulator output)

	Mean ± SD	Min - Max	Ranges of	Normal values	Normal limits	Outlier values	Pathology
ADM							
Rest	8.0 ± 8.2	0.0-40.0	upper	8-16 (7)	17-25 (2)	26-40 (1)	>40 (-)
n - 30			lower	7-1 (16)	0 (4)	-	-
Activation	8.0 ± 6.8	0.0-37.0	upper	8-12 (6)	13-22 (3)	23-37 (1)	>37 (-)
			lower	7-3 (15)	2-0 (5)	-	-
EDB							
Rest	7.0 ± 6.1	0.0-25.0	upper	7-14 (7)	15-21 (3)	22-25 (1)	>25 (-)
n - 30			lower	6-1 (13)	0 (5)	-	-
Activation	7.0 ± 6.2	0.0-25.0	upper	7-14 (6)	15-20 (3)	21-25 (1)	>25 (-)
			lower	6-2 (17)	1-0 (3)	-	-

ADM, abductor digiti minimi; EDB, extensor digitorum brevis; ( ), number of measurements.

examination in order to make the persons undergoing the examination relax mentally. In spite of these efforts, the individual differentiation of threshold values was significant (large standard deviations). It is, however, expected that the developed standards will allow us to characterize groups of persons with a particular pathology. The ranges of normative values developed according to the principles given in the methods showed that in a group of healthy persons there were no threshold values which would correspond to pathology in any case. Outlier values were encountered sporadically, at a maximum of 3% of measurements in all the groups studied. It seems to correspond to the distribution according to the 95% confidence interval principles (Johnson and Bhattacharyya 1987). With such a distribution of normative data, it seems reasonable to consider outlier values as indicators of a mild pathology. Similar principles concern absolute differences between the intensity of the threshold stimulus for the left and right hemisphere. These differences were estimated based on the assumption that they will be of diagnostic significance upon the evaluation of one-sided pathology. These differences are on the average 1% lower for EDB than for ADM, probably due to the different geometry of the stimulating current in the double cone coil. The separation of outlier and pathological values as well as upper and lower ranges of standards should help in the evaluation of disturbances of cortical excitability threshold, especially since in some diseases the threshold can become either higher (Caramia et al. 1991, Hömberg et al. 1991, Meyer et al. 1992) or lower (Hufnagel et al. 1990, Hömberg et al. 1991).

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Received 5 May 1997, accepted 1 December 1997