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Effects of sex, height and age on motor evoked potentials with magnetic stimulation

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Abstract Magnetic stimulation of the brain and cervical and lumbar spinal roots was performed on 48 healthy subjects in order to investigate the effects of sex, height and age on motor evoked potentials (MEPs). The compound muscle action potentials were recorded from the abductor pollicis brevis and abductor hallucis muscles. The central motor conduction time (CMCT) was measured between the cerebral cortex and the cervical root and also between the cerebral cortex and the lumbar root. A multiple regression analysis was used to determine which of the physical variables, namely sex, height and age, were significant. A significant gender difference was observed in the MEP latencies and CMCT of the leg, but not in those of the hand. Both height and age had a significant effect on the leg MEP latencies with a lesser effect on the hand MEP latencies. The leg CMCT was also significantly influenced by height and age, while the hand CMCT was not. These results thus suggest that physical variables are very important in defining normal MEPs, especially in the lower limbs. Therefore, when we assess motor function in patients with neurological disorders, both the patients and control groups should be matched for sex, height and age distribution.

Key words Magnetic stimulation · Motor evoked potentials · Sex · Height · Aging

Introduction

Transcranial magnetic stimulation, a non-invasive method for stimulating the motor cortex in humans, was first introduced by Barker et al. [2]. Since then, it has been shown that the motor evoked potentials (MEPs) produced with magnetic stimulation are very useful in assessing motor function in normal subjects as well as in patients with neurological disorders [3, 10, 19]. The reliable identification of abnormal MEPs requires the statistical characterization of MEPs in an appropriate population of neurologically normal subjects. Based on previous studies, sex, height and age have all been clearly shown to influence the characteristics of MEPs [4, 8, 10, 11]. However, most studies have concentrated on the 20–50-year age range, and there has been no comprehensive description of the normative results of hand and leg MEPs over a wide range of ages in a substantial sample of male and female subjects. Therefore the purpose of the present study was to assess the factors that are likely to be important for defining normal MEPs. Special attention was paid to the statistics, because an increase in age is in parallel with a decrease in height [1] (see also Fig. 1).

Subjects and methods

The subjects consisted of 48 healthy adults ranging in age from 19 to 74 years. Their heights ranged from 144 to 180 cm. The mean age of 22 male subjects was 41.6, 15.6 years (mean, SD), and that of female subjects was 47.5, 18.4 years. The mean height of male subjects was 169.7, 5.0 cm, and that of female subjects was 155.6, 5.9 cm. All were in good health according to the findings of an interview and a personal history questionnaire. All subjects gave their informed consent for the study.

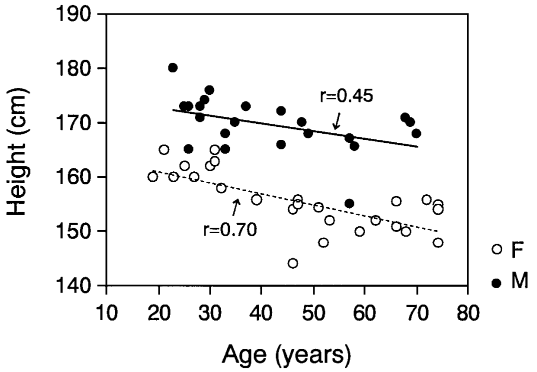

Fig. 1 Relationship between height and age. The *open circles* refer to female, while the *closed circles* indicate male subjects. The *dashed line* and the *solid line* represent the linear regression lines of female and male subjects, respectively. A significant inverse linear relationship was observed between the height and age for both sexes (female subjects: $P<0.0001$; male subjects: $P<0.05$)

Magnetic stimulation

All studies were performed using a Nihon Kohden SMN 1100 and a Magstim 200 unit. Two different types of magnetic coils were used: an eight-shaped coil (YM-111B, Nihon Kohden) in which the direction of the maximal induced current occurs beneath the central contiguous segment of the coil, and a double cone coil (Magstim Co. Ltd., type 9902) that can induce an eddy current in a deep part of the brain [24]. The eight-shaped coil consists of two wings with an inner diameter of 5 cm and an outer diameter of 9 cm. The double cone coil consists of two loops with a diameter of 11 cm, and the planes of the two loops are set at an angle of about 110° [24]. The stimulus intensity was set at 90% of the maximal output.

For recording hand MEPs, the subjects were seated in a chair. To stimulate the hand motor area, the centre of the eight-shaped coil was placed over a point 2 cm anterior to either C3 or C4 (using the international 10–20 system) in which the current flowed from back to front [5, 15], presumably perpendicular to the central sulcus. To magnetically stimulate the cervical root, the centre of the coil was placed posteriorly over the 7th cervical spinous process. The coil orientation was such that the maximal induced current flowed horizontally in the tissue towards the midline from the ipsilateral side of the target muscle [16].

For recording leg MEPs, the subjects lay in a supine position on a bed. To stimulate the leg motor area, the double cone coil was positioned over the vertex [24]. Magnetic stimulation to lumbar roots was performed with the subject in a prone position, and the centre of the eight-shaped coil was placed over the 4th lumbar spinous process. The coil orientation was such that the maximal induced current in the tissue flowed parallel to the spinous processes from the proximal to the distal side.

Recording

The surface silver-silver chloride electrodes were applied to the abductor pollicis brevis and the abductor hallucis muscles bilaterally. The compound muscle action potentials were thus obtained from the left and right sides, while the subjects were instructed to keep their muscles relaxed. Electromyographic signals were recorded by Neuropack 8 (Nihon Kohden) with the filter set at between 50 and 3000 Hz. To ensure the reproducibility of the responses, at least two stimuli to the brain and spinal regions were applied.

Data analysis

The onset latencies of MEPs were measured with a cursor on the computer display. The central motor conduction time (CMCT) was determined by subtracting the latency of the cervical (or lumbar) MEPs from that of the cortical MEPs. The absolute difference in latency between the components evoked by left and right stimulation was also determined.

Student's *t* test was used to compare both the left and right data and also the female and male data. A simple linear regression analysis and a multiple regression analysis were carried out to determine which of the physical variables, including sex, height and age, had a significant influence on the MEPs. In a multiple regression analysis, sex was coded as 0 if female and 1 if male to indicate that these data are binary variables [17].

Results

The difference in height between the genders was statistically significant (unpaired *t* test, $P<0.0001$), while there was no statistically significant difference in age. Figure 1 shows the relationship between height and age. There was a significant decline in height as age increased (female subjects: $P<0.0001$; male subjects: $P<0.05$).

In all subjects, the motor responses to magnetic cortical and spinal stimulation were always obtained. Representative examples of the MEPs in the upper and lower limbs are shown in Fig. 2. Since we did not find any significant difference in the latency between the right and left responses (Table 1), we averaged the right and left data. Therefore, each individual contributed only one observation for each of the measurements [9]. Table 1 summarizes the normal values and the gender differences in the MEPs. Except for the CMCT, the cortical and spinal MEP latencies showed significant gender differences (unpaired *t* test).

Initially, a simple linear regression analysis was carried out (Fig. 3). No significant effects of height and age were observed on all components of hand MEPs except for the cervical latency of the male data, which positively correlated with age ($P<0.01$). In contrast, height and age had a significant effect on the leg MEPs. For example, the cortical latency of the female data positively correlated with height, while that of the male date positively correlated with age (Fig. 3). The CMCT of the male data also positively correlated with age ($P<0.05$). In addition, a multiple regression analysis was used to determine the effects of sex, height and age on the MEPs. It was shown that combined analyses with sex, age and height provided a better prediction than each variable alone (Table 2). The cortical and lumbar MEP latencies and the CMCT of the leg were significantly influenced by all of the physical variables, while the effect of each physical variable on the hand MEPs was less pronounced. There was a significant gender effect in the MEP latencies and the CMCT of the leg, but no difference was observed for those of the hand MEPs. Height and age also had a significant effect on the

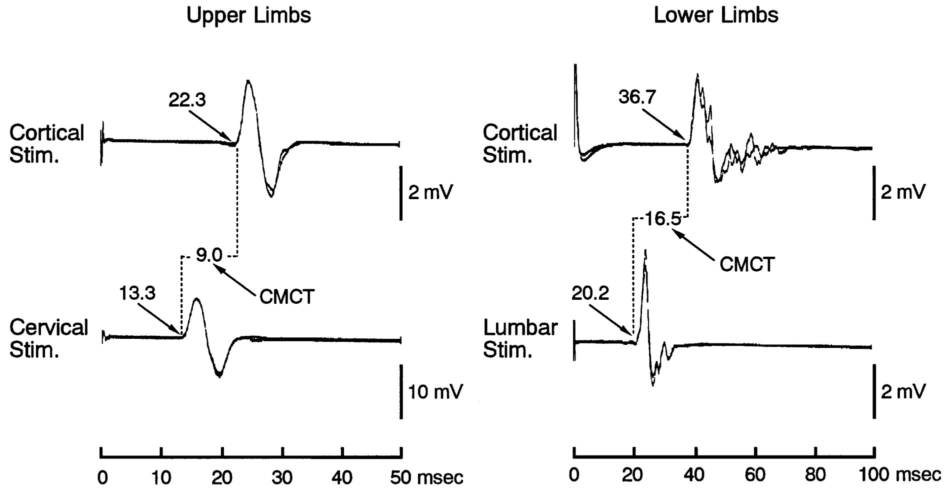

Fig. 2 The magnetic evoked motor potentials recorded from the abductor pollicis brevis muscle (*left column*) and the abductor hallucis muscle (*right column*) in a normal subject. Negativity at the active recording electrode results in an upward deflection

Table 1 Normative MEP values and gender differences[a] (*MEP* motor evoked potential, *CMCT* central motor conduction time)

	Upper limbs (ms)			Lower limbs (ms)		
	Cortical	Cervical	CMCT	Cortical	Lumbar	CMCT
All (n=48)	21.76, 1.11	13.34, 0.80	8.42, 0.68	39.34, 2.42	22.03, 1.40	17.31, 1.79
Side difference	0.50, 0.44	0.37, 0.34	0.41, 0.43	0.51, 0.49	0.33, 0.32	0.47, 0.60
Male (n=22)	22.48, 0.75	13.88, 0.50	8.60, 0.67	40.15, 2.40	22.62, 1.32	17.54, 1.93
Female (n=26)	21.14, 1.00	12.87, 0.72	8.27, 0.65	38.65, 2.27	21.53, 1.28	17.12, 1.67
P value	<0.0001	<0.0001	0.09	<0.05	<0.001	0.43

[a] Data are means, SD

leg MEP latencies and, to a lesser degree, on the hand MEP latencies. The CMCT of the leg was significantly affected by height and age, but no difference was seen for the hand CMCT. The predicted normative values can be calculated from the multiple regression equations given in Table 3.

Discussion

Although it has been shown that the MEPs recorded from the leg are more difficult to elicit and of smaller amplitude than those recorded from the hand [3], and in addition they cannot be recorded in 8% of normal subjects [10], we did not experience any difficulty in recording the leg MEPs at rest by using the double cone coil. We were therefore able to compare the effects of each physical variable on the hand and leg MEPs. We did not study the MEPs with a slight voluntary contraction because the ongoing muscle activity of a facilitatory contraction sometimes makes the precise measurement of the onset latency impossible when the MEP responses are small because of central nervous system (CNS) deficits [21].

It has previously been shown that MEP latencies positively correlate with height and age [4, 8, 10, 11], but disagreements about the CMCT remain. Some investigators thus found that the CMCT was independent of both height and age [4, 12, 14], while others have reported that the CMCT is significantly affected by height and age [8, 10, 11]. Furthermore, the leg CMCT may correlate positively with height, while no difference was seen for the hand CMCT, even in the same subject group [8, 11], and the same applied for gender difference. In some previous reports, no significant difference was observed between the genders [11], while other investigators found a significant gender difference [8]. The reasons for such discrepant results remain unclear. They might be attributed to the different methods used in different studies and different demographic characteristics of the subjects. An alternative explanation could be that all of the previous studies adopted the simple linear regression analysis instead of using a multiple regression analysis. Based on our findings, it is evident that the simple linear regression analysis was insufficient to analyse the effects of physical variables on the MEP. This is probably owing to a significant inverse linear relationship between height and age (Fig. 1) and gender differences (Table 1, Fig. 3). Our results clearly demonstrated that combined analyses with sex, height and age provide a better prediction than each variable alone, and these findings are in agreement with the results of the somatosensory evoked potentials (SEPs) [1, 7] and visual evoked potentials [6].

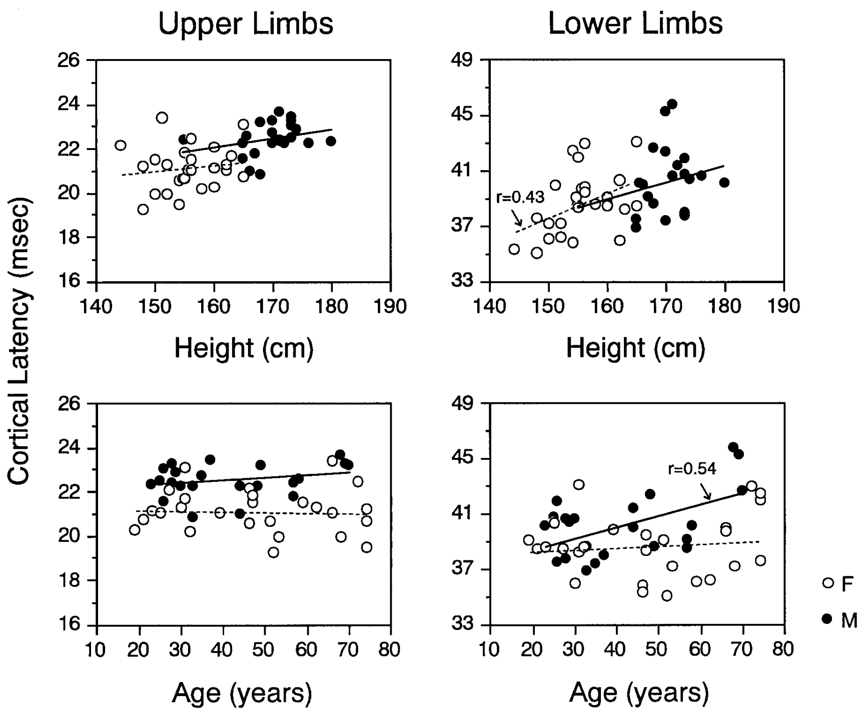

Fig. 3 The effects of height and age on the cortical motor evoked potential (MEP) latency in upper and lower limbs. The *open circles* refer to female and the *closed circles* to male subjects. The *dashed line* and the *solid line* represent the linear regression lines of female and male subjects, respectively. No significant effect of height and age on the cortical MEP latency was observed in the upper limbs. In contrast, the height has a significant effect on the female data ($P<0.05$), while age has a significant effect on the male data ($P<0.01$)

Table 3 Regression equations of the MEP components in relation to sex, height and age

Component	Regression equation (L=aH+bA+cS+d)[a]	*r*	*P* value
Upper limbs			
Cortical latency	0.063H+0.015A+0.538S+10.619	0.654	<0.0001
Cervical latency	0.038H+0.017A+0.565S+6.093	0.696	<0.0001
CMCT	0.025H–0.0021A–0.026S+4.553	0.334	0.153
Lower limbs			
Cortical latency	0.368H+0.108A–3.038S–23.688	0.760	<0.0001
Lumbar latency	0.181H+0.037A–1.241S–8.4000	0.669	<0.0001
CMCT	0.187H+0.071A–1.797S–15.288	0.570	<0.0001

[a] L latency (ms), H height (cm), A age (years), S sex (1 for male and 0 for female subjects) d y intercept

Table 2 The effects of sex, height and age on the MEP components (*NS* not significant, *S* significant)

Components	Sex	Height	Age
Upperlimbs			
Cortical latency	NS	S*	NS
Cervical latency	NS	NS	S*
CMCT	NS	NS	NS
Lower limbs			
Cortical latency	S**	S***	S***
Lumbar latency	S*	S***	S**
CMCT	S*	S**	S***

* $P<0.05$; ** $P<0.01$; *** $P<0.001$

Although all MEP components showed significant latency changes related to sex, height or age, the effect of these changes on the hand MEP was mild. The effect of sex on the leg MEPs was significant, but no difference was observed for the hand MEPs. This findings thus probably reflects the difference in height as observed in this study. However, Chu [8] compared two subgroups of female and male subjects with a homogenous height and found a gender difference in the leg CMCT, but no difference for the hand CMCT. Therefore, the reason for gender difference still remains to be clarified. As expected, the effect of height was more pronounced in the leg MEPs than in the hand MEPs. The finding that the different effect of height on the CMCT is consistent with previous studies [8, 11]. It has been shown that the central conduction time of the posterior tibial nerve SEPs correlates with height, while that of the median nerve SEPs does not [7]. This thus suggests a similar relationship with height in the sensory and motor pathways.

An interesting finding in this study is the different effect that was seen regarding age on the hand and leg CMCT. One of the underlying mechanisms of this finding is probably owing to the fact that age-dependent changes affect the cervical and lumbosacral pools of spinal motoneurons differently [23, 25]. There is a progressive temporal dispersion of descending impulses with a less synchronized effect on the foot α–motoneurons [18–20]. The cervical cord also receives many more corticospinal fibres per unit of muscle mass than the lumbosacral cord [18–20]. Such physiological factors could thus influence the age-dependent changes in the motor pathway. In the cortical motor area, 75% or more of Betz cells showed age-related morphological changes, while changes of small pyramidal neurons were less severe than those of Betz cells [22]. The study by Lassek [13] showed that 75% of Betz cells were in the motor area supplying the leg, 17.9% in the arm region, and only 6.6% in the head area, despite the dedication of far more extensive cortical areas to the head and arm than to the leg. Since the CMCT mainly reflects the function of fast-conducting pyramidal cells [18], namely Betz cells, the more pronounced effect of age on the leg CMCT could account for the slowing activities affecting the lower limbs in the elderly.

In conclusion, our results suggest that sex, height and age are all very important in defining the normal MEPs, especially in the lower limbs. Therefore, these physical variables should be taken into consideration in order to construct normograms of the MEPs.

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