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Magnetic and Electrical Transcranial Brain Stimulation: Physiological Mechanisms and Clinical Applications

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The human brain can be stimulated by electric shocks or by brief intense magnetic fields. The latter cause only a trivial scalp sensation. Stimuli exciting the motor cortex cause contralateral muscle responses, but the threshold for excitation is markedly reduced by slight voluntary contraction of the target muscle. For small hand muscles, the overall latency from scalp to muscle is shorter by 1.8 ms when electrical stimuli are used than when stimuli are magnetic. Central motor conduction time (CMCT) can be estimated by stimulating over the scalp and then over the cervical area. In healthy subjects, the CMCT is 6.1 ± 0.8 (SD) ($n = 29$). Physiological studies have shown that the facilitation of responses in hand muscles produced by voluntary contraction is also present when contralateral muscles are used, but not when a leg muscle is contracted. The mechanism of facilitation may involve neural activity at both spinal and cortical levels. Single motor units can be caused to discharge by threshold brain stimuli. These motor units are the same ones activated first during weak voluntary contractions. Clinical studies have shown that the CMCT may be greatly prolonged in patients with multiple sclerosis and that subclinical motor pathway lesions can be detected. Central conduction may also be abnormal in patients with motor neuron disease and cervical myelopathy. Side effects have not been encountered with either type of stimulator. (*Neurosurgery* 20:164–168, 1987)

Key words: Magnetic stimulation, Motor cortex, Motor evoked potential, Spinal cord, Transcranial stimulation

INTRODUCTION

Stimulation of the human brain is proving to be an exciting new technique, not only for the investigation of patients with neurological disease but also for furthering our understanding of the physiology of motor control. Electrical stimulation of exposed primate motor cortex was first tried over a century ago (15, 16) when it was discovered that contralateral muscle responses could be obtained and that anodal stimuli were more effective than cathodal. Stimulation of the neurosurgically exposed human motor cortex followed quickly (4, 26), and subsequently detailed mapping of the motor areas was achieved (39).

It was not until the brain could be stimulated percutaneously in fully alert and cooperative subjects that the mechanisms of human motor control could be probed by this technique. Early attempts at this used repetitive stimuli, but failed because they became painful even when shocks were subthreshold (17). In 1980, Merton and Morton, using a high voltage stimulator of a type developed to stimulate muscle fibers directly, discovered that they could excite the human brain percutaneously with a single large shock (31). They also found, by accident when performing control experiments, that motor responses could be obtained when stimuli were applied over the spinal cord, and this immediately gave a means of estimating central conduction time (30). Since these initial studies, electrical stimulation has been used in a number of clinical and physiological applications (5, 7–12, 14, 27, 29, 34, 36, 42–46). One problem with the technique, as developed in the United Kingdom (UK), is that it is relatively painful. Rossini et al. seem to have partially solved this problem by using unipolar anodal stimulation over the motor area, with the cathode being a belt or a series of plates around the head (42, 43).

In 1978 through 1982, Barker, an electrical engineer working in Sheffield, UK, was developing a magnetic stimulator for use on peripheral nerve. In 1982, he published a report with Polson and Freeston in which they described how human nerves could be excited with a brief, time-varying field. Although magnetic stimulation of neural tissue had been achieved previously (6, 18, 47), this was the first convincing demonstration of maximal muscle action potentials obtained from magnetic stimuli. The device was presumed to work by inducing currents in the vicinity of the nerve. Subsequently, Barker became aware of the work of Merton and Morton on electrical brain stimulation. In May 1985, a prototype magnetic stimulator was brought to the National Hospital, Queen Square, and was tried on the heads of P. A. Merton and other workers. The first records of motor responses to magnetic brain stimulation were thus obtained (1, 3). It was clear that the magnetic stimulator was a significant advance because sensation over the scalp was trivial, some subjects reporting no sensation at all. Since then, further magnetic stimulators have been constructed (28, 32) and the technique is beginning to be applied in the study of neurological diseases (2, 13, 19–22). We review the National Hospital experience with both types of stimulator.

DESCRIPTION AND COMPARISON OF ELECTRICAL AND MAGNETIC STIMULATORS

The electrical stimulator (Digitimer Type D180; Digitimer Ltd., Welwyn Garden City, England) has a high output voltage (maximum, 750 V) and a low output impedance. The shape of the stimulus is a spike with a fast rise time and then an exponential decay with a time constant of either 50 or 100 μs. The stimulus is applied through saline-soaked pad electrodes with an approximate area of skin contact of 1 cm^2. The anode is placed over the motor area of interest, and the cathode is placed 6 cm anterior. For excitation of small hand muscles, a point 7 cm lateral to the vertex on the interaural line has been used; for the leg muscles, the anode has been placed at the vertex. The threshold for excitation of muscle is considerably reduced by slight voluntary contraction, and this phenomenon has been used widely to "amplify" responses.

The electrical stimulator has also been used to stimulate the motor roots in the cervical area and so provide an estimate of central motor conduction time (CMCT). Here the same

electrodes are used with the cathode in the midline in the C-7, T-1 interspinous space and the anode 6 cm lateral. Motor root stimulation has been used in the investigation of peripheral nerve disorders, such as acute Guillain-Barré syndrome and chronic demyelinating peripheral neuropathies, and of the spinal cord (35–37, 45, 46).

The magnetic stimulator is a flat helical coil 9 cm in mean diameter, which is placed on or very near the scalp. A large current (5000 amperes at maximal output) is passed through the coil by the discharge of capacitors; the magnetic field, which approaches 2 Tesla, has a peak at about 150 μs, passes unattenuated through the scalp and skull, and is presumed to induce stimulating currents within the brain. The time course of induced current follows the first differential of the magnetic field and reaches a maximum at about 80 μs. The direction of current in the coil has been found to determine which hemisphere is preferentially excited; with the inducing current clockwise viewed from above, the left hemisphere is excited. The strength and direction of currents induced in the brain are difficult to predict because the brain is an anisotropic medium, but it has been found empirically that, with the coil centered at the vertex, small hand muscles are most easily activated. Placing the coil 5 to 6 cm posterior in the midline tends to activate the legs, but this has not been consistent in all individuals. The magnetic stimulator is also capable of stimulating peripheral nerves (41), but location of the point of stimulation is less precise than with conventional electrical stimulation.

The most noticeable difference between the stimulators is the scalp sensation during the shock. In 12 healthy subjects, a 10-cm horizontal visual analogue pain scale was used to compare the sensations of electrical stimuli to peripheral nerve and electrical and magnetic stimuli to scalp. The mean (± SD) pain ratings for these stimuli were 1.6 ± 1.1 cm, 5.6 ± 1.2 cm, and 0.9 ± 0.8 cm, respectively; i.e. subjects found magnetic scalp stimuli less painful than peripheral nerve shocks.

Most of the work that we describe has been on small hand muscles that are by far the easiest to activate. In 12 healthy subjects, onset latency and amplitude of compound muscle action potentials (CMAPs) in abductor digiti minimi (ADM) in response to the two types of scalp stimulus were compared (20); conduction time to the muscle was on average 1.8 ms shorter with electrical stimulation (Table 1). It is probable that strong electrical stimuli reach deeper structures than magnetic stimuli. The amplitudes of responses were larger and more reproducible with magnetic shocks (Fig. 1).

PHYSIOLOGICAL STUDIES

Structures activated by the stimuli

Considering firstly electrical stimuli over the cervical vertebral column, a number of experiments have indicated that the site of excitation is at the exit foramina of the motor roots from the spinal canal (38). If stimulus strength is increased beyond that required to produce maximal CMAPs in small hand muscles, then responses are seen in the legs clearly due to activation of descending spinal cord motor pathways (38, 45).

Currently, it is uncertain which neural elements are excited by scalp stimuli: dendrites, presynaptic terminals, cell bodies, efferent axons, or some combination are all possibilities (48). From single motor unit recordings from small hand muscles, it is thought that the site of stimulation with weak magnetic stimuli is probably the presynaptic terminals, with stronger stimuli exciting cell bodies or axons, or both. Electrical stimuli may act partially on the axons distal to the cell body.

The conduction time from cortex to cervical area of about 6 ms leaves sufficient time for only 1 or 2 synapses to be interposed. The pathway must involve fast myelinated fibers, and for the small hand muscles it is likely to be the corticomotorneuronal tract known to make monosynaptic connection with skeletomotor neurons in primates (40).

Facilitation (24)

One of the most interesting phenomena encountered during experiments on electrical stimulation is the facilitation of responses by background contraction of a muscle (22, 33). The stimulus can, in a manner of speaking, be focussed on the target muscle by slight contraction. What is the mechanism of this facilitation? There are two main possibilities: the

TABLE 1
Data on CMCT to Upper Limb Muscles (May 1986)[a]

Muscle	Type of Stimulation	No. Controls	Facilitation	Conduction Time (ms)		Reference
				Cx-muscle	Cx-Cv	
APB	Eb	11	+	19.6	5.0	12
Biceps	Eb	11	+	10.0	4.1	12
APB	Eb	11	+	16.9[b]	6.8	43
APB	Eu	23	+	16.4[b]	6.5	43
F/flexor	Eb	15	+	13.1	4.4	34
ADM	M	27	−	22.5	9.4[c]	2
ADM	Eb	12	+	18.5	5.0	20
ADM	M	12	+	20.3	6.8	20
APB	Eb	3	±	20.9/24.1	NQ	13
FDI	Eb	3	±	20.8/24.1	NQ	13
APB	M	3	±	23.3/24.6	NQ	13
FDI	M	3	±	23.0/24.3	NQ	13
ADM	M	29	+	19.6	6.1[d]	
ADM	M	10	±	20.8/24.1	NQ[d]	

[a] Cx-muscle: Scalp to muscle; Cx-Cv: Scalp to cervical area; APB, Abductor Pollicis Brevis; Eb: Bipolar Electrical Stimulation. Eu: Unipolar Electrical Stimulation; F/Flexor, Forearm flexor; ADM: Abductor Digiti Minimi; M, magnetic stimulation; NQ; Values not quoted; FDI: First Dorsal Interosseus.
[b] Conduction time to wrist.
[c] Magnetic stimulation at Erb's point.
[d] Mills et al., unpublished data.

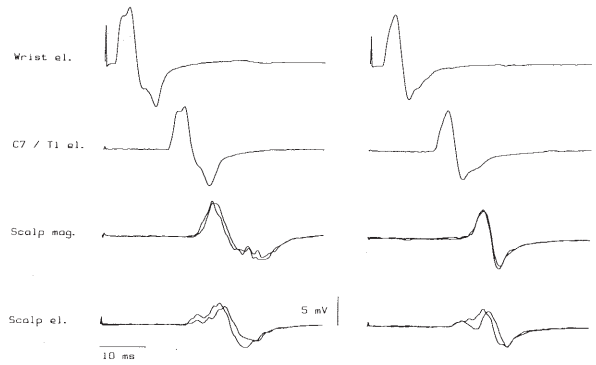

FIG. 1. Comparison of electrical and magnetic scalp stimulation in two healthy subjects. Surface recordings were from ADM. Electrical stimuli were applied at the wrist (*Wrist el.*), over the C-7, T-1 interspace (*C7/T1 el.*), and over the hand area of the motor cortex (*Scalp el.*). Magnetic stimuli were applied with the coil over the vertex (*Scalp mag.*). The responses to electrical scalp stimuli have an earlier onset latency.

spinal cord could be involved, or the mechanism may be in the cortex itself, and afferent input to either structure may play a part. A contraction strength of as little as 1.5% of the maximal isometric strength of the muscle is sufficient to cause facilitation (22). Facilitation of right ADM responses can be obtained by background contraction of right 1st dorsal interosseus (FDI) or left ADM, but only minimally by left FDI and not at all by quadriceps. In addition, small forces (>5% maximum) are able to facilitate responses when they are exerted in the same hand as the target muscle; such small forces exerted in the contralateral hand do not facilitate. Forces of 10 to 25% are needed in the contralateral homologous muscle to cause the facilitation. It seems that the phenomenon is complicated and may involve a rise in the excitability of homologous spinal motor neuron pools and an effect at small forces, probably cortical, where the subject is focussing his attention on the accurate motor performance of a particular hand. We studied one patient with an above elbow amputation of the left arm who could still facilitate responses to scalp stimulation of the right motor pathways; this makes afferent input to the nervous system not obligatory for the facilitation (24).

Single motor unit (MU) recordings (19, 23)

It is remarkable that such gross stimuli to the brain, even at threshold, can cause the discharge of single MUs in the muscle (19). Nevertheless, we were successful in achieving this on 15 consecutive occasions. Furthermore, we were able to show that the units activated by threshold brain stimulation were the same ones that were recruited first during weak voluntary effort. The latency of these units varied from 22.4 to 32.1 ms. It seems then that the spinal mechanism whereby there is orderly recruitment of motor units by increasing voluntary effort also operates when the descending volley is set up by a stimulus to the brain.

By making stimuli just suprathreshold or by studying with stronger shocks patients with few surviving MUs in the muscle, we shortened the latency of these units by about 1.5 ms. This cannot be explained by a distal move of stimulation site down the same axon because, for an axon conducting at 60 m/second, this would represent a conduction distance of 9 cm. Rather, it is more likely that threshold stimuli activate presynaptic terminals, whereas stronger ones cause excitation at the axon hillock.

CLINICAL STUDIES

Determination of CMCT

Determination of the central component of the conduction time from scalp to muscle requires subtraction of the peripheral nerve conduction time from the total. For the small hand muscles, we have used electrical stimulation over the C-7, T-1 interspace to estimate this peripheral latency. Thus, CMCT, as determined here, contains a small peripheral component due to synaptic delay at the motor neuron and conduction down a short segment of the motor root (34). The term CMCT is preferable to pyramidal tract conduction time or corticospinal tract conduction time because it makes no assumptions as to the pathways involved (48). Also, conduction distances are difficult to estimate and so the calculation of a conduction velocity is not warranted. Table 1 summarizes all of the data on CMCT to upper limb muscles.

Results in patients with multiple sclerosis (MS)

The initial series of patients with definite MS was studied using electrical scalp stimulation and recording from the forearm flexor muscles (34). In eight patients with definite MS, the CMCT was prolonged or responses from scalp stimulation were absent. No correlation was found between prolongation of the CMCT and clinical features. With the advent of the magnetic stimulator, electrical scalp stimulation has now been abandoned in patients because of the discomfort involved.

With magnetic stimulation, 15 patients with clinically definite or laboratory-supported probable MS have been studied (25). Recordings have been made from ADM, and peripheral conduction has again been estimated from electrical stimulation over the cervical spine (Fig. 2). Of the MS patients with pyramidal signs in the upper limbs, all but 1 had prolongation of the CMCT. In 2 patients, the CMCT was prolonged despite minimal clinical signs in the upper limbs, which gave evidence of a subclinical lesion affecting motor pathways. In some patients, there was extreme prolongation of the CMCT (21), with values up to 39 ms being recorded. A pathological finger jerk was the only clinical sign that correlated with a prolonged CMCT, and there was a striking lack of correlation between strength in the hand muscles and the CMCT.

CMCT in other neurological conditions

We investigated five patients with motor neuron disease. Three showed no abnormality, one showed mild prolongation in CMCT, and one showed no response to scalp stimulation on one side. Abnormalities of CMCT were also found in one case each of the following: cervical myelopathy, radiation myelopathy, and hereditary spastic paraparesis. No abnormality was found in one case each of spinocerebellar degeneration and spinal arteriovenous malformation.

Both electrical and magnetic stimulators are safe; no subject or patient has reported any untoward side effect. Patients and controls with a history of epilepsy have thus far been excluded; for magnetic stimulation, patients who have had neurosurgical procedures on the head or who have cardiac pacemakers are also excluded.

Although the abnormalities in CMCT cannot in any way be claimed to be specific for particular diseases, we think that brain stimulation is a significant addition to the armamentarium of neurophysiologists and warrants continued careful evaluation.

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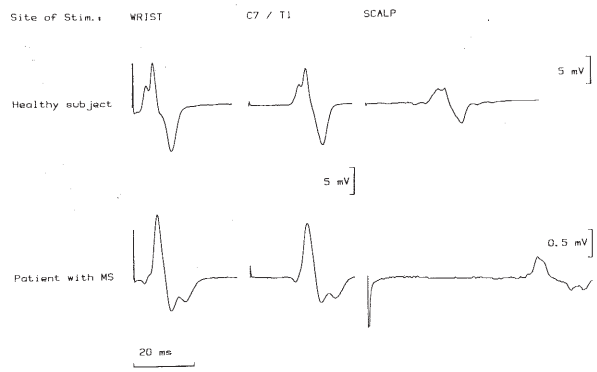

FIG. 2. Surface recordings from ADM in a healthy subject (*top*) and in a patient with MS (*bottom*) in response to electrical stimuli at the wrist and C-7, T-1 interspace and magnetic stimuli over the vertex. The response to scalp stimulation in the patient is markedly delayed.

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COMMENTS

Amassian: I was curious in the case of MS: when muscle power was not reduced, but there was a prolonged conduction time, did you measure the dispersion? One might argue that a plaque affected the function in the corticospinal fibers more or less simultaneously, so that there was a fairly uniform delay. As far as the α-motor neurons are concerned, the EPSP would sum just as well because it doesn't know when the impulse originated in the cortex. On the other hand, if there is a significant dispersion, there is a major problem in reaching the threshold for firing. So the dispersion could be a very important correlate of whether there is a clinical effect associated with a given lesion.

Mills: All responses that we have seen that have been delayed in MS patients have been dispersed. We have the impression that there may be two populations of types of slowing. One may have delays up to 4 ms, only a minor slowing, and a second population may have very gross delays, 5 or 6 times the normal central conduction time. The disparity between the delay in conduction and the strength of muscle contraction is quite striking. We have the impression that we are stimulating only a specific part of the corticospinal tract, perhaps the corticomotoneuronal tract, with specific monosynaptic connections. And that is not necessarily responsible for maintaining a strong contraction. Other parts of the corticospinal tract could well do that.

Question: Was the order of firing of the motor neurons constant in amyotrophic lateral sclerosis? Did they always fire in the same sequence?

Dr. Mills: Yes.