



X INTERNATIONAL CONGRESS OF EMG
AND CLINICAL NEUROPHYSIOLOGY

Satellite Symposium (SS9)

Transcranial Magnetic Stimulation

**The 6th Symposium on
Clinical Use of Magnetic Stimulation**

—第6回磁気刺激法の臨床応用と安全性に関する研究会—

PROCEEDINGS

October 18, 1995

Kyoto International Conference Hall, Japan

Study Group on Application and Safety of Magnetic Stimulation



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AND CLINICAL NEUROPHYSIOLOGY

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INTRODUCTION

— Magnetic Stimulation —

Jun Kimura

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Bickford in 1965 and a few years later Barker tried to use a pulsed magnetic field to stimulate peripheral nerves. Subsequent attempt to use Barker' device for noninvasive and painless stimulation of the motor cortex by Merton and coworkers at the National Hospital, London 1985 opened a new era of clinical electrophysiology with vast diagnostic and theoretical implications.

In Japan, the Study Group for Clinical Application and Safety of Magnetic Stimulation was formed in 1990. The Ministry of Health and Welfare approved the sale of magnetic stimulators as a medical instrument in 1993. The technique has since been applied to study the basic physiology of the motor system in normals in a wide range of neurological disorders in our country. To review these developments periodically, the Study Group met yearly in conjunction with the annual meeting of the Japan EEG and EMG Society.

The 6th Annual Meeting for Clinical Use of Magnetic Stimulation is organized as a Satellite Symposium of the 10th International Congress of EMG and Clinical Neurophysiology. It is particularly timely now to explore this fruitful area for further clinical research as this marks the 10th anniversary after the introduction of magnetic coils for cortical stimulation.

As the Convener of the X-ICEMGCN and the President of the Japanese Study Group, I am pleased to welcome many distinguished researchers in this field who came from different corners of the world to participate in this symposium. On behalf of the organizer, I wish to express my sincere appreciation to the Eisai Co., Ltd., Tokyo, Japan, for sponsoring the Study Group for Clinical Application and Safety of Magnetic Stimulation during the past five years and generously supporting the Satellite Symposium on Clinical Use of Magnetic Stimulation this year.

PROGRAM

2:15PM Opening Remarks

Jun Kimura

Kyoto University Hospital, Japan

Chair: Roger Q. Cracco

2:20 The microphysiology of human corticospinal connections
studied with transcranial magnetic stimulation

Kerry R. Mills

The Radcliffe Infirmary, University of Oxford, UK

2:50 Localized magnetic stimulation of the human brain and nerve
excitation models

Shoogo Ueno

Institute of Medical Electronics, University of Tokyo, Japan

3:20 Mapping the cerebral cortex

Mark Hallett

*National Institute of Neurological Disorders and Stroke, NIH,
USA*

3:50 Facilitatory and inhibitory mechanisms of brain transcranial
stimulation in the healthy and in neurological disorders

Paolo M. Rossini

Ospedale "S. Giovanni Calibita", Fatebenefratelli, Italy

— Coffee Break —

Chair: Mark Hallett

4:40 Flow of symbolic visual information from retina to vocaliza-
tion

Roger Q. Cracco

*State University of New York Health Science Center at Brooklyn,
USA*

-
- 5:10 Motor reorganization in central and peripheral nervous system diseases
Yukio Mano
Nara Medical University, Japan
- 5:40 Motor evoked potentials — Neurophysiological correlates of clinical signs and symptoms
Nicholas M.F. Murray
The National Hospital for Neurology and Neurosurgery, UK
- 6:10 Specificity and sensitivity of magnetic stimulation techniques in neurological disorders
Christian W. Hess
INSELSPI TAL, University of Berne, Switzerland
- 6:40 Closing Remarks
Mark Hallett

—— Satellite Symposia Reception ——

Chairpersons

Jun Kimura

Kyoto University Hospital, Kyoto, Japan



Roger Q. Cracco

*State University of New York Health Science
Center at Brooklyn, New York, USA*



Mark Hallett

*National Institute of Neurological Disorders
and Stroke, NIH, Bethesda, MD, USA*



The Microphysiology of Human Corticospinal Connections Studied with Transcranial Magnetic Stimulation

Kerry R. Mills

*Clinical Neurophysiology Unit, University Department of Clinical Neurology,
The Radcliffe Infirmary, Oxford, UK*

The discharge of a single human motor unit (MU) reflects the firing of a single spinal motoneurone (MN). When recruited during a weak steady voluntary contraction, MUs begin firing at about 10Hz; the firing frequency is modulated upwards as force is increased, reaching a maximum of 25–30Hz. Each MN has in the order of 10^5 synaptic connections covering its soma and dendritic tree. Many of these are corticospinal inputs, which are relayed via spinal interneurons. Monosynaptic corticomotoneuronal connections also exist allowing direct driving of MNs from the primary motor cortex. There is considerable divergence of connectivity within a MN pool; it is believed that some corticospinal fibres may contact all the MNs of a pool. There is also considerable convergence of

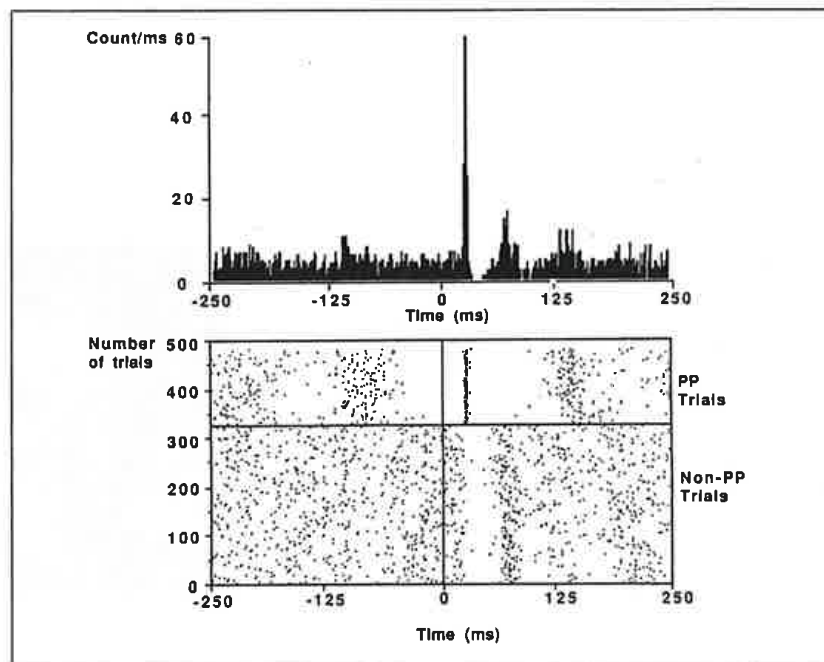


Fig. 1. Above is a PSTH (1ms binwidth) constructed from the discharge times of a single MU in the first dorsal interosseous muscle of a normal subject. A series of 495 stimuli were given at time zero. The primary peak at 25ms is followed by a short period of zero firing probability and then a secondary peak with peak latency 70ms is seen. Below, the same data are presented in a sorted raster plot. Trials which caused a PP discharge have been separated from those which did not. It can be clearly seen that the firing history of the MU influences its response to stimuli; only if the MU fires 60–110ms before the stimulus is a PP discharge seen.



inputs on to single MNs⁹). We are now able to study these corticospinal synaptic connections by recording the modulation of tonic voluntary discharge of a MU by defined inputs from the cortex excited by magnetic stimuli^{4, 5, 10}).

Modulation of MU discharge is studied by logging the times of occurrence of spikes in relation to stimuli on multiple trials. This results in a peristimulus time histogram (PSTH) (Fig. 1). Small deviations from the baseline firing level are detected by cusum analysis of the PSTH. The effect of the time-history of firing is assessed by producing a sorted raster plot.

If a PSTH is constructed whilst a large series of weak magnetic stimuli are given to motor cortex, MU discharge probability is seen to fall transiently²). In small muscles of the hand which have been most extensively studied, the onset of this inhibitory effect is 27 to 36 ms after the stimulus. As stimulus intensity is increased the duration and depth of this down-modulation increase. Over a very narrow range of stimulus intensity, however, slowing of discharge quickly turns into an increase in firing probability. The PSTH now reveals a brief (3–8ms) increased firing probability at a latency of 25–30ms and termed the primary peak (PP)¹¹. This is followed by a cessation of firing and then a second, more dispersed increase in firing probability, lasting 10–50ms and having a peak latency of about 70ms which we have termed the secondary peak (SP)⁷).

Analysis of PP at higher time resolution shows that there are often a number of distinct subpeaks within PP. In normal MUs, these subpeaks occur at intervals of 1.4–1.8ms (Figs. 2 & 3). By analogy with the known effects of single stimuli applied to primate motor cortex, these subpeaks are thought to represent the sequential arrival at the MN of separate impulses over the corticospinal fibres³). Each impulse engages the MN and evokes in it an excitatory post-synaptic potential (EPSP) (Fig. 2). The size of PP is thought to correlate with the rise time of the underlying EPSP and for this reason is believed to represent a monosynaptic corticomotoneuronal connection.

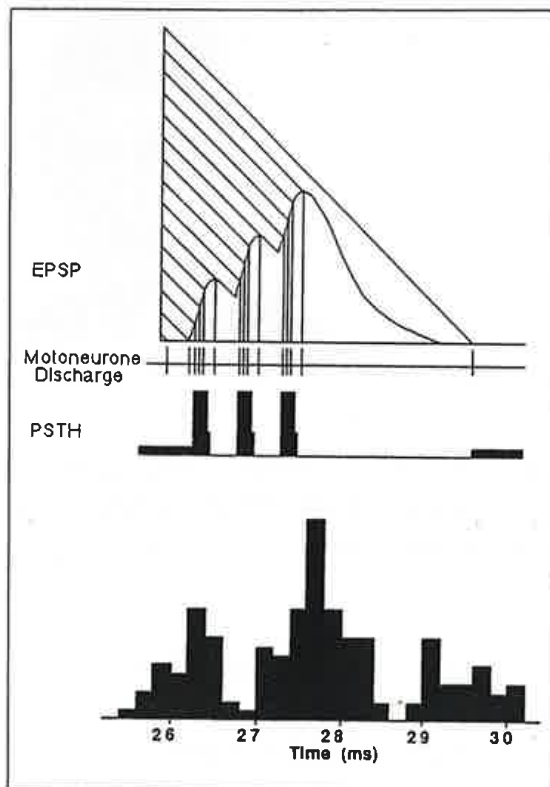


Fig. 2. Above is a model of events occurring at the MN membrane during tonic voluntary activation when a stimulus evoked train of corticospinal impulses arrives. The oblique lines represent the trajectory of the membrane potential as it progressively moves towards threshold, represented as the x-axis. When the trajectory cuts the EPSP waveform a discharge is produced and the PSTH is seen to contain 3 subpeaks corresponding to the 3 phases of the composite EPSP. Below is a PSTH (0.2ms binwidth) from the data in Fig. 1. showing 3 subpeaks at inter-sub-peak intervals of 1.8ms.

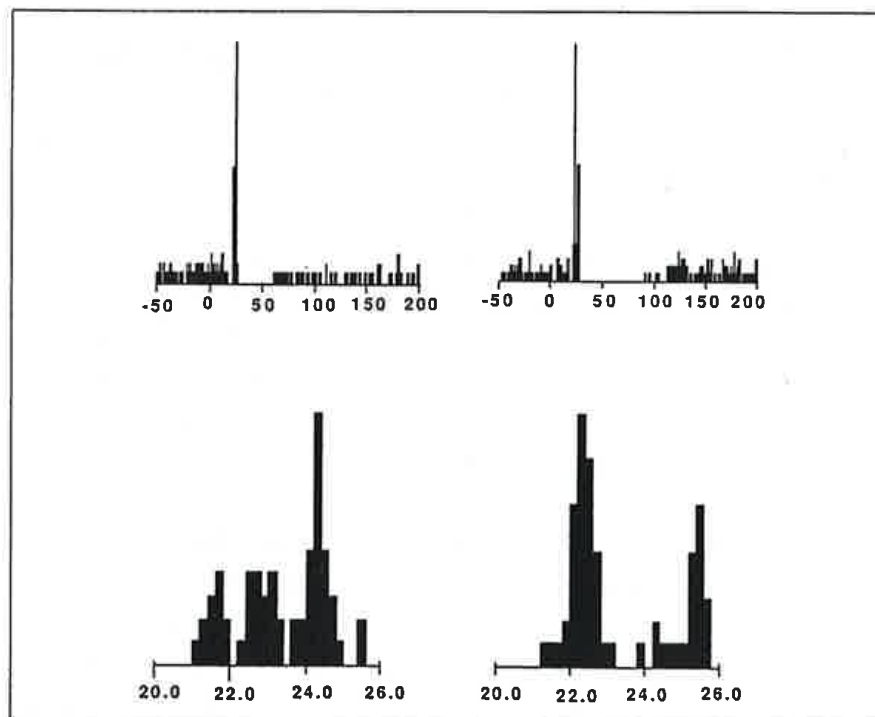


Fig. 3. On the left are PTSHs (1ms binwidth above and 0.2ms binwidth below) from a MU in the first dorsal interosseous of a healthy subject. On the right are similar PSTHs from a patient with multiple sclerosis. The inter-subpeak interval in the control is 1.4ms and in the patient is 3.6ms. It appears as if a single sub-peak is missing in the patients PSTH, suggesting frequency-dependent conduction block.

The above techniques are not intended for diagnostic purposes; they are used to investigate pathophysiological mechanisms in patients. Two examples follow. In multiple sclerosis, PP is often delayed and dispersed as expected from the demyelination of central motor fibres¹¹. However, in some patients PP is of normal latency but the inter-subpeak interval is about twice that found normally, suggesting that a subpeak is absent. Frequency-dependent conduction block could be responsible for this effect and is postulated as a possible mechanism for weakness in these patients (Fig. 3).

In some patients with amyotrophic lateral sclerosis, PP may be larger than anticipated given the stimulus intensity used⁶; this implies that in these MNs, larger than normal EPSPs are generated suggesting that MNs are hyperexcitable at certain stages of the disease (Fig. 4).

Another technique used to study the corticospinal drive on to MNs is to record from pairs of MN and estimate the degree to which they share connectivity. This is done by constructing a cross-correlogram (CCG). The times of discharge of one MU are logged in relation to the discharge of another MU. MNs are found to discharge together more frequently than

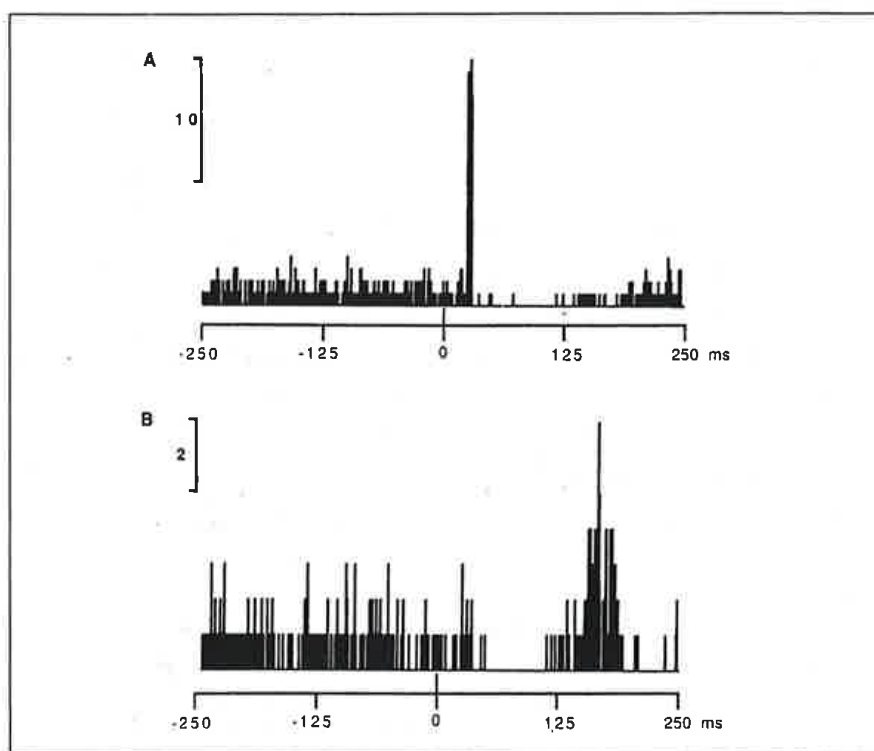


Fig. 4. PSTHs from 2 patients with amyotrophic lateral sclerosis. In A, stimulus intensity was 30% maximum stimulator output, an intensity which is usually below the threshold for excitation in normals. The primary peak is much larger than anticipated and implies an abnormally large underlying EPSP. In B, a stimulus intensity of 68% has caused a period of inhibition followed by a pronounced secondary peak.

expected by chance (Fig. 5). These paired firings are thought to represent the arrival of impulses over branched input fibres driving the two MNs. The size of the CCG peak is an estimate of the strength of common input to the two MNs.

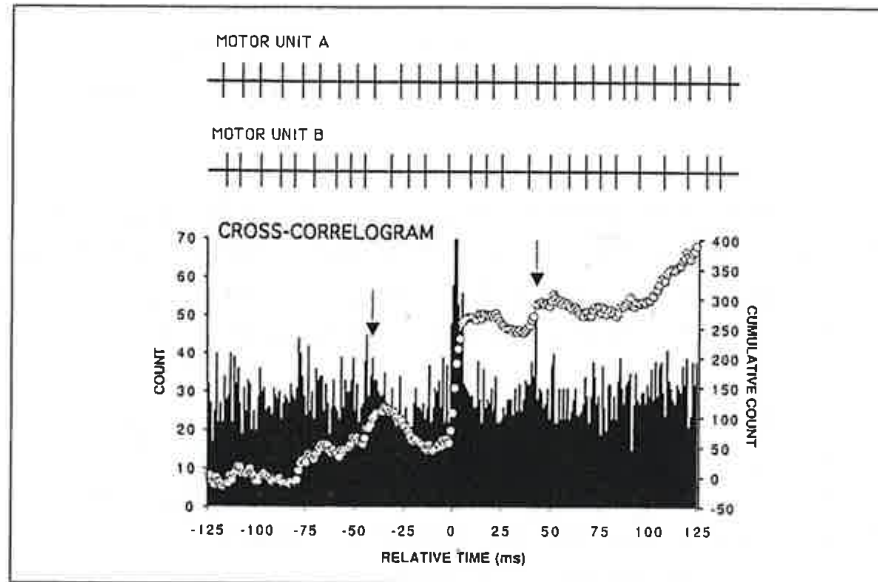


Fig. 5. Above are two spike trains derived from MUs in the first dorsal interosseous muscle of a healthy subject. Below is the cross-correlogram of the discharges of motor unit A in relation to motor unit B. The central peak in the cross-correlogram has a duration of 12ms and indicates operation of common inputs to the two MNs. The central peak in the cross-correlogram can be better defined by the cusum (open circles).

Magnetic stimuli applied during the recording of pairs of MUs allows us to estimate the degree to which the fast corticomotoneuronal connections are also shared between MNs. The observed probability of both MUs firing in response to a stimulus can be compared with the expected paired firing probability. It is found, rather unexpectedly, that MUs are discharged together by stimuli no more often than by chance, i.e. the two MNs appear to behave independently to the descending volley⁸. This may be interpreted as a mechanism whereby motor cortex can engage individual MNs which might be required in a specific task.

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Localized Magnetic Stimulation of the Human Brain and Nerve Excitation Models

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Magnetic nerve stimulation has been widely used in neurophysiological research and clinical diagnosis¹⁾. We have developed a method of focal and vectorial magnetic stimulation. The basic idea is to concentrate induced eddy currents in a target with a pair of oppositely pulsed magnetic fields which can be produced by a figure-eight coil²⁾. Using this method, we were able to stimulate the motor cortex of the human brain within a 5 mm resolution³⁾. Figure 1 shows the results of localized magnetic stimulation of the brain, innervating the thenar muscle.

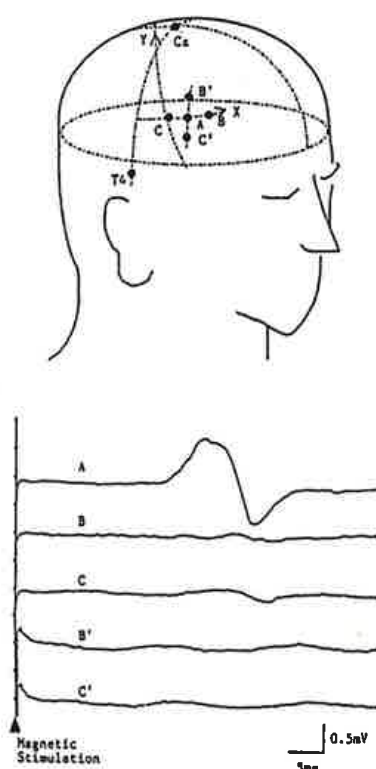


Fig. 1. Electromyographic (EMG) responses to magnetic brain stimulation. A: Thenar point stimulation. B: Stimulation at a point 5 mm posterior to the thenar point. C: Stimulation at a point 5 mm anterior to the thenar point. B': Stimulation at a point 5 mm above the thenar point. C': Stimulation at a point 5 mm below the thenar point.

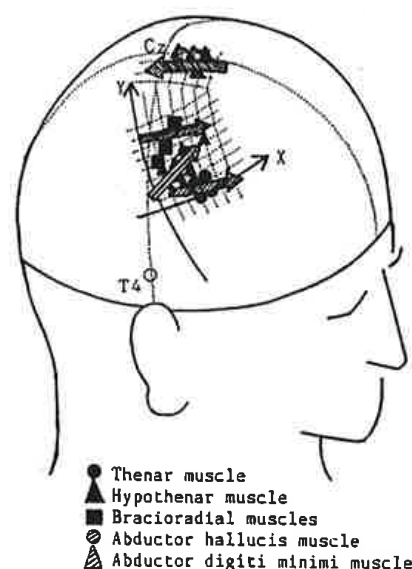


Fig. 2. Functional distribution of the human motor cortex related to the hand and foot areas. The arrows show current directions for neural excitation. The distance between grid points is 5 mm.



Since the concentrated eddy currents at the target beneath the intersection of the coils flow in a direction parallel to the tangent of the two circular coils, vectorial stimulation can be achieved. The neural fibers can be excited easily when the fibers are stimulated by the eddy currents which flow parallel to the neural fibers, in contrast to the case in which the currents flow perpendicularly to the neural fibers. Based upon this principle, we have obtained functional maps of the human motor cortex related to the hand, arm, and foot areas⁴⁾. As shown in Figure 2, we have observed that an optimal direction of stimulating currents for neural excitation exists in each functional area in the cortex.

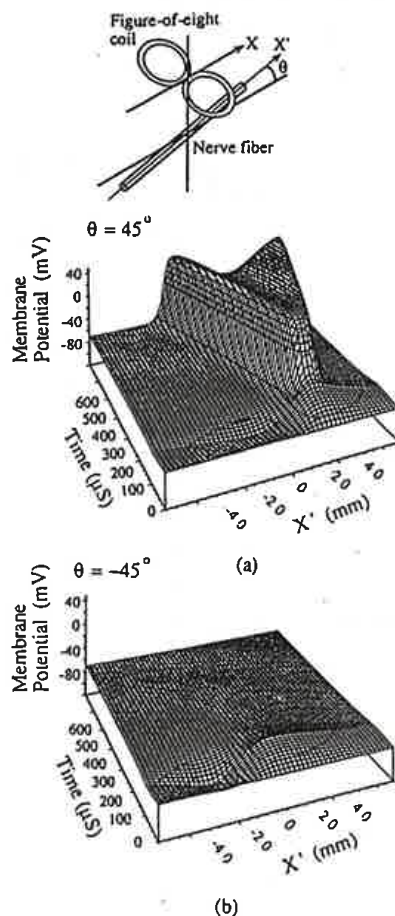


Fig. 3. Stimulation of nerve excitation elicited by magnetically induced eddy currents. The X axis runs parallel to the direction of the tangent of both circular coils. In this simulation, currents in the coil flow along the -X axis at the intersection. The X' axis runs in a direction parallel to the nerve fiber. When the angle between the figure-eight coil and nerve is 45 degrees, as shown in (a), the nerve is excited at point $X' = (20\text{mm})$, and the excitation propagates to both sides of the nerve fiber. In contrast, when the angle between the figure-eight coil and the nerve is -45 degrees, as shown in (b), the nerve fiber is not excited.

To explain these vectorial characteristics in magnetic brain stimulation, we developed a model of neural excitation elicited by magnetic stimulation^{5,6}. Figure 3 shows a simulation of nerve excitation elicited by magnetically induced eddy currents using a figure-eight coil. The nerve fiber and the induced eddy current must be at least parallel to one another and the eddy current must exhibit a spatial gradient field in order to elicit excitation in the nerve fiber. When the nerve fiber is inclined toward the surface of the coil plane or the surface of the body, excitation is facilitated and, as the nerve fiber is declined away from it, excitation becomes increasingly difficult. The model explains our observation that the directions of the induced current vectors reflect both functional and anatomical organization of neural fibers in the brain. We need to emphasize here the point of excitation is neither at "0" nor under the intersection with the coil. Instead it is 20 mm away from the point of intersection. And, in this case, the coil diameter used was 50 mm and the distance between the coil and the nerve fiber was 10 mm.

We have also developed a method of repetitive magnetic stimulation with train pulses using frequencies of up to 50 Hz. Using such a magnetic stimulator, we observed arm muscle contractions responding to the stimulation of spinal roots at the neck and median nerves with varying frequencies of stimulation. We induced continuous muscle contraction with frequencies of higher than 6–7 Hz and found that muscle movement was proportional to the frequency used. Up until now, we have limited our experimentation with peripheral nerve fibers in the body and have hesitated to use this method in experiments with the human brain. Although the method does appear to be safe for use in experimenting with the brain, no such experimentation will be done until further investigation into possible hazards is done in order to insure the uncompromisable safety of any possible subject.

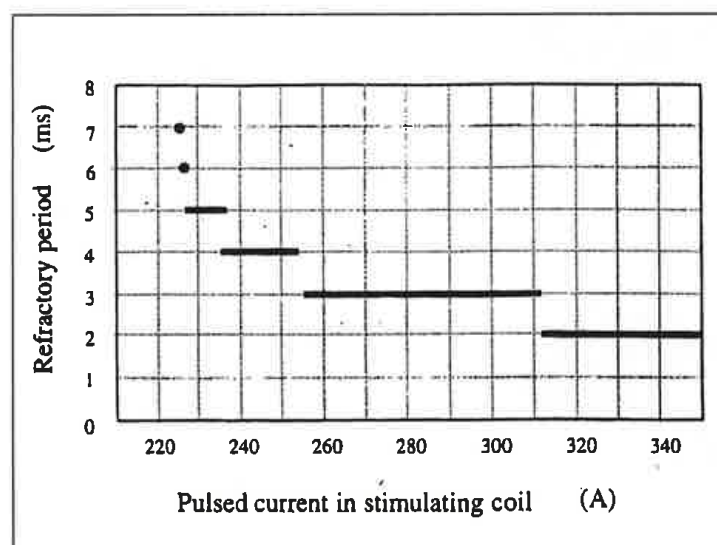


Fig. 4. Relationship between the refractory period in nerve excitation and pulse current flowing through a stimulating coil. The pulse duration is 100 μ sec.

In addition to repetitive stimulation, we also did a computer simulation to see how the threshold for nerve excitation and the refractory period changes when using train-pulsed nerve stimulation⁷⁾. The results show that the threshold for nerve excitation is reduced by previous stimulation and that the refractory period is reduced with the increase of stimulating current. As shown in Figure 4, the refractory period is inversely related to the stimulating current; i.e., the higher the current induced, the shorter the refractory period.

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Mapping the Cerebral Cortex

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Most mapping studies using transcranial magnetic stimulation (TMS) have been of the motor cortex although other areas can also be mapped. Direct stimulation of the motor cortex at neurosurgical operation shows extensive representation of each muscle with overlap of muscles within the same body part. This is compatible with the idea that the motor cortex is organized in terms of movements and not muscles. Nevertheless, since we do not have a good method for describing movements, we generally map muscles. Use of the figure-8 shaped coils gives the most accurate maps. The usual method is to use a standard stimulus magnitude and move the stimulator systematically over the scalp and measure the motor evoked potential (MEP) at each site. This will produce a map of MEPs with variable amplitudes, and typically the amplitude will be highest in the center of the map and taper off to the edges. The site of the maximal amplitude can be called the "optimal position."

When mapping muscles of the upper extremity at rest, stimulation of a similar area on the scalp will evoke MEPs in most upper extremity muscles (Fig. 1)¹⁾. Optimal scalp positions for stimulating distal arm muscles will tend to be more lateral than those for proximal muscles.

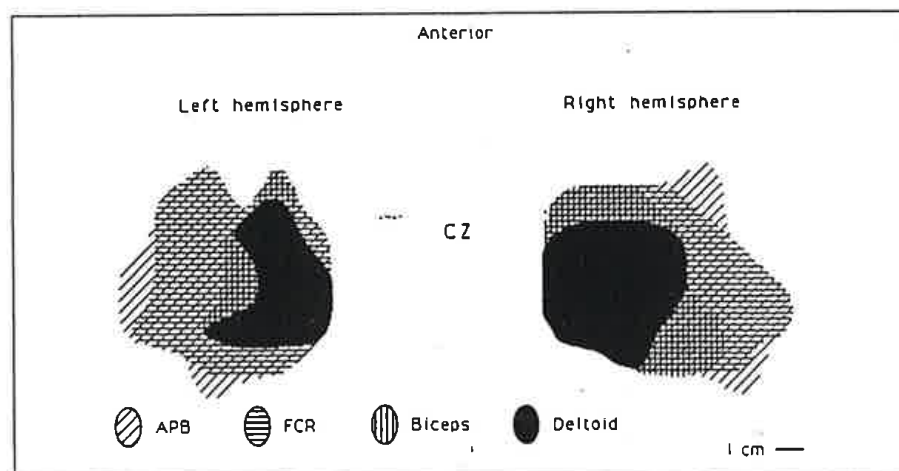
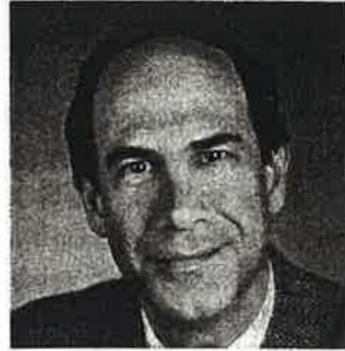


Fig. 1. Superimposed topographic plots of the excitable scalp areas for four upper extremity muscles from the two sides in one normal subject. Areas for different muscles overlap, but more distal muscles are more lateral. APB is abductor pollicis brevis and FCR is flexor carpi radialis. From 1).



Optimal scalp positions for stimulating leg muscles, on the other hand, will be distinct from those for stimulating arm muscles and will be closer to the midline. Latencies of MEPs vary according to the scalp locations stimulated²⁾. The longest latencies of MEPs are always evoked by stimulation of either the medial or the lateral border of the motor representation areas. The optimal direction of currents induced in the brain is approximately perpendicular to the central sulcus, flowing diagonally from back to front³⁾.

We have performed studies to see how accurately TMS would localize the motor cortex⁴⁾. After mapping each subject, we digitized the 3-dimensional locations of the magnetic stimulation positions and about 400 positions on the surface of the head. The amplitude-weighted center of gravity of each subject's map was found and a line perpendicular to the local head surface was projected inward. The digitized heads were registered with the subjects' MRIs using scalp contours. In all cases the magnetic stimulation lines encountered the surface of the brain at the anterior lip of the central sulcus. In other, unpublished studies (Cohen *et al.*), we have compared the location of the TMS optimal position with direct

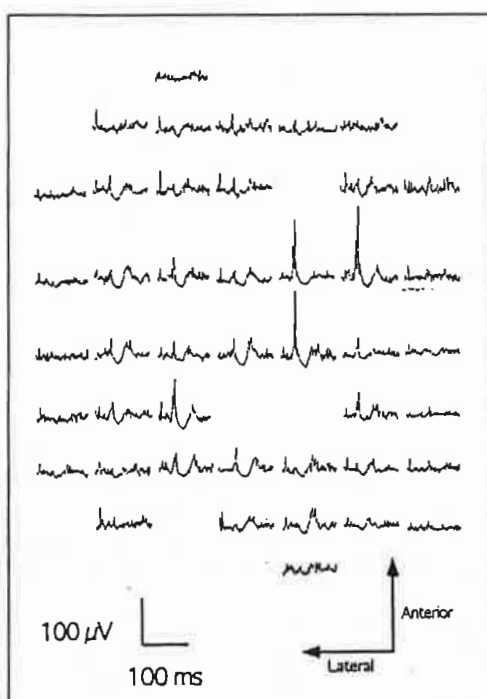


Fig. 2. Averaged EMG traces from 30 trials of stimulation at different scalp sites in one normal subject during voluntary activation of the contralateral abductor pollicis brevis. Traces are arranged in topographic order. Note more inhibition compared with excitation at the lateral sites. (From 5).

corticography in patients with subdural grid monitoring of epilepsy. Projection of the site of the TMS optimal position onto the cortex corresponded well with the best site for direct stimulation of the muscle.

We studied the excitatory (MEP) and inhibitory (silent period, SP) responses to focal TMS in the abductor pollicis longis (APB) of normal subjects to see whether the scalp topography of the two effects differed (Fig. 2)⁵⁾. On averaged trials, a stimulus intensity just above the threshold of the MEP at its optimal position produced MEPs followed by silent periods at a cluster of scalp locations 1 cm apart on the central scalp (medial area) and silent periods with very slight or no preceding facilitation in 3 to 9 locations lateral to the MEP area (lateral area). These maps also showed that MEPs from stimulation in the medial area occurred 4–6 ms earlier than in the lateral area. The ratio of the size of the silent period to the MEP tended to be larger in the lateral area.

In a recent study, we sought to determine whether MEPs as well as SPs could be produced in hand and shoulder muscles by TMS of the ipsilateral cerebral hemisphere and, if so, whether their cortical representations could be mapped with respect to those of contralateral muscles⁶⁾. In

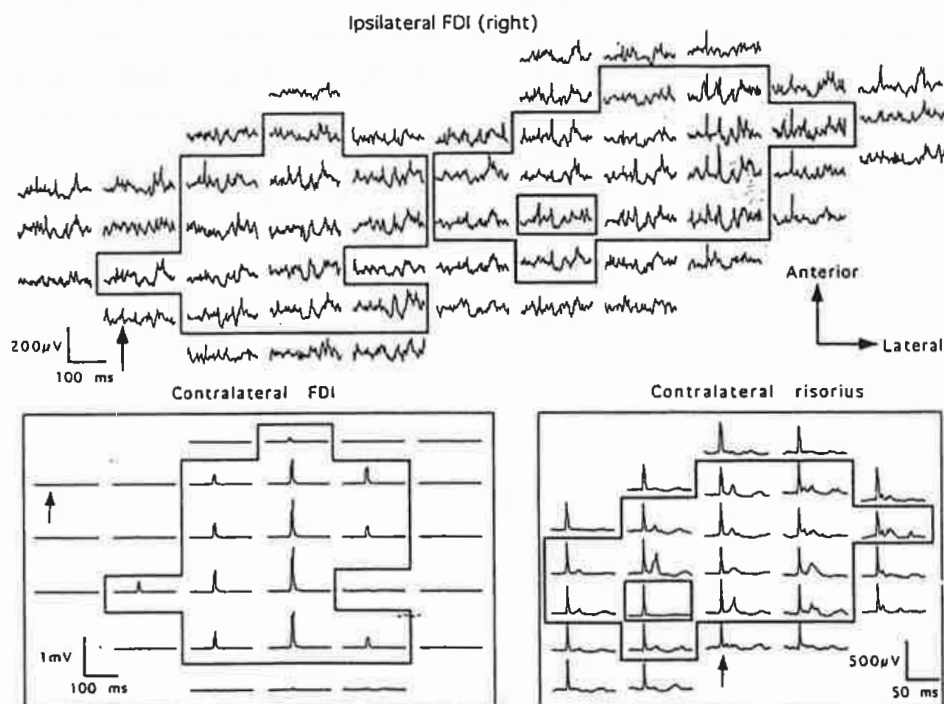


Fig. 3. Map of responses from the right first dorsal interosseus (FDI) (the ipsilateral hand) of a normal subject to TMS at sites 1 cm apart on the scalp over the right hemisphere. Traces are arranged in topographical order. Each trace is the average of ten trials of stimulation. Arrows indicate the time of delivery of the stimulus. Stippled areas indicate scalp positions where ipsilateral MEPs achieved statistical significance. Stippled and solid lines indicate areas where MEPs with an amplitude >25% of maximum were evoked in the contralateral hand (FDI) and face (risorius), respectively. Traces from the muscles in these areas are shown in the boxes. Note that the majority of the map of the ipsilateral FDI is co-localized with the map of the contralateral risorius. (From 6).

normal subjects, we delivered stimuli each to a grid of sites 1 cm apart on the scalp. The EMG was recorded and averaged from the contralateral first dorsal interosseous (FDI) and risorius (facial) muscles at rest and the ipsilateral FDI muscle, which was voluntarily contracted. All subjects had at least one scalp site where magnetic stimulation produced MEPs in the ipsilateral FDI. A few subjects had rich ipsilateral hand representations with multiple ipsilateral MEP sites. They had ipsilateral MEP sites near the representation of the contralateral FDI, but the largest ipsilateral MEPs occurred with magnetic stimulation at more lateral sites, which were near the representation of the contralateral risorius (Fig. 3). Ipsilateral magnetic stimulation also produced silent periods in the FDI in all subjects. These silent periods were much more frequent than the ipsilateral MEPs and tended to occur with stimulation near the representation of the contralateral FDI.

TMS mapping of the motor cortex can be used to study plasticity. One interesting example is what happens after hemispherectomy⁷⁾. TMS of the remaining hemisphere induced bilateral activation of arm muscles. Evaluation of MEPs indicated that muscles ipsilateral to the preserved hemisphere were activated by stimulation of scalp positions anterior and lateral to those activating homologous muscles on the normal side. These results indicate that ipsilateral and contralateral representations in the remaining hemisphere are topographically differentiated, with ipsilateral representations having a more anterior and lateral scalp distribution. The ipsilateral representation appears to be an enhancement of the normal, and ordinarily much smaller, representation.

Other brain areas can be mapped. Using repetitive TMS, reproducible speech arrest can be induced only by stimulation of infero-lateral posterior frontal areas of the left hemisphere (Broca's area)⁸⁾. TMS of the occipital cortex can block the detection of visual stimuli presented approximately 100 ms earlier⁹⁾. TMS of the sensorimotor cortex can occasionally trigger somatotopically organized paraesthesias. In addition, TMS of the sensorimotor cortex appropriately timed in relation to an electric stimulus to a finger of the contralateral hand can block the detection of the sensory stimulus¹⁰⁾. Amassian and colleagues demonstrated that single pulse TMS to the region of the SMA could cause sequence errors in a sequential finger tapping task¹¹⁾. Recently, we have done similar studies showing that TMS over the SMA region would interfere with the synchrony of bimanual movements¹²⁾.

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Facilitatory and Inhibitory Mechanisms of Brain Transcranial Stimulation in the Healthy and in Neurological Disorders

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Surface and depth (needle) recordings permit to analyse the firing probability of Motor Units after TransCranial Stimulation (TCS): in fact, TCS is modulating Motor Unit firing by inducing an initial increment (excitatory descending events = Motor Evoked Potentials = MEPs), and a successive decrement (inhibitory output = suppression of the evoked EMG burst = silent period, SP). Sometimes such an alternating effect triggered by the stimulus can be repeated for many hundred of milliseconds following individual TCS. Spinal as well as cortical structures are mutually involved in the regulation of these effects. It is worth mentioning that facilitatory and inhibitory mechanisms can be "modulated" both in the healthy and in different types of patients by incoming sensory signals. In fact, Mariorenzi *et al.* (1991) showed that a conditioning electrical pre-stimulation on the peripheral nerve is followed by two epochs of decreased cortical excitability (with Inter Stimulus Intervals -ISIs- of 16 and 34 ms, respectively) separated by an epoch of clearcut excitability increment between 22 and 30 ms. The peak of maximal facilitation was ascribed to the temporal coincidence between the arrival of the afferent volley to the contralateral sensorimotor cortex and the magnetic stimulus impinging upon it, lowering the excitability threshold of brain motor areas for MEPs elicitation (Fig. 1). Interestingly, such a period of facilitation is lost in parkinsonian patients who have depressed or absent pre-rolandic components of Somatosensory Evoked Potentials -SEPs- (Rossini *et al.* 1991a, see Fig. 2), suggesting that this method could be useful to study sensorimotor integration processing in selected patients. In parkinsonian subjects shorter than normal SPs have been described and related to the lack of voluntary input to the corticospinal system (Cantello *et al.* 1992). Abnormal excitability of the motor brain circuitries in parkinsonians has also been found by using a double stimulus: this showed a decrement of corticocortical inhibition at short (1-5 ms) ISIs (Ridding *et al.* 1995). Also, peripheral pre-stimulation paradigms have been used to record lower limbs MEPs in patients with myelopathy in which no responses in relaxation could be otherwise recorded, even following TCS at maximal intensity (Hayes *et al.* 1992).

On the other hand, in healthy subjects it is possible to evaluate cortical excitability changes to TCS while strongly reducing the sensory flow from the "target" body area. In this respect, we recently performed an



experimental study on healthy volunteers based on simultaneous anaesthetic block of median (sensory and motor) and radial (sensory) nervous fibers at wrist by injecting mepivacaine (10 ml at 0.5%) and recording from two ulnar-nerve supplied muscles of the hand: the First

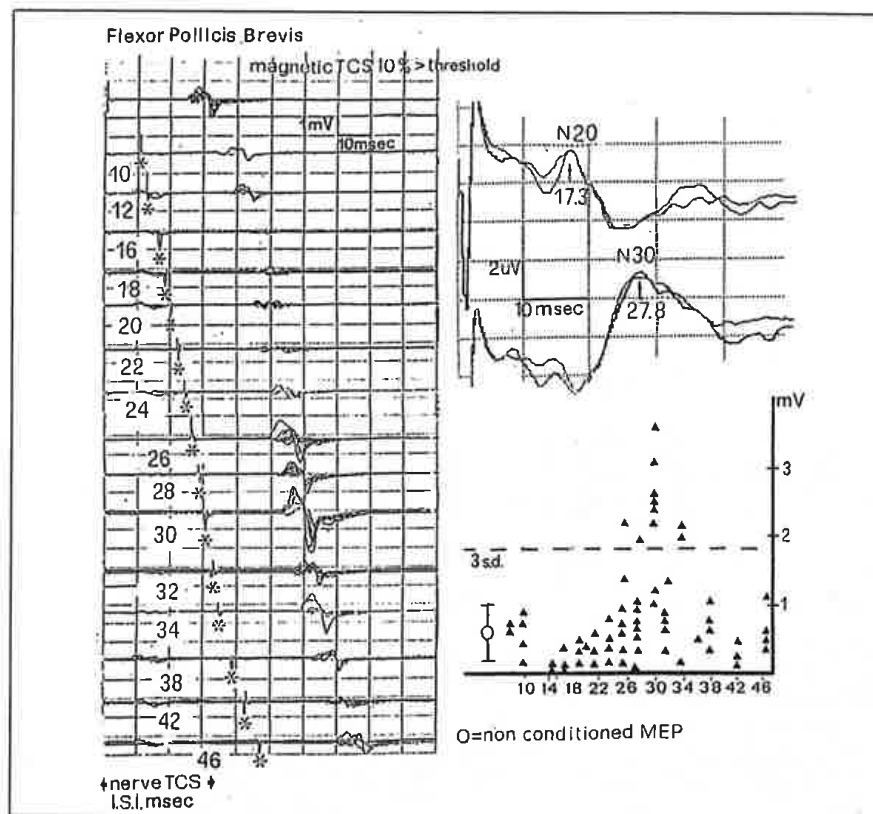


Fig. 1. Effect of a conditioning pre-stimulation (median nerve at the elbow) on MEPs amplitude recorded in full relaxation from Flexor Pollicis Brevis (each trace is the superimposition of 8 responses). Inter Stimulus Intervals (ISIs) between conditioning stimulus and TCS (=asterisks) are indicated by numbers in the left side. The first couple of traces -without conditioning- are randomly recorded intermingled with conditioned stimuli. In the diagram on the right, MEPs amplitude are plotted for each ISI; the dotted line indicates the maximal amplitude variability of non-conditioned MEPs. Traces on the right (top) are parietal (=N20) and frontal (=N30) median nerve SEPs. Note the clearcut initial period of inhibition, reaching the nadir at 16 msec, followed by a facilitation peak that is maximal at about 30 msec, when the N30 too is maximal (from Mariorenzi *et al.* 1991, with permission).

Interosseous Dorsalis muscle (FDI), which remained entirely “enveloped” inside the area of anaesthetised skin (=loss of cutaneous feed-back), and the Abductor Digiti Minimi muscle (ADM), whose cutaneous input was free of pharmacological block. Cortical representation of these muscle, as revealed by the average amplitude of MEPs gathered from each muscle following TCS on 10–12 scalp positions, showed different behaviour: ADM representation was increased (=MEPs of higher amplitude) and enlarged (Fig. 3), while FDI representation generally decreased (Fig. 4). Since no change following anaesthesia was observed in the cortical representation of the contralateral homologous muscles to the anaesthetised ones, it is reasonable explain such findings on the basis of “short-term” rearrangements of cortical motor output, probably linked with cortical disinhibition and/or to some mechanisms of “functional plasticity” (i.e., unmasking of pre-existing, functionally silent, synapses). It is worth mentioning another observation from the same experiment: the latency jump and amplitude potentiation when passing from relaxation to contraction was less evident in the FDI with respect to ADM. This supported the view that

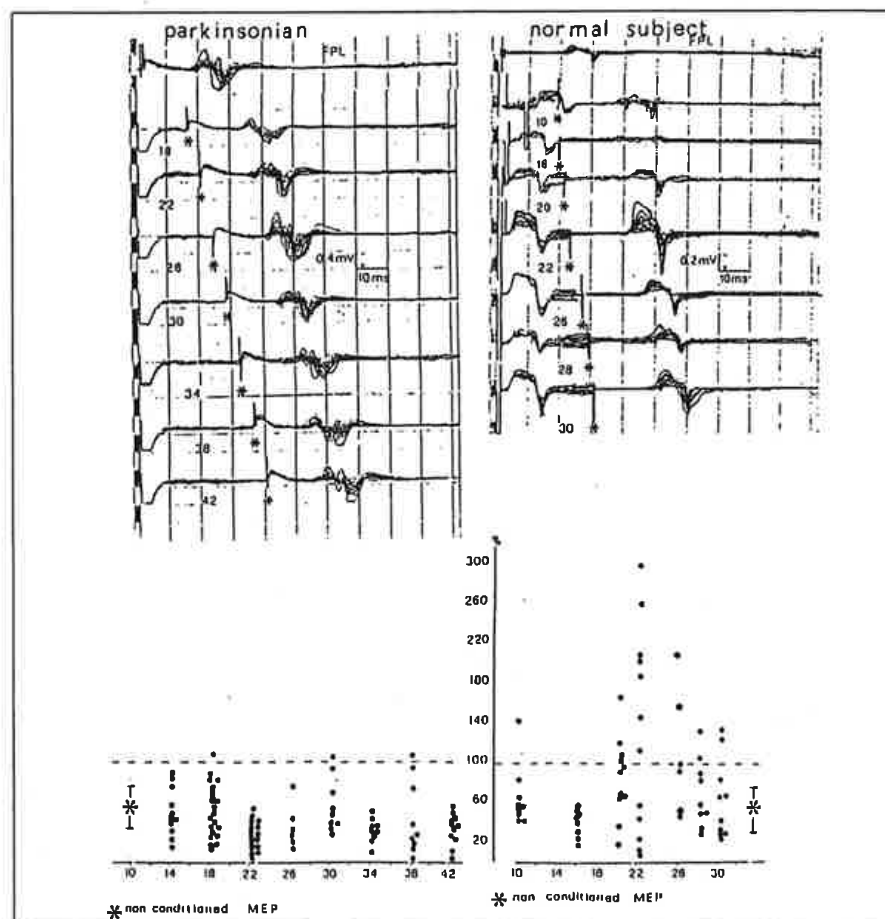


Fig. 2. MEP conditioning as in the previous figure in a 48-year-old male patient suffering of Parkinson's Disease and showing rigidity in his left hemibody (left column) compared to a normal subject. Notice the prolonged, poorly defined and smoothed conditioned curve which is neither as steep in onset and offset nor organised in a sink of depression and peak of facilitation as in the healthy (cfr. also previous figure). (from Rossini *et al.* 1991a).

Abductor Digiti Minimi muscle (ADM)

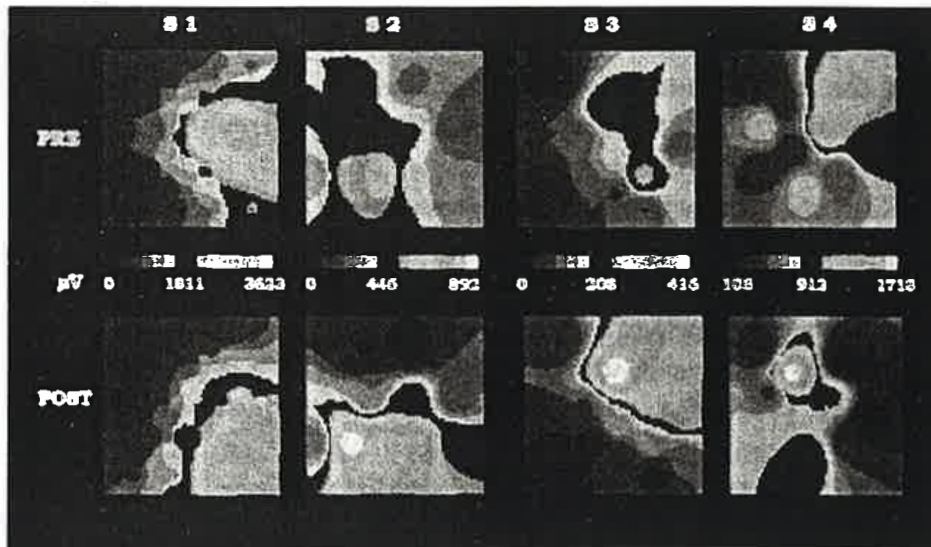


Fig. 3. Motor maps of the cortical representation of right ADM muscle in the left hemisphere of four subjects (S1, S2, S3, S4) before (upper line) and after (lower line) simultaneous anaesthetic block of median and radial nerves at wrist. For each of the scalp positions stimulated, spaced about 10 mm, 6–8 MEPs were gathered; the average value of these responses was assigned to each position for computing the map. In the original maps, amplitude values were represented in 16 colour gradation and computed through a cubic interpolation algorithm. Each vertical couple of maps is shown with the same scale (in the middle). Note that post-anaesthesia amplitude values are higher and scalp topography is generally enlarged. Shifts in maximal sites cortical representation can be appreciated.

First Dorsal Interosseous muscle (FDI)

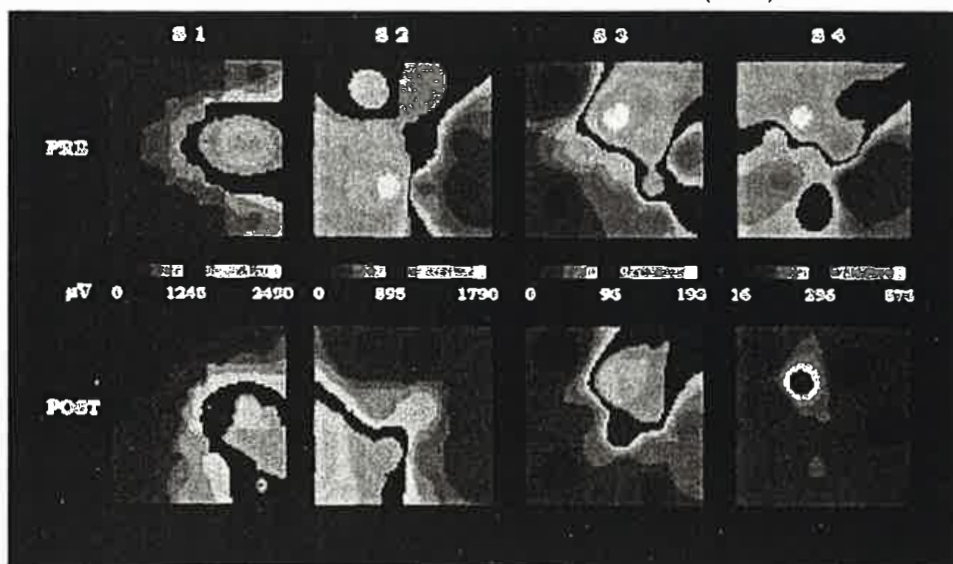


Fig. 4. Same organisation, subjects and experimental sessions of Fig. 3. In this case, MEPs are gathered from the right FDI muscle, entirely covered by anaesthetised skin. Cortical representations of this muscle are generally restricted following anaesthesia, the maximal site of representation being unchanged despite a lowering of MEPs amplitude (=higher threshold).

“facilitation” of MEPs induced by active contraction is partly dependent upon the sensory feed-back from the moving part.

In the last years, and also due to the proven safety of the method, the attention of the Researchers has been devoted to magnetic TCS in epilepsy: it was demonstrated that the cortical excitability threshold (as defined according to standard guidelines, Rossini *et al.* 1994) is usually enhanced by AntiEpileptic Drugs (AED) administration (Hufnagel *et al.* 1990). Reutens *et al.* (1993) confirmed these findings in patients with progressive myoclonic epilepsy (in whom giant short-latency SEPs are usually recorded), moreover describing an exaggeration of the peak of TCS facilitation induced by the pre-stimulation of the median nerve. More recently, Caramia *et al.* (1995) studied two groups of patients suffering respectively from Juvenile Myoclonic Epilepsy (JME) and Gran Mal (GM) seizures. In the attempt to identify some difference in excitatory and inhibitory patterns of the brain excitability, a neurophysiological examination was made combining threshold measurements using individual stimuli with a protocol employing paired stimuli (= conditioning subthreshold + test-suprathreshold). In JME patients undergoing AED administration, threshold values were higher than in non-treated subjects, furthermore, unlike normal controls, MEPs inhibition was greatly diminished during paired shocks stimulation. In these patients, a cascade of consecutive stimuli (up to 50) was able to increase MEPs amplitude in spite of the “physiological” decremental trend previously observed in normal subjects (Rossini *et al.* 1991b) and ascribed to a progressive increase of cortical inhibition possibly due to self-protection mechanisms –evidently lost in JME patients– against overstimulation. In the two cases with GM seizures the recovery cycle matched that of the controls in the range of 1 to 4 ms. The authors (Caramia *et al.* 1995) suggest that the pattern of cortical inhibition, as investigated with the paired stimuli protocol, could be related to GABA influences on neuronal firing level (Kujirai *et al.* 1993), probably –as known from experimental studies– by hyperpolarization mechanisms at postsynaptic cell membrane level by increasing the conductance of the Cl^- ions. As recently confirmed by Macdonnel and Donnan (1995) on a series of paraplegic patients suffering from spinal cord traumatic lesions and assuming Baclofen (a potent GABA agonist acting at spinal level reducing anterior horn excitability) the evaluation of changes in motor excitability threshold to TCS should be always take into account the concomitant pharmacological therapy.

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Flow of Symbolic Visual Information from Retina to Vocalization

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We attempted to track the flow of symbolic visual information (letters or a digit) from retina to voice production using magnetic coil (MC) stimulation. In an alert individual, the latency to initial vocalization of a visually presented symbol is about 350 ms. This time can be divided into the following intervals: Retina to calcarine cortex and relay from calcarine cortex; arrival of visual representation in frontal lobe; time required for coding of visual representation of symbol into appropriate motor output for language; frontal lobe activation of laryngeal EMG; time for initiation of voice by laryngeal EMG. Each interval was investigated. Finally, the question as to whether calcarine cortex can be bypassed in a visual reaction time task (e.g. Blind Sight) was addressed.

Retina to Calcarine Cortex and Relay from Calcarine Cortex:

MC (Round coil 9.4 cm O.D.) stimulation of occipital cortex was tested on perception of 3 briefly presented randomly generated alphabetical characters. MC stimuli were delivered up to 200 ms after the letters were presented at 20 ms intervals. When the visual stimulus-MC interval was less than 60 ms or more than 120 ms, letters were correctly reported; at test intervals of 80 and 100 ms, a blur or nothing was seen. At a test interval of 100 ms, moving the MC to the right over the occiput resulted in reporting of only the letter furthest to the right and vice versa which is consistent with the topographical representation in visual cortex but incompatible with an affect on attention or suppression from an eyeblink. The MC pulse probably acts by eliciting IPSPs in visual cortex. This data suggests that in this task the visual information arrives in calcarine cortex by 60 ms which is consistent with VEP data and that the last bit of the information required for visual recognition is relayed from calcarine cortex by 120 ms.

Arrival of Visual Representation of Symbol in Frontal Cortex:

Vocal responses of perceived digits and EMGs from external laryngeal or lower facial muscles were recorded on multichannel tape. An oval MC (5.5×6.0 cm) delivered individual pulses over frontal cortex; the MC windings lay variously over Broca's area, dorsal pre-motor cortex and part of the precentral gyrus. The MC stimulus intensity was adjusted just above threshold laryngeal response when the digit was flashed 60 ms earlier, at which interval the visual input could not yet have arrived in frontal



cortex, thus controlling for any non-specific facilitating effect on the response to the MC stimulus. Laryngeal EMG latencies were 11.5–13.5 ms. An increase in the amplitude of the laryngeal and facial EMGs was usually first detected when the MC pulse was delivered 120–140 ms after the visual stimulus. The latency of the facilitated response was reduced by approximately 2 ms. The initiation of the facilitated response at 120–140 ms implies that the initial portion of the visual representation of the digit arrives in frontal cortex at this time.

The short time elapsing between the relay of the visual information from calcarine cortex and its arrival in frontal cortex as indicated by the minimum delay for facilitation of the laryngeal EMG by MC stimulation of frontal lobe suggests the visual output goes directly to the frontal lobe rather than taking the traditional route through Wernicke's area. A direct route to frontal lobe has also been implied by recent PET data (Posner *et al.* 1988). However, these findings do not exclude a steady state influence of Wernicke's area and parietal areas on frontal lobe as is implied by the severe impact on language receptive functions of a lesion in these areas.

Frontal Lobe Activation of Laryngeal EMG:

Edge stimulation was used from a round MC (9.4 cm O.D.) which was tilted antero-medially over frontal lobe to direct magnetic flux away from temporalis muscle. A microphone recorded the voice and the sound of the subject's enunciation of an alphabetic letter was used to trigger the MC pulse. Laryngeal EMG was recorded using surface electrodes. Triggering the MC pulse by vocal activity which produced laryngeal EMG greatly increased the amplitude of the laryngeal CMAPs elicited by MC stimulation.

With voice triggering, CMAPs of 6–8 ms latency were elicited upon MC stimulation of motor cortex. This latency was greater than minimum peripheral motor conduction time to the extrinsic laryngeal muscles which was only 1.6–2.0 ms. CMAPs with latencies of 13–20 ms were elicited with MC stimulation of the lateral extremity of the precentral gyrus, more anteriorly from presumed Broca's area, and very medially from presumed supplementary motor area. Thus transit time from frontal cortex to laryngeal EMG was 6–20 ms, depending on the area of frontal lobe

stimulated. The inclusion of the lateral extremity of the precentral gyrus with other "higher level" speech motor areas rather than with motor cortex is consistent with the observation that this portion of the precentral gyrus cytoarchitecturally resembles area 6 rather than area 4.

Laryngeal Activation of Voice:

The laryngeal EMG typically preceded the beginning of vocalization by about 80 ms.

Conclusion:

The 350 ms delay for vocalizing the visual presentation of a digit includes the retinal-calcarine cortex transfer time (60 ms), relay of the symbolic representation out of calcarine cortex (120 ms), its arrival in and facilitation of frontal cortex (120–140 ms), frontal lobe activation of laryngeal EMG (6–20 ms) and initiation of voice (80 ms). There remains about 125 ms [$350 - (130 + 15 + 80)$] for the visual representation in frontal cortex to be coded into appropriate motor output for language. The data suggests that a more direct calcarine-frontal pathway exists than the traditional pathway which tranverses angular gyrus and Wernicke's area.

Bypassing of Calcarine Cortex in a Visual Reaction Time Task (Blind Sight):

The hypothesis that calcarine cortex can be bypassed in a visual reaction time task was tested. Alert subjects responded as quickly as possible only with a noise (grunt) when brightly illuminated words or pictures were flashed. Abdominal EMGs were recorded with disc electrodes. In 5 subjects, mean latencies of the noise expiratory EMGs were 105 ms. In 4 subjects the continuous distribution of EMG latencies included responses in the 80–90 ms range. Such latencies are too brief to be explained by the sum of the estimated *minimum* transmission delays including retina to calcarine cortex (60 ms), calcarine cortex to motor cortex (5 ms), motor cortex to abdominal EMG (20 ms) plus cortical relays within calcarine cortex (5 ms) and motor cortex (5 ms) totalling *at least* 90 ms.

Additionally when calcarine cortex was stimulated with a MC 90 ms after the visual stimulus was presented, e.g. at a time optimal for visual perceptual suppression, the subjects were uncertain that a visual stimulus had been presented even though their EMG latencies and voice latencies were appropriate.

We conclude that calcarine cortex can be bypassed in a visual reaction time task (e.g. "Blind Sight") but not when a language symbol is consciously identified and vocalized.

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Motor Reorganization in Central and Peripheral Nervous System Diseases

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Neural plasticity within the human central motor system has been studied with transcranial magnetic stimulation in patients with peripheral and central nervous system disorders.

I. The Site of Action of Transcranial Magnetic Stimulation¹⁾

The exact site of activation of human motor evoked potentials (MEPs) by cortical magnetic stimulation has not been determined. Day *et al.*²⁾ reported that a few interneurons connected to pyramidal cells were the site of activation by cortical magnetic stimulation.

We studied a patient with motor neuron disease in whom a few remaining motor units in small hand muscles could be evoked by magnetic stimulation^{3, 4, 5, 6)} using a twin coil^{7, 8)}. Central motor conduction time was within normal limits. Cortical mapping of the motor evoked potentials was carried out stimulating the motor cortex transcranially at intervals of 1 cm along the coronal axis and 1–2 cm along the sagittal axis using a twin magnetic coil. As the site of cortical stimulation was moved from the center, the latency of the MEPs increased by 0.7–0.8 ms suggesting one synaptic delay. This study provides further data that magnetic stimulation of the human cortex indirectly activates pyramidal cells via interneurons (Fig. 1, 2).

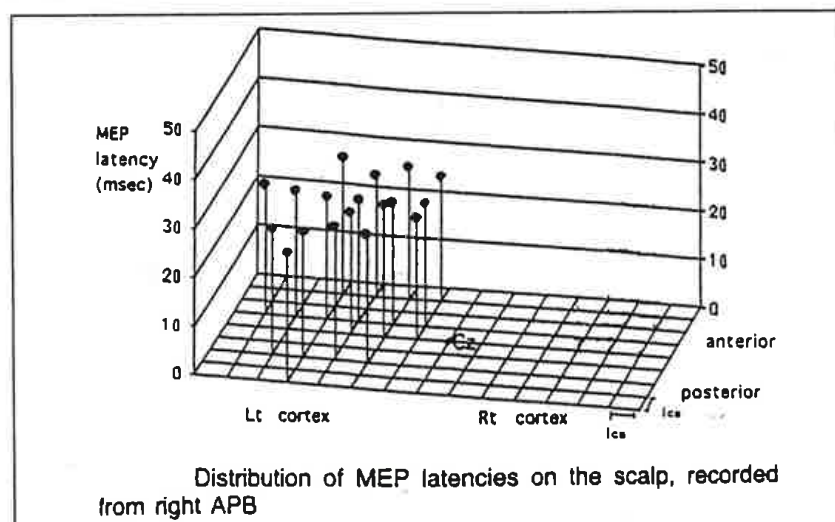


Fig. 1. Distribution of the motor evoked potential (MEP) latencies on the scalp, recorded from the right abductor pollicis brevis muscle.

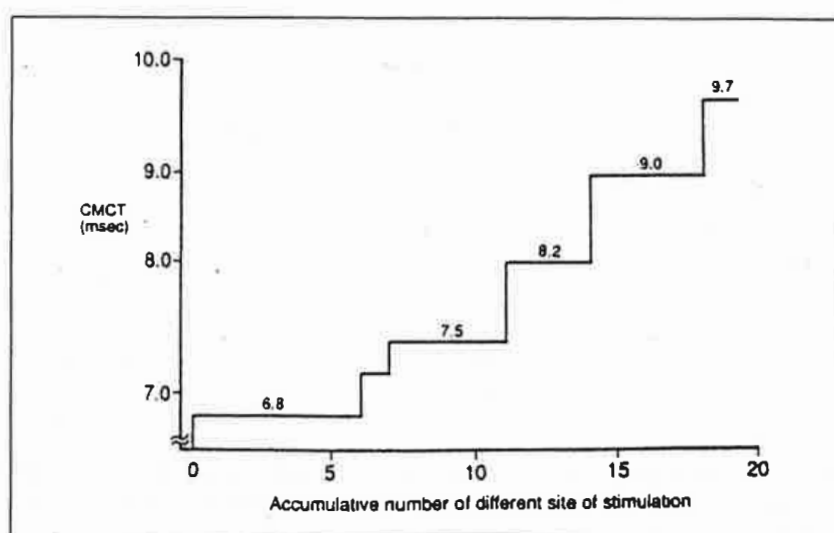


Fig. 2. Central motor conduction times (CMCTs) recorded from the right abductor pollicis brevis muscle stimulating the left cranium at different sites.

II. Motor Reorganization after Peripheral Nerve Injury⁶⁾

Paralysis of an upper extremity due to traumatic cervical root avulsion is usually permanent, since there is minimal root regeneration. Many operative procedures, including nerve grafts, have been tried in the past with limited success. Anastomosis of intercostal nerves with the musculocutaneous nerve has been performed and reported to be one of the most successful methods in restoring function in the biceps brachii muscle^{9, 10)}.

In a study of 4 patients with a complete upper limb palsy due to traumatic cervical root avulsion, surgical anastomosis of intercostal to musculocutaneous nerves was performed to restore function in the biceps brachii muscle⁶⁾. Four to 6 months after the operation, motor unit discharges were recorded from the biceps brachii muscle on the operated side during deep breathing and by cortical magnetic stimulation. The motor unit discharges became independent from respirations gradually over 1 to 2 years. The latencies of the motor potentials evoked by cortical and thoracic root magnetic stimulation decreased gradually over 2 to 3 years, although cortical conduction time changed minimally. Motor cortex mapping of the reinnervated biceps muscle showed a gradual change over 4 to 33 months from the area of the intercostal muscles to that of the arm

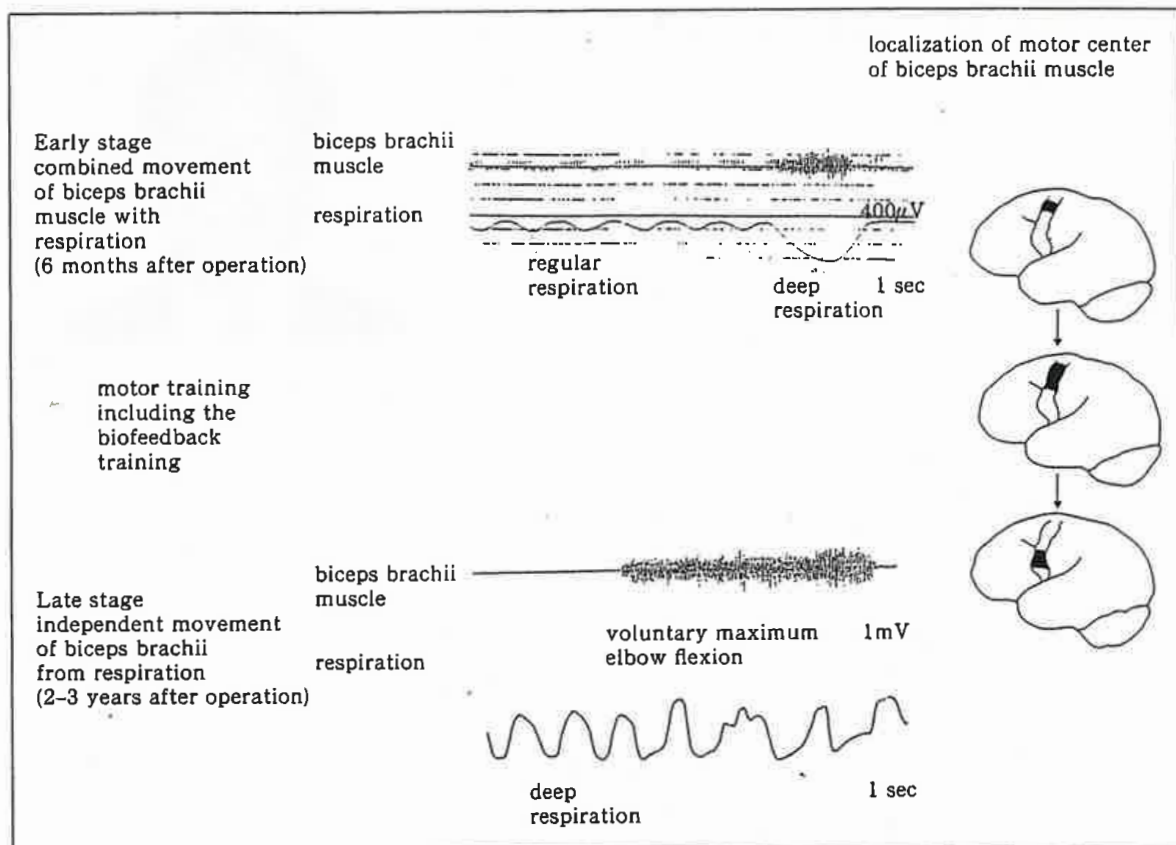


Fig. 3. The relationship between motor unit discharges of the biceps brachii muscle and respirations and the localization of the motor center of the biceps brachii muscle are shown in the early and late stages after nerve anastomosis of intercostal and musculocutaneous nerves.

area, which was more lateral on the motor cortex (Fig. 3). These findings suggest that reorganization of the motor cortex can occur following peripheral nerve anastomosis.

The age of the patient at the time of the neural damage is important in regard to the ability of the nervous system to regenerate or alter its function¹¹⁾. Following peripheral nerve anastomosis, the successful cases usually occurred in patients who were less than 25 years of age at the time of the injury and the unsuccessful cases occurred in patients over 40 years of age.

The prolonged latency of the MEPs recorded from the reinnervated biceps muscle gradually became shorter over 20 to 30 months due to peripheral nerve regeneration, and there was little change in central motor conduction time. With transcranial magnetic stimulation, the site that is most excitable and produces the largest MEP is thought to be the cortical area of that muscle. After the intercostal nerves were anastomosed to the musculocutaneous nerve innervating the biceps brachii muscle, the cortical motor area of the biceps was located in the area of the intercostal muscles. After time for nerve regeneration and reinnervation of the muscle, biofeedback training, and voluntary control of flexion of the elbow, the excitable area of the biceps motor cortex moved laterally towards the cortical area of the arm segment of the upper limb. This sug-

gests that there was reorganization of the cortical motor area that projects to the arm flexor muscles. Initially the excitable area was enlarged as reported in previous studies of cortical motor reorganization^{12, 13}. The excitable area of the motor cortex to the biceps muscle became localized at the time when the patients developed the ability to flex the elbow and control elbow flexion without respirations.

III. Motor Reorganization following Upper Motor Neuron Lesions

In contrast to the motor reorganization after lower motor neuron lesions, motor reorganization following upper motor neuron lesions is more complex. Neurologic sequence after a lesion of the central nervous system (CNS) are not only due to the central reorganization but also reflect the effects of the lesion, its location as well as its recovery.

In 8 patients with chronic cerebral infarction with hemiplegia, localized cortical magnetic stimulation was carried out. Four of 8 patients did not show MEPs in the paralytic hand muscles using contralateral cortical stimulation, but did show small MEPs with ipsilateral cortical stimulation. These cases had large cortical infarctions unilaterally by CT scans. The other four patients showed small MEPs in the paralytic hand muscles with contralateral cortical stimulation. They had subcortical infarction unilaterally on CT scans. These findings suggest that there was reorganization of the motor cortex following unilateral cerebral infarction (Fig. 4).

In three out of four patients with severe hemiplegia due to intracerebral hemorrhage involving the subcortical area, the magnetic cortical stimulation of the involved motor cortex did not evoke a MEP from the contralateral paralytic hand muscles. In two of the patients stimulation of

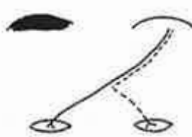
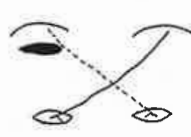
Chronic Cerebral Infarction						
involved site of brain	cortex		subcortex I		subcortex II	
cortex stimulation	involved hemisphere	non-involved hemisphere	involved hemisphere	non-involved hemisphere	involved hemisphere	non-involved hemisphere
						
MEP recordings from hand muscle (ADM)	non-paralytic muscle	paralytic muscle	non-paralytic muscle	paralytic muscle	non-paralytic muscle	paralytic muscle
MEP latency	normal	prolonged	normal	normal~prolonged	normal	normal~prolonged
MEP amplitude	normal	low	normal	low	normal	low
threshold	normal	high	normal	high	normal	high

Fig. 4. The relationship between motor evoked potentials (MEPs) from hand muscles by cortical stimulation and the sites of the brain lesion in chronic cerebral infarction with severe hemiplegia.

Table 1. MEP recordings from paralytic hand muscles in patients with intracerebral hemorrhage

case	age	lesions	approach of operation	transcranial MEP stimulation	
				involved cortex	contralateral cortex
NA	48	lt subcortex	frontal	absent	absent
KI	54	lt subcortex	frontal	absent	26.4 msec (70 μ V) (with effort)
WK	70	rt subcortex	frontal	absent	22.6 msec (60 μ V)
MK	42	rt subcortex	frontal	19.6 msec (10 μ V)	absent

Motor evoked potentials (MEPs) from hand muscles by cortical stimulation in patients with residual hemiplegia following the subcortical hemorrhage and surgical removal of hematoma frontally.

the non-involved cortex evoked a MEP from the ipsilateral paralytic hand muscles. These patients had an operation to remove the hematoma by the frontal approach (Table 1).

Although chronic lesions of the motor subcortex due to cerebral infarction or by cerebral hemorrhage were very similar in location, the motor reorganization was different. One reason for this might be due to the marked compression of the brain by the hematoma in the acute stage of the cerebral hemorrhage. The anterior area of the primary motor cortex has a very important role in recovery of motor functions especially the pre-motor, supplementary motor and prefrontal cortex. Although we don't know the effects of the operative procedure via the frontal approach, it may have some effect on CNS plasticity. The studies using magnetic stimulation show that motor center of the cortical area can change following lesions of the peripheral or central nervous system. This can happen in the ipsilateral or contralateral hemispheres and in the brainstem and spinal cord.

Some of these changes in motor reorganization^{6, 14, 15)} may be due to unmasking of preexisting connections in the nervous system, but it is likely that new neural connections are established during long-term recovery.

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Motor Evoked Potentials — Neurophysiological Correlates of Clinical Signs and Symptoms

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From the early clinical studies examining central pathways by means of transcutaneous magnetic stimulation of the motor cortex, it has been clear that correlations between clinical and neurophysiological findings have been less than satisfactory. Certainly, motor evoked potentials (MEPs) are rarely entirely normal when recorded from a paretic limb, and equally it is unusual to find any abnormality among the various neurophysiological indices studied in a limb that is clinically entirely normal¹⁾. In between, there is a grey area with some "false positives" (subclinical abnormalities) and more false negatives. The reasons for these discrepancies are straightforward and they explain why the clinical diagnostic role of magnetic stimulation is likely to be restricted and its chief value as a technique for enhancing our understanding and stimulating our thoughts about central motor processes and their clinical expressions²⁾.

Neurologists are good at the clinical examination of central motor pathways and objective evidence of dysfunction is much easier to come by than in the case of sensory pathways. There are a multiplicity of clinical signs including weakness, hyperreflexia and spasticity. Few if any of these signs are specific to a single disease entity or even a single pathophysiological process. Similarly, the various neurophysiological indices which can be studied during clinical studies with magnetic stimulation of the cortex, including central motor conduction time, MEP amplitude, onset variability and stimulus intensity threshold may all be affected by a variety of processes, including neuronal or axonal degeneration, demyelination and inhibition³⁾. However, it has become clear that some clinical signs correlate better with certain MEP abnormalities than others and this information can be of real clinical value. It should be noted that clinical / neurophysiological correlations vary somewhat between distal and proximal muscles, upper and lower limbs. In particular, the largest responses with the lowest thresholds tend to occur in the muscles of the hand and forearm; this preferential innervation reflects pyramidal tract projections with monosynaptic connection between the corticospinal tracts and spinal motor neurones.



index studied clinically. In an early report, recording from Abductor Digiti Minimi (ADM) in patients with multiple sclerosis, CMCT was prolonged in three-quarters of sides where ADM was weak and in half where ADM was clinically normal¹⁾. The strongest clinical correlate to CMCT prolongation was exaggeration of the finger flexor jerks. Conversely that study showed normal CMCT in almost a third of arms where there were abnormal neurophysiological signs. Another multiple sclerosis study demonstrated CMCT prolongation in half of 80 upper limb muscles examined, whereas maximal isometric strength was reduced in only two of these⁴⁾. There was poor correlation between tendon reflexes and CMCT here. Interestingly, there is a high correlation between absolute latency and CMCT to leg muscles and extensor plantar responses⁴⁾. A further multiple sclerosis study where patients had either normal strength or minimal weakness of small hand muscles, demonstrated a strong inverse correlation between central motor conduction time and voluntary phasic force in the tested muscle⁵⁾. The authors pointed out that conventional clinical examination assesses tonic muscle contraction strength rather than phasic muscle strength. Like Hess *et al.*, they correlated CMCT with tests of manual dexterity.

MEP onset latency may be abnormally variable in disease states; Britton *et al.* demonstrated increased variability in half of 40 hand muscles in patients with multiple sclerosis — in 3 this was the only neurophysiological abnormality⁶⁾. Abnormal onset latency variability associated with both impaired fine finger movements and increased finger jerks, whereas abnormal CMCT in these cases was associated with increased finger jerks only.

MEP amplitude is more problematic as a neurophysiological index and is best expressed as a percentage of the response to distal stimulation rather than in absolute terms. Abnormalities of amplitude tend to be more of a feature of neuronal degeneration than of demyelination but clinical correlations are generally similar. Thus, hyperreflexia and weakness in ALS associate with absent or low amplitude of MEPs to brain stimulation — these small responses may be of either normal or prolonged latency^{7, 8)}.

The stimulus threshold intensity necessary to evoke a minimal MEP may be pathologically elevated. Caramia and co-workers showed abnormal threshold in three-quarters of 49 patients with a variety of neurological disorders⁹⁾. Excluding ALS patients, there was a significant linear correlation between CMCT prolongation and increased threshold. While MEPs with prolonged CMCT had elevated thresholds, 14 patients showed increased threshold but normal CMCT. Spasticity and hyperreflexia associated more frequently with increased threshold than CMCT prolongation. Interestingly, early in the course of ALS cortical excitability may be increased and thus large MEPs (and even fasciculations) evoked by low intensity stimuli. Later on the threshold tends to increase, in fact more than in multiple sclerosis^{7, 9)}. In untreated epilepsy cortical thresholds are low, and this hyper-excitability is reversed by anticonvulsants¹⁰⁾.

The cortical silent period may be abnormal in diseases of central motor pathways. Whereas the onset latency of the silent period to brain stimulation correlates quite well with CMCT, its duration seems to be an independent and more sensitive index of pathology, at least where clinical abnormalities are minor¹¹⁾. A further, recently developed technique for assessing motor excitability is the use of paired stimulation to examine corticocortical inhibition. New techniques allow two magnetic stimuli of different intensities to be delivered through the same coil close together. In normals, a subthreshold conditioning stimulus suppresses EMG responses in hand muscles to a suprathreshold test stimulus at inter-stimulus intervals of 1–7ms, perhaps due to activation of an intracortical inhibitory mechanism. Whereas in generalised epilepsy there are comparable responses to stimulus pairs over both hemispheres, in patients with focal epilepsy, conditioned responses are larger after stimulation on the side of the epileptic focus than on the opposite side. These findings suggest a differential increase in cortical excitability or decrease in inhibition of the affected hemisphere in patients with focal epilepsy¹²⁾.

The phenomenon of muscle fatigue may be investigated by cortical stimulation, both in normal subjects and in patients with neurological disease. In normals, amplitudes of MEPs to trains of stimuli decrement after exercise and this decrement is maximal at 0.3Hz and correlates with the sensation of fatigue¹³⁾. Muscle fatigue is a common symptom of muscle sclerosis, and failure to transmit high frequency trains of impulses is a hall mark of demyelinated fibres. However, we have been unable to demonstrate abnormal MEPs to high frequency paired stimuli (2–20ms interval) in multiple sclerosis patients despite exercise provoking considerable central fatigue, and have thus been unable to confirm frequency-dependent block as the pathophysiological mechanism underlying fatigue in MS.

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Specificity and Sensitivity of Magnetic Stimulation Techniques in Neurological Disorders

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By its simplicity motor evoked potentials (MEP) have become a widely used diagnostic test to assess the pyramidal system in central nervous diseases. However, the diagnostic yield of MEPs in clinical practice is not always obvious. In multiple sclerosis (MS) and compressive cervical myelopathy (CM) a relatively high sensitivity of the MEPs was repeatedly reported (Hess *et al.* 1987, Brunhölzl *et al.* 1994, Ravnborg *et al.* 1992). Subclinical involvement of corticospinal tract has also been disclosed but is less frequent. Furthermore, specificity of MEPs seems low and it seems questionable whether the method helps to differentiate between these diseases.

Summarising some recent results of MEP studies in progress (Beer *et al.* 1995) on multiple sclerosis (MS) and compressive cervical myelopathy (CM), two questions are specifically addressed: 1. Can sensitivity and specificity be enhanced by taking several target muscles into account; 2. What is the true diagnostic yield of MEP.

Methods

MEPs were recorded bilaterally from Abductor digiti minimi muscle (ADM), Biceps brachii muscle (BB), and Tibialis anterior muscle (TA). To assess the central motor conduction, the peripheral conduction was estimated by using high voltage cervical root stimulation, and central motor conduction time (CMCT) was obtained by subtracting the peripheral conduction time from the corticomuscular latency. CMCT (beyond the mean ± 2.5 SD) and MEP amplitudes ($< 15\%$ / $< 6\%$ of the peripherally elicited CMAP) were compared with the normal value of our laboratory. Checkerboard VEP were performed and the latency of the P100 (VEP) component was compared with our normative data (P100 amplitude and latency beyond the mean ± 2.5 SD). CSF was evaluated for the presence of oligoclonal banding by silver staining after isoelectric focusing on polyacrylamide gel. Most cranial MRIs were performed using a 1.5 Tesla General Electric Scanner. In all studies, T1 and T2 weighted sequences were available, as well as axial, coronal, and sagittal slices.

Patients were recruited from a consecutively referred cohort of 200 patients with definite or suspected MS and 80 patients with clinical and imaging evidence of CM. MS patients were classified according to Poser's



criteria (Poser *et al.* 1983) and assigned into two groups: 1. Clinically or laboratory supported definite cases; 2. Suspected if they complied to "probable" or did not comply to the Poser criteria. A baseline classification according to the clinical data only was also defined in order to assess the reclassification rate for MEP, VEP, CSF testing, and MRI. CM patients were allocated according to the highest site of significant compression as viewed in the cervical MRI or myelogram into two groups: 1. Compressive lesion between C5 and C7 (CM C5-C7), or 2. between C1 and C4 level including the intervertebral disc C4/C5 (CM C1-C4).

Results

The sensitivity could be increased by 20% to 50% by recording from three as opposed to one target muscle. The TA was the most rewarding muscle, being particularly beneficial for suspected MS and in combination with ADM for CM (Fig. 1). The diagnostic yield of the three target muscles as opposed to ADM & TA was little (not statistically significant). In MS patients, a reclassification sensitivity by the MEP (3 target muscles) of 20% resulted as opposed to 30% of the visual evoked potentials or oligoclonal bands in CSF or 60% of MRI (Fig. 2).

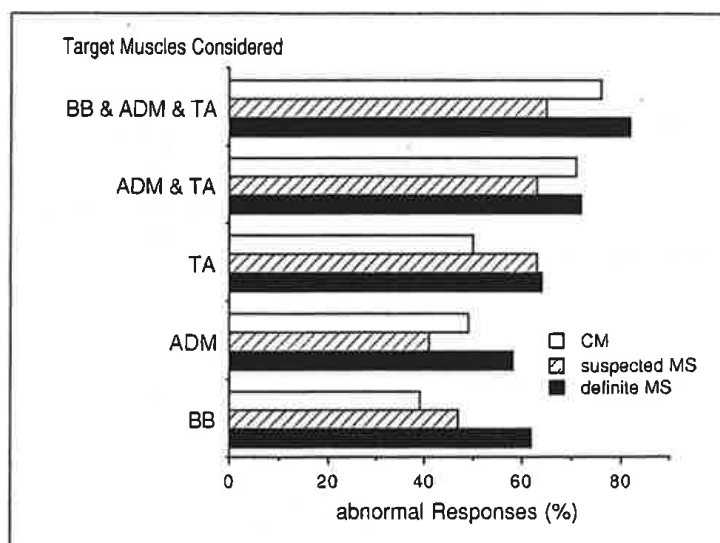


Fig. 1. Incidence of abnormal MEPs from target muscles BB, ADM, or TA taken alone or in combination in CM (n=71) and MS (n=100).

In CM C5–C8 the pattern of abnormal MEPs from ADM and normal MEPs from BB was observed in 33% as opposed to 10% in MS ($p < 0.01$) (Fig. 3). In CM C1–C4 this pattern was found in 19%. Abnormal MEPs from BB were significantly more frequent in MS as compared to CM ($p = 0.005$). The “reverse” pattern of abnormal BB-MEP and normal ADM-MEP was nevertheless found in 20% of CM C5–C8.

Discussion

As anticipated, the *sensitivity* of the method can be enhanced by recording from several target muscles. By taking three target muscles, the rate of MEP abnormality reached 60% to 80% in CM and MS, and TA proved particularly suitable target muscle with this respect (Fig. 1). However, the additional diagnostic yield by taking all three target muscles (BB, ADM, TA) as opposed to two (ADM, TA) was modest.

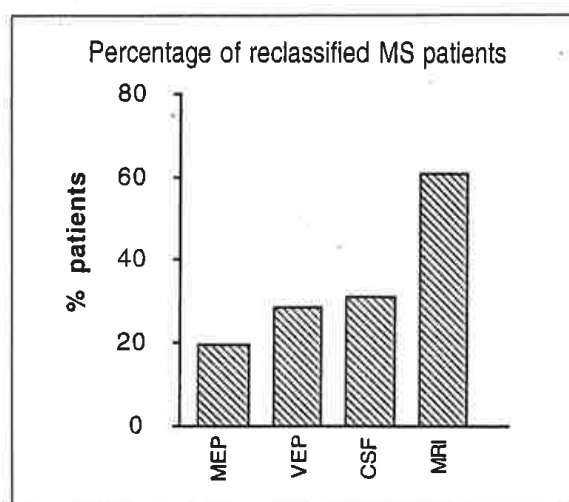


Fig. 2. Percentage of reclassified MS patients (one or more steps increased in the Poser criteria) by MEP, VEP, CSF (oligoclonal bands), or MRI ($n = 142$).

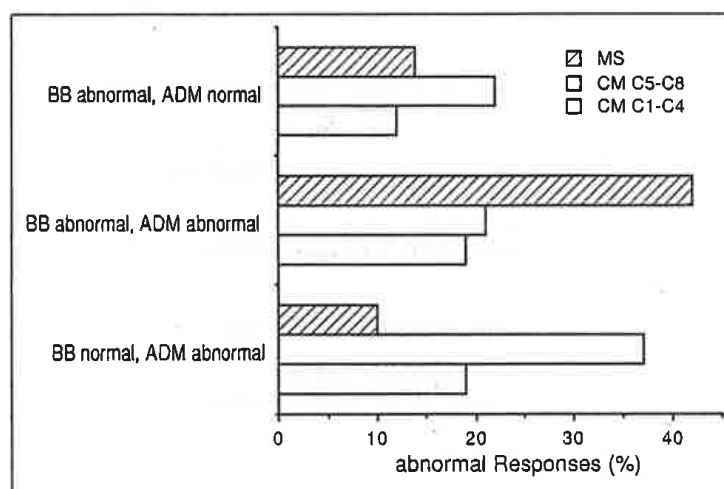


Fig. 3. Incidence of three patterns of MEP abnormality from target muscles BB and ADM in the three patient groups MS, cervical myelopathy of higher level (CM C1 – C4), and lower level (CM C5 – C8).

The great sensitivity of MEPs in definite MS being in close agreement with earlier reports is, however, not so relevant for the *diagnostic power* in patients with suspected MS. Furthermore, since MEPs tend to confirm clinical signs and rather infrequently disclose subclinical involvement, a high sensitivity does not imply an equally high diagnostic capacity. The percentage of patients who could be reclassified (diagnostic certainty increased) by an abnormal MEP was in fact clearly lower than percentage of patients with an abnormal MEP result and also underscored the reclassification rate of VEPs and CSF-testing (Fig. 2).

The idea of identifying specific patterns of MEP abnormality in CM depending on the site of cord compression, when taking target muscles supplied by motor roots of distinct segmental levels, seemed attractive (Tavy *et al.* 1994). Recording from the two upper limb muscles BB and ADM could, in fact, to some extent increase the *specificity* to differentiate between lower level (C5–C8) and higher level (C1–C4) CM on one hand, and between CM and MS on the other hand. The pattern of normal MEPs to BB and abnormal MEPs to ADM was most frequently encountered in CM C5–C8, and the pattern of abnormal MEPs to both BB as well as ADM proved typical of MS (Fig. 3). However, in the individual patient one cannot rely on the pattern of MEP abnormality, since misleading patterns were also encountered in a considerable number of patients. For instance, the lower level CM pattern of normal MEPs to BB and abnormal MEPs to ADM was found in almost 20% of CM C1–C4, and even the “reverse” pattern of abnormal MEPs to BB and normal MEPs to ADM was found in about 20% of CM C5–C8 (Fig. 3).

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