ABSTRACT: Since 1985, when the technique of transcranial magnetic stimulation (TMS) was first developed, a wide range of applications in healthy and diseased subjects has been described. Comprehension of the physiological basis of motor control and cortical function has been improved. Modifications of the basic technique of measuring central motor conduction time (CMCT) have included measurement of the cortical silent period, paired stimulation in a conditioning test paradigm, repetitive transcranial magnetic stimulation (rTMS), and peristimulus time histograms (PSTH). These methods allow dissection of central motor excitatory versus inhibitory interplay on the cortical motor neuron and its presynaptic connections at the spinal cord, and have proven to be powerful investigational techniques. TMS can be used to assess upper and lower motor neuron dysfunction, monitor the effects of many pharmacological agents, predict stroke outcome, document the plasticity of the motor system, and assess its maturation and the effects of aging, as well as perform intraoperative monitoring. The recent use of rTMS in the treatment of depression and movement disorders is novel, and opens the way for other potential therapeutic applications.

MAGNETIC STIMULATION OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

MARKUS WEBER, MD,1 and ANDREW A. EISEN, MD, FRCP(C)2

1 Department of Neurology, Kantonsspital, CH-9007 St. Gallen, Switzerland
2 Neuromuscular Diseases Unit, Vancouver General Hospital, Vancouver, British Columbia, Canada

Early experiments in humans used high-voltage, short-duration electrical stimulation applied to the scalp overlying the motor cortex, a rather uncomfortable procedure and inappropriate for routine clinical use. In 1985, Barker and colleagues5 introduced the technique of transcranial magnetic stimulation (TMS) which led to a new era of research in motor control and cortical function. Since that time, interest in TMS has steadily increased and a vast literature has already accumulated.

This minimonograph considers current concepts of the anatomical and physiological basis of TMS, discusses methodological aspects, reviews the different techniques and measurements in use, and critically analyzes its utility in clinical practice and basic neuroscience.

ANATOMY AND PHYSIOLOGY OF THE CORTICAL MOTOR NEURONAL SYSTEM

Motor function in humans is subserved by several distinct yet interconnected anatomical regions. They include the primary motor cortex, also known as Brodmann area 4, the premotor areas and supplementary motor cortex, basal ganglia, thalamus, cerebellum, brain stem, and reticular formation. The primary motor cortex is different from other regions of the cerebral cortex in that it is thicker but has a lower cell density. The main output cells are the large pyramidal cells in lamina V and smaller cells in lamina III. Their dendrites show a preferential orientation parallel to the main axis of the precentral gyrus.

The spinal motoneurons (SMNs) of the cord are the “final common pathway” of the motor system to which the higher centers and pyramidal cells make...
direct or, more commonly, indirect connections via multiple descending tracts. In non-human primates and other mammals, these descending tracts converge on the spinal motoneuron. In humans, the sophistication and complexity of motor control, particularly in the face and distal aspects of the limbs, has largely sacrificed many of these indirect tracts with the expansion of the cortical motor neuronal (CM) system. This CM system originates from large pyramidal cells in the primary motor cortex and is the only descending motor pathway that makes monosynaptic connections with the SNMs. (See Porter and Lemon, for a comprehensive review of corticospinal function in humans.) Each cortical motor neuron synapses with many SNMs, and each SMN receives input from many different CM cells. This arrangement of convergence and divergence is most abundant for the distal muscles—especially those of the hand and facial musculature. It is what affords humans their amazing degree of fractionated control and allows for a large repertoire of different movements served by the same muscle. CM control is largely responsible for delicate control of force, precision grip, angulation, rate of change of movement, and muscle tension. It is likely that the CM system is vital to the acquisition of new motor skills, which, once learned, are probably transferred to more caudal parts of the nervous system, including the spinal cord. Glutamate is the primary excitatory neurotransmitter of the CM system.

The CM system is subject to excitatory and inhibitory modulation. The stellate or basket cells are located primarily in laminae III and V. Their axon terminals form predominately inhibitory, gamma-aminobutyric acid (GABA) synapses on dendritic shafts, somata, and/or proximal axonal segment of the pyramidal neuron (cortical motor neuron) and are horizontally orientated. These interneurons modulate the response of pyramidal neurons to excitatory inputs.

**NATURE OF TRANSCRANIAL MAGNETIC STIMULATION**

Since the introduction of TMS, there has been a debate over which structures are activated by the magnetic stimulus. A rapidly changing magnetic field is generated that induces electrical currents within the cortex. Short-latency contractions are evoked in contralateral limb muscles. The latency is in keeping with a monosynaptic connection.

A single low-intensity anodal electrical stimulus delivered to the exposed surface of the cortex in monkeys preferentially activates pyramidal tract, neurons directly in the region of the axon hillock (Fig. 1, left). This results in a single descending volley recordable from the pyramidal tract, which has been termed the D wave or direct wave.

Increasing the stimulus intensity activates input cells, causing indirect, transsynaptic activation of pyramidal tract neurons. A series of recordable volleys, named I waves to indicate their indirect origin, follow the initial D wave. The I waves are separated by intervals of about 1.5 to 2 ms. Anesthesia and cooling of the motor cortex have a profound depressant effect on the I waves but not on the D wave. Epidural recordings of multiple descending volleys from the spinal cord of conscious human patients have provided evidence that transcranial electrical stimulation activates the motor cortex in humans and animals in the same way.

The same experiments have also confirmed that threshold transcranial magnetic stimuli over the hand area of the motor cortex preferentially activate the pyramidal cells indirectly (transsynaptically) through excitatory interneurons (Fig. 1, right). The onset latency of the compound muscle action potential (CMAP) from small hand muscles is approximately 2 ms later (Fig. 1, bottom right, solid line) than the electrically induced response. However, with higher stimulus intensities or certain lateral coil positions, the latency may shorten, consistent with D wave activation (Fig. 1, bottom right, dotted line). The different activation of pyramidal cells probably is related to the orientation of the induced current. Electrical stimulation causes the current to flow in all directions parallel and radial to the surface, thus penetrating the radially oriented pyramidal cells. TMS, however, induces current flow parallel to the surface of the brain, preferentially exciting horizontally oriented neurons. The result is that radially oriented neurons will have a higher threshold for magnetic stimulation than electric stimulation. This is why coil orientation is important; even a slight positional change of the magnetic coil on the scalp can profoundly affect the size and latency of the motor evoked potential (MEP).

The response of lower limb muscles has a similar latency with electrical and magnetic stimulation. This suggests that both techniques have the same activation site in the rostral pyramidal axons as they leave the cortex and readily produce D wave activity. Whether TMS activates a bi- or polysynaptic pathway in healthy subjects is presently unclear. Studies on monkeys have failed to identify disynaptic excitation of motoneurons from the pyramidal tract.

TMS also activates the local circuit inhibitory interneurons. Several ipsi- and contralateral inhibitory phenomena have been revealed with double (condi-
stimulating) stimulus paradigms and rTMS, which will be discussed below.

**Facilitation.** When TMS is performed with the target muscle steadily contracting, it shows different results than when the muscle is relaxed. Muscle contraction has three main effects: the threshold for evoking the motor response is reduced, the latency of the MEP is shortened, and the amplitude of the MEP is markedly increased. These facilitatory effects can also be induced simply by the subject’s thinking about the maneuver or contraction of another muscle (either on the same or opposite side), but the extent of facilitation is less than that induced by contraction of the target muscle. The underlying mechanisms for facilitation are not entirely understood but likely include increased cortical and spinal excitability. With voluntary contraction, the resting potential of the anterior horn cell (AHC) is closer to threshold, requiring less temporal summation of descending volleys, which means that the discharge can occur at an earlier I or D wave, thus shortening the onset latency. Furthermore, with increasing force, according to the Henneman size principle, larger and faster conducting spinal motoneurons will be recruited, thus shortening the onset latency. The increase of the CMAP amplitude indicates recruitment of a greater number of spinal motoneurons. This could also be due to increased spinal excitability, increased synchronization of spinal motoneuron firing, or an increasing number of I waves bringing more AHCs to threshold.

**MAGNETIC STIMULATOR AND COILS**

The components of a magnetic stimulator consist of a capacitor and an inductor (the stimulating coil). The energy for stimulation is derived from charging a bank of capacitors up to about 4 kV, which when discharged induces a current of up to 5,000 A that passes through the copper stimulating coil, creating a brief but intense magnetic field. Tissues, skull, and scalp present little or no impedance to a magnetic field. The intensity of the magnetic field is represented by flux lines around the coil and is measured in tesla (T). The stimulating current, which is maximal in an annulus underneath the coil, may be either biphasic.
or monophasic. Because the direction and phases of current flow determine which neuronal elements are activated within the cortex, a biphasic impulse may stimulate different populations of cells than a monophasic impulse. The responses to monophasic stimuli tend to be unilateral, whereas responses to multiphasic stimuli may be bilateral. If the initial current flow in a circular coil positioned over the vertex is clockwise, the left hemisphere will be activated. Reversing the direction of the initial current will activate the right hemisphere. Large round coils produce fields that penetrate the deepest, and the magnetic fields are distributed through a larger volume of tissue, resulting in nonfocal stimulation. Centered over the vertex, the circumference of the coil overlies the hand area of the motor cortex. Smaller coils, especially butterfly or figure-eight shaped, elicit more focal stimulation with activation occurring beneath the intersection site, but produce a relatively weak and less penetrating magnetic field. For small hand muscles, the optimal stimulation site is some 5 cm lateral to the vertex on the interaural line with the figure-eight coil orientated 45° to the parasagittal plane.

METHODS AND MEASUREMENTS

For routine studies, the magnetic stimulator is connected with standard needle electromyographic (EMG) equipment (Fig. 2). A synchronization pulse occurring at the moment of the stimulator’s discharge serves as an external trigger that starts a sweep that will display the recorded motor response of a target muscle. Measurements include the cortical threshold, latency and central conduction time, amplitude, and MEP/CMAP ratio.

CORTICAL THRESHOLD

In a relaxed target muscle, the cortical threshold reflects the global excitability of the motor pathway, including large pyramidal cells, cortical excitatory and inhibitory interneurons, and spinal motoneurons. Even slight voluntary contraction of the target muscle reduces the cortical threshold. Threshold to magnetic stimulation is usually defined as the stimulus required to elicit reproducible responses of 50 to 100 µV in about 50% of 10 to 20 consecutive trials. When motor potentials are recorded from a modestly activated target muscle, the response should be around 200 to 300 µV so that it can be distinguished reliably from background activity. The position of a circular coil centered over the vertex is less critical than positioning a figure-eight coil. The optimal coil position and orientation of the figure-eight coil may even be different for each intrinsic hand muscle. Mills and Nithi have recently developed a more reliable measure of threshold. A single stimulus at 20% of maximum stimulator output is given and single trials at 10% increments are then performed until a response is obtained. The intensity is then decreased 1% at a time until 10 stimuli fail to give any response. This is referred to as the lower threshold. The stimulus intensity is then increased by 1% increments until all of 10 stimuli induce a response of greater than 20 µV in amplitude with a latency of

FIGURE 2. Principle of TMS and calculation of central motor conduction time (CMCT). MEP₁ is recorded after transcranial magnetic stimulation (S₁), MEP₂ after cervical stimulation (S₂). CMCT is estimated by onset latency of T₁ minus onset latency of T₂.
17 to 30 ms. This is referred to as the upper threshold. Using this approach, the lower threshold measured 38 ± 8.6% and the upper threshold 46.6 ± 9.4%. Threshold in adults is independent of age, gender, and hemisphere, but varies with different target muscles.\textsuperscript{88,131} It is lowest for hand muscles and highest for proximal arm muscles, leg muscles, and axial muscles. This is in keeping with the more extensive cortical representation of hand versus more proximal muscles.

**LATENCY AND CENTRAL CONDUCTION TIME**

Latency and central conduction time depend on whether the MEP was recorded at rest or with activation, which shortens the latency by several milliseconds. However, the latency does not change much once 20% or more of maximum voluntary contraction is used. Thus, if latency is the only consideration, force does not need to be accurately controlled and the subject can be asked to moderately contract the muscle. The onset of the MEP is usually readily identifiable. The shortest of four to five responses should be measured. In some diseases, the MEP may be markedly reduced in amplitude and, when facilitation is used, partially buried in the background EMG. This often makes the onset latency difficult to recognize, and superimposing a number of potentials may then be helpful. To calculate the central motor conduction time (CMCT), conduction in the peripheral segment of the motor pathway (AHC to muscle) is estimated and then subtracted from the onset latency of the MEP (Fig. 2).

For cervical root stimulation, the most active part of the coil is positioned just rostral to the spinous process of C7 in the midline or within 2 cm lateral to this position. Because a peripheral nerve is being stimulated, it is of no consequence which way the coil faces. The lumbosacral roots can be stimulated by positioning the coil with the midpoint of its leading inner edge midline over the particular vertebral body of interest. There is no need to obtain a maximal response. The primary aim is to elicit several superimposable responses from which an accurate onset latency can be measured. However, for peripheral electrical stimulation of motor nerves, latency depends critically on the axons stimulated in a submaximal response. As response amplitude increases, latency almost always shortens. The same may apply for magnetic root stimulation, but this has not yet been systematically investigated. Nevertheless, stimulating the nerve roots either magnetically or electrically excites the nerve roots in the region of the intervertebral foramen.\textsuperscript{28,79} The onset latency does not, therefore, include the conduction time from the AHC to the intervertebral foramen and the CMCT will be estimated as slightly too long. This is not the case when using the F-wave method. The conduction time from spinal motor neuron to muscle is given by the formula \((F + M−1)/2\) where \(F\) is the shortest F-wave latency, \(M\) the onset of the direct muscle response, and 1 ms is allowed for the turnaround time at the AHC. Latency varies with height and arm length, therefore, central motor conduction is slightly faster in women than men.\textsuperscript{56,54,88} Latency and central conduction increase in a linear fashion with increasing age, but the correlation is weak.\textsuperscript{50,88}

**AMPLITUDE AND MEP/CMAP RATIO**

The absolute amplitude of the MEP depends on complex interactions between the CM and the AHC at the moment of stimulation. It reflects the sum of upper and lower motor neuron activity. There can be considerable inter-trial as well as intra-individual variation especially when stimulating with threshold or slightly suprathreshold intensities. With increasing stimulus intensity, the response becomes more stable.\textsuperscript{71} Many factors account for this variability, most of which are difficult or impossible to control in the clinical setting. Coil position is critical; minimal angulation of the coil even at the same site may drastically change the amplitude of subsequent responses. As discussed above, even modest muscle contraction greatly facilitates the response and it is imperative to state whether the response was elicited with the target muscle relaxed or under voluntary contraction. If facilitation is used for amplitude measurements, force or overall muscle activity should be estimated. This can be accomplished by either using isometric strain gauges or rectifying and integrating the background needle EMG to provide a measure as a percentage of the maximum.\textsuperscript{48} The amplitude is usually measured peak-to-peak.

Because of its variability, the absolute amplitude is of limited clinical value. However, in the authors’ experience, a side-to-side difference of 50% or greater can be regarded as abnormal in patients without lower motor neuron disease. The MEP/CMAP ratio takes account of the lower motor neuron contribution and is a more useful indicator of disease originating in the cortex. However, the ratio is very variable, ranging in normal subjects from 10 to 100%. The recently developed triple stimulation technique provides a more accurate and less variable estimate of upper motor neuron activation. It has been applied in a variety of upper motor neuron disorders,\textsuperscript{15,81,82,113} but the technique can be uncomfortable for patients.
CORTICAL MAPPING

The motor cortex is organized in terms of movements rather than muscles. Individual muscles have multiple representations (convergence) and a given CM may provide input to several spinal motoneurons of different muscles (divergence). Because TMS preferentially activates fast-conducting corticospinal fibers, maps reflect only the output function and distribution of the most direct fast-conducting cortical motor neuronal fibers. For mapping the topographic structure of cortical motor areas, a butterfly (figure-eight) coil is usually used, because the more focused field gives a more accurate map. The surface of the cortex is marked out in 1 cm squares using Cz (international 10 to 20 system) as the zero-zero mark. Points are extended anteriorly and posteriorly along the sagittal plane and over the left and right hemispheres in the coronal plane. With a standard stimulus magnitude, the coil is systematically moved over the motor cortex, which then produces a map of different MEP amplitudes at each site. The greatest MEP amplitude is evoked in the center of the map (optimal position) and declines as the coil is moved away from it. With the figure-eight coil, the optimal position to elicit responses in small hand muscles is 5 to 7 cm lateral to the vertex on the interaural line. Other measurements include the number of excitable scalp positions and the center of gravity. A frameless stereotactic system allows more precise coil placement.

PLASTICITY OF THE MOTOR CORTEX

Motor mapping experiments that use the magnetic coil in conscious humans have now clearly documented plasticity of the motor cortex and its ability to reorganize in certain circumstances. Piano practice for a few days tends to increase the size of the cortical motor area for relevant muscles. In congenital atresia of the forearm and hand akin to that seen in thalidomide teratogenicity, the proximal arm develops a larger than normal representation. When hemispherectomy is performed early in life, ipsilateral motor representation becomes much more pronounced, and cortical stimulation induces bilateral responses. In adults, learning-induced representational plasticity has been demonstrated in blind Braille readers. In long-standing Braille readers, the representation of the first dorsal interosseous muscle of the reading finger is much larger than the homologous muscle on the other side, whereas the adductor digit minimi of the reading hand is smaller than that of the non-reading hand and control subjects. In other words, the cortical representation of the reading finger has become enlarged at the expense of other fingers. Also, the acquisition of new fine motor skills in normal subjects is associated with reorganization of the motor cortex output map. Different areas of the motor map enlarge depending on the newly acquired skill. Spinal cord injury also results in enlargement of output maps projecting to muscles proximal to the lesion level. Reorganization of the motor cortex output map has also been shown with altered sensory input associated with immobilization, ischemic nerve block, dystonia, stroke, and facial palsy.

Mapping of cortical areas other than the motor cortex is also possible. Depending on the exact coil position and current direction, TMS of the occipital cortex evokes phosphenes in different areas of the visual field. TMS of the sensorimotor cortex occasionally triggers somatotopically organized paresthesias but may also block detection of an electrically evoked sensory stimulus.

THE CORTICAL SILENT PERIOD

As mentioned earlier, TMS also produces inhibitory phenomena, the most consistent being the presence of a long period of needle EMG silence during a sustained voluntary contraction (Fig. 3). This is akin to the silent period obtained by stimulating a peripheral motor nerve during contraction of a muscle. The duration of the silent period, usually defined as the time from the beginning of the MEP to the return of voluntary needle EMG activity, is linearly related to stimulus intensity but independent of the level of background contraction. For clinical consistency, measurements should be made with defined stimulus intensities in relation to individual motor thresholds. Silent periods are longest in small hand muscles (200 to 300 ms) and less prominent in proximal arm muscles and leg muscles. Weak stimuli can depress EMG activity while eliciting no motor response, indicating that the threshold for this inhibitory effect is less than for the excitatory effect. Spinal inhibitory mechanisms such as Renshaw inhibition are considered to contribute only to the first 50 ms to 60 ms of the TMS-induced cortical silent period, whereas most of the suppression is due to different cortical inhibitory mechanisms. The neuronal elements responsible for these effects are topographically close to the corticospinal neurons and are most likely the local inhibitory interneurons, which use GABA as their transmitter.

PAIRED CORTICAL STIMULATION

Two transcranial magnetic stimuli delivered in a conditioning test paradigm can be used to assess intra-
cortical inhibitory and excitatory mechanisms. The effects depend on the type of stimulus (electrical or magnetic), the scalp site at which stimuli are applied, the intensity of both the conditioning and test stimuli, the muscle activity, and the interstimulus interval (ISI). With the muscle at rest, the response of a suprathreshold stimulus is inhibited by a subthreshold conditioning stimulus at intervals of 1 to 5 ms and facilitated from about 10 to 20 ms. The inhibitory effect is reduced with voluntary contraction. The inhibition is due to the effects of local-circuit inhibitory interneurons and also the result of inhibitory collaterals from excited corticospinal fibers. Threshold pairs of stimuli of equal strength result in inhibition of the test response at ISI of 5 to 30 ms, and facilitation at ISI of 40 to 90 ms. A different pattern occurs with higher stimulus intensities: ISI of 25 to 50 ms cause facilitation, and ISI of 60 to 200 ms cause inhibition. Using pairs of threshold stimuli (0.9 to 1.1 times threshold or a suprathreshold conditioning stimulus) followed by a subthresh-

old test stimulus, short-latency excitatory effects (ISI 1 to 6 ms) can be demonstrated. These effects show periodicity reminiscent of the I waves recorded directly from the pyramidal tract. The paradigm can be used to assess drug effects and pathological conditions.

**REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION**

Repetitive transcranial magnetic stimulation (rTMS) is only possible with special stimulators that have technical features allowing the generation of fast rates of stimulation. The technique permits modulation of corticospinal excitability. The effects, ranging from inhibition to facilitation, depend on the stimulation parameters (stimulus intensity, interstimulus interval, number of stimuli, and interval between successive trains) and may last beyond the duration of the rTMS itself. Lasting effects of high-frequency rTMS (greater than 1 Hz) on clinical symptoms have been seen in Parkinson’s disease and depressed patients, whereas low-frequency rTMS can transiently improve symptoms in patients with task-specific dystonia. Further clinical applications include treatment of focal epilepsy, cortical myoclonus, spasticity, and obsessive-compulsive disorders. Other effects outside the motor areas include interference with language, cognitive processes, and memory. The different therapeutic benefits of rTMS are not easy to explain but may include neuromodulatory effects from released neurotransmitters and changes in cerebral blood flow.

High frequency and intensity rTMS may cause epileptic seizures. Secondarily generalized seizures following rTMS have been reported in healthy subjects and patients with epilepsy and depression, but there is no evidence for the development of epilepsy after an rTMS-provoked seizure. Spread of excitation in the cortex, as evidenced by CMAPs appearing in muscles remote from the target muscle and needle EMG activity that persists after the stimulus ends, is considered an indicator of induced epileptic activity. These observations were used as the basis on which the maximum safe combinations of stimulus intensity, frequency, and duration of single trains of rTMS were defined.

**DIRECT STIMULATION OF CORTICOSPINAL TRACT AXONS**

It is usually not possible to stimulate the pyramidal tract axons directly (postsynaptically) with a magnet. However, Ugawa et al. demonstrated that this is feasible with a double cone type of coil that is capable of delivering stimuli to deep structures. The
coil is placed over the inion stimulating ipsilateral to the side of recording. Latency to the hand muscles is about 16.5 ms, compared to about 20 ms after cortical and 12.5 ms after cervical root stimulation, which suggests that the corticospinal pathway is stimulated at the level of the pyramidal decussation. Indicators that the response indeed originates in the tract and not pyramidal cells include consistency of latency and shape of the response and a latency that is identical to that evoked by electrical stimulation at the same site.

This method is useful to confirm that prolonged latency of a MEP elicited by cortical stimulation is due to slowed conduction within the spinal tracts and not the result of increased temporal or spatial dispersion resulting from impaired intracortical initiation of the descending volley at the level of the pyramidal cell.127

**PERISTIMULUS TIME HISTOGRAMS**

The cortical motor neuronal system (the CM and its target spinal motoneuron) can be investigated using peristimulus time histograms (PSTHs) (Fig. 4). The firing probability of a voluntarily activated motor unit is modulated when it is subjected to a series of transcranial magnetic stimuli.18,42 The PSTH recorded from forearm and hand muscles typically shows a marked increase in the firing probability occurring at about 20 to 25 ms after the stimulus, which is referred to as the primary peak. The onset latency of the primary peak is in keeping with a volley descending through the fast-conducting monosynaptic (corticospinal) pathway. The configuration of the primary peak (amplitude, duration, and dispersion) reflects the rising phase of the composite excitatory postsynaptic potential at the AHC induced by the descending cortical volley. This technique has been applied to several diseases but has been of particular value in amyotrophic lateral sclerosis (ALS).134

**USE OF THE MAGNETIC COIL FOR PERIPHERAL NERVE STIMULATION**

Use of the magnetic coil for study of the peripheral nervous system is presently limited by its inability to deliver a controlled focal stimulus. For example, it is difficult to stimulate the median and ulnar nerve independently when the coil is placed over the wrist. It is also difficult to elicit maximum amplitude CMAPs in a reproducible manner as is possible with conventional electrical stimulation. However, more advances in coil design show promise in improving the precision and thus the utility of magnetic peripheral nerve stimulation.11

Peripheral nerves are most readily stimulated by the magnetic coil at sites where there is an abrupt change in the volume conductor or at sites of nerve bending.78,79 This may explain the paradoxical ease with which proximal rather than distal nerves are stimulated. This can be helpful for stimulating the deeply placed phrenic nerve in the neck. The direction of current flow is critical in cortex stimulation but not in peripheral nerve stimulation. However, the CMAP latency may change by a fraction of a millisecond when the current direction is reversed, possibly as a result of the “cathodal-anodal reversal” effect and/or shallower rise-time in the strength of the magnetic field with reversed flow.

**SAFETY CONSIDERATIONS AND SIDE EFFECTS**

Since Barker’s development of the first commercial magnetic stimulator, many thousands of patients and normal individuals throughout the world have undergone magnetic stimulation without ill effect. Adverse effects of single pulse magnetic stimulation
of the motor cortex are extremely rare. Induction of epileptic seizures and kindling have caused the most concern but there have only been a few reports of seizures occurring at or shortly after the time of magnetic stimulation.\cite{35, 64, 66} Formal studies on known epileptics have failed to induce either clinical seizures or electroencephalographic epileptiform activity.\cite{139} However, it has become clear that rTMS, depending on the stimulation parameters (see above), can evoke seizures in normal subjects and patients with neurological disease.\cite{130} Other concerns have included possible brain damage with cognitive and other dysfunction and complications from dislodging neurosurgically inserted metal clips. It is possible that magnetically induced currents could damage the internal electronics of biomedical devices such as cardiac pacemakers. The coils should therefore not be placed in the vicinity of cardiac pacemakers. Cardiac muscle can only be stimulated with the magnetic coil if it is placed directly over the open heart; applying a magnetic coil over the lateral chest wall in the process of stimulating the intercostal nerves has not caused cardiac irregularities. Nevertheless, it is advisable to avoid stimulating directly over the precordium.

Formal psychometric testing before and after single pulse magnetic stimulation has indicated no associated cognitive impairment. Endocrine assessment of the pituitary-hypothalamic axis after TMS has shown no consistent changes.\cite{67, 84}

Magnetic stimulation can activate the auricular muscles, especially in young children. The noise level of older stimulators raised the concern of temporary hearing impairment but no lasting effects were found with the small number of stimuli applied to most subjects.\cite{97} For routine clinical practice, 10 to 15 stimuli are usually more than sufficient to achieve the desired information. Several hundred subthreshold stimuli, as required for PSTHs, are equally safe. As a general guide, previous cranial neurosurgery, the wearing of an electrically sensitive biomedical device such as a cardiac pacemaker or intrathecal pump, and a history of seizures are relative contra-indications.

**MATURATION OF THE CORTICAL MOTOR NEURONAL SYSTEM AND AGE-RELATED CHANGES**

Magnetic stimulation is ideal for the study of the maturation of motor pathways. Adult values for central motor conduction velocity are attained a few years after central sensory conduction. In both instances, adult values for peripheral conduction are reached earlier than central conduction, implying that peripheral myelination precedes central myelination. In children, CMCT linearly declines with age. Adult values for central motor conduction can usually be attained by 4 years of age. However, cortical threshold remains high until the end of the first decade.\cite{92} The disparity between attainment of adult values of central motor conduction velocity and cortical threshold is consistent with the notion that central myelination is completed before synaptogenesis. On the other end of the age spectrum, MEP amplitude declines and central motor conduction time gradually increases with increasing age. Injury to the motor cortex in young children can be followed by excellent functional recovery of the affected limb(s). In such situations, magnetic stimulation of the unaffected cortex induces not only the usual contralateral response but also a large ipsilateral one. This is probably the result of corticospinal sprouting within the pyramidal tract leading to an elaboration of ipsilateral projections.\cite{18} It has been morphologically confirmed that sprouting of central fibers can occur, using labeling of corticospinal cells.

**MAGNETIC STIMULATION IN DISEASE**

Many abnormalities revealed by magnetic stimulation are not disease specific and, like most other neurophysiological tests, the results must be considered in the light of clinical data. Frequently the correlation between clinical deficit and degree of MEP abnormalities is rather poor. In general, demyelination of central motor pathways is associated with more marked conduction slowing and prolongation of central conduction times. On the other hand, in neuronal disease, the MEP, if recordable, is of reduced amplitude but usually is only modestly prolonged in latency.

**Amyotrophic Lateral Sclerosis.** Earlier studies in ALS using electrical stimulation of the cortex showed modest prolongation of central motor conduction time, frequently marked MEP attenuation, and, in some cases, absence of the MEP.\cite{68} TMS reveals similar abnormalities. The prominent abnormality is an absent or small MEP that is frequently dispersed (Fig. 5). This correlates with the occurrence of dispersed primary peaks in the PSTH (Fig. 4, bottom), which may reflect hyperexcitability of CM connections. In general, the correlation of central motor conduction prolongation with other MEP abnormalities and with clinical upper motor neuron signs (hyperc reflexivity, finger flexion, impaired fine finger movement) is poor.\cite{117}

Various neurophysiological methods employing TMS have also indicated hyperexcitability of the motor cortex in ALS.\cite{47, 58, 73, 87, 95} The threshold required
to stimulate the motor cortex with a magnetic coil is reduced early in the disease, especially in patients with preserved muscle bulk and prominent fasciculations. Other TMS studies suggest that cortical inhibitory mechanisms are also impaired in ALS. For example, the cortical silent period, a measure of corticospinal inhibition, is shortened compared to normal subjects (Fig. 3, bottom), and a subthreshold conditioning stimulus delivered shortly before a suprathreshold test stimulus fails to inhibit the test response in ALS.

PSTHs in patients with ALS show a diversity of abnormalities ranging from the primary peak being small (or absent) to being large and increased in temporal dispersion. Over time, the dispersion increases and double primary peaks occur, suggesting activation of slow-conducting indirect pathways. Indirect evidence suggests that these abnormalities are supraspinal in origin and are not the result of AHC disease. In Kennedy’s disease (bulbar-spinal muscular atrophy), the primary peak of the PSTH is normal (Fig. 4, middle), which confirms that the abnormal PSTH in ALS is due to supraspinal disease.

Patients with primary lateral sclerosis (PLS) show significantly elevated thresholds to TMS and longer central conduction time to both upper and lower limbs. However, using PSTTHs, it can be demonstrated that the onset latency of the primary peak in ALS and PLS does not significantly differ, implying that TMS activates the same population of CM connections in ALS and PLS.

**Multiple Sclerosis.** Demyelination induces conduction block, slowed conduction, and inability to faithfully sustain rapid trains of impulses. These characteristic physiological disturbances in multiple sclerosis (MS), individually or in combination, account for prolongation of CMCT, reduced MEP/CMAP ratio, increased variability of onset latency of the MEP (latency jitter), and dispersed morphology (Fig. 6). Slowing of central motor conduction, the most commonly seen abnormality, can be very marked and correlates to some degree with the presence of upper motor neuron signs and clinical deficit. A common site of demyelination in MS is the corpus callosum, and interhemispheric conduction through the corpus callosum is significantly slowed in this disease. Ipsilateral cortical stimulation causes transcallosal inhibition of a contracting target muscle, and this fact can be used to measure conduction through the corpus callosum. A significantly increased excitability threshold in resting or preactivated muscles is frequent. This is usually associated with prolonged central conduction but may also occur as an isolated abnormality. MEP studies may detect subclinical involvement of motor pathways and the overall sensitivity is comparable to visual evoked potentials.
Studies with PSTHs in MS have shown delayed and dispersed primary peaks consisting of multiple subpeaks. A similar abnormality is seen in ALS but the underlying mechanism is different. In MS, conduction through the descending motor tracts is delayed, whereas in ALS, conduction slowing and temporal dispersion is caused by selective loss of large, fast-conducting pyramidal neurons.

Movement Disorders. Conduction time through the descending motor pathways is normal in Parkinson’s disease, Huntington’s disease, primary dystonia, essential tremor, and myoclonus.\textsuperscript{7,23} Determining the cortical threshold in Parkinson’s disease has produced inconsistent results: decreased, normal, and elevated thresholds have all been reported.\textsuperscript{23} The cortical silent period is shortened or normal and, when short, the abnormality can be reversed after levodopa therapy.\textsuperscript{106} Corticocortical inhibition, tested at short conditioning test intervals and with the muscle at rest, is reduced in Parkinson’s disease. On the other hand, interstimulus intervals of between 40 to 75 ms show greater than normal inhibition of the test response.\textsuperscript{9} The physiological abnormalities in Parkinson’s disease revealed by TMS probably result from a combination of increased inhibition and reduced excitation occurring at both cortical and subcortical levels.\textsuperscript{7} In dystonia and Huntington’s disease, double stimulation paradigms have produced conflicting findings, most likely due to different stimulation parameters.\textsuperscript{2,59,118} Nevertheless, it is likely that future studies will reveal useful insight into the pathophysiological mechanisms and mode of drug action.

Stroke. In stroke patients, the response after cortical stimulation is often absent.\textsuperscript{106} In patients in whom a response is obtained, the MEP is quite often of small amplitude and dispersed. CMCT is usually only slightly prolonged. The cortical threshold is commonly found to be raised.\textsuperscript{25} In a formal study, the duration of the silent period was markedly longer on the affected side when compared with a control group. This parameter also seems to detect mild, subclinical disturbances.\textsuperscript{1} TMS appears to be a good predictor of stroke outcome.\textsuperscript{3,33,60,123,125,126} A recordable MEP in early stages correlates with a favorable outcome, whereas an absent response predicts poor recovery. Patients with delayed but present MEPs recover more slowly than those with normal MEPs, but are similar at 12 months. The CMCT correlates well with the grade of weakness. The finding of an increased threshold correlates with the presence of brisk tendon jerks.

Hereditary Spastic Paraplegia and Spinocerebellar Ataxias. In patients with hereditary spastic paraplegia, lower limb responses are almost always abnormal: absent, reduced, or delayed. Upper limb responses, however, are usually normal even in the presence of clinical upper motor neuron signs. A similar pattern can be seen in patients with hereditary motor and sensory neuropathy with pyramidal signs. The CMCT to small hand muscles in Friedreich’s ataxia is most often prolonged.\textsuperscript{41} Moreover, the MEP is frequently of small amplitude and dispersed. The sensitivity is even greater when recording from lower limb muscles. In other cerebellar ataxias, abnormalities are less severe and less frequent, with the highest rate of impairment being seen in spinocerebellar ataxias. Prolongation of central motor conduction is also a common finding in patients with human T-cell lymphotrophic virus type I-associated tropical spastic paraparesis. Responses in the lower limbs typically show marked prolongation. Upper limb responses may be normal or show slowing of central conduction less prominent than recordings from leg muscles.\textsuperscript{138}

Epilepsy and Drugs. Attempts have been made to use TMS for localization of epileptic foci, but it appears that the epileptic focus cannot be localized with sufficient resolution using this approach.\textsuperscript{2,32,136} One would expect that cortical excitability might be increased in patients with epilepsy but threshold measurements have revealed conflicting results. Intracortical inhibition in epilepsy is reduced, but this is a nonspecific finding which can be seen in many other disorders. It is unclear whether changes in cortical excitability are due to medication or to epilepsy itself. Antiepileptic drugs which act on sodium channels (carbamazepine, phenytoin, lamotrigine) increase motor threshold but do not have a significant effect on intracortical inhibition. In contrast, antiepileptic drugs or medication modulating activity of GABA receptors (e.g., benzodiazepines) have no significant effect on motor threshold but enhance intracortical inhibition and suppress intracortical facilitation.\textsuperscript{139} In patients evaluated for epilepsy surgery, rTMS applied to the dominant hemisphere can produce speech arrest but does not always correspond directly with Wada test results.\textsuperscript{10,34}

Radiculopathy and Spondylotic Myelopathy. Magnetic stimulation over the spinal enlargements excites the nerve roots a few centimeters distal to the AHC in the vicinity of the intervertebral foramen.\textsuperscript{30} The response latency is reproducible but the stimulus is usually submaximal. This precludes standard-
ization based on the amplitude of the response and
detection of a more distal conduction block. The
value of magnetic root stimulation to evaluate ra-
diculopathies is thus limited. As with other conduc-
tion techniques used to evaluate radiculopathies (F
waves, somatosensory evoked potentials, H reflexes,
and magnetic stimulation), conduction block is dif-
ficult to interpret given the variability of MEP ampli-
tude and uncertainty in obtaining a maximum am-
pitude potential.

A high percentage of abnormalities in the MEP
has been described in spondylotic myelopathy.15
The CMCT is frequently prolonged, the threshold
raised, and the response dispersed and of small am-
pitude. Abnormalities of central conduction may
precede clinical evidence of myelopathy. Slowed
central conduction may be an early manifestation of
cord compression before it is evident on magnetic
resonance imaging.124

Plexopathy. Although magnetic stimulation can be
used in plexopathies, the technique has not been
able to substitute for electrical stimulation. With
magnetic stimulation at the plexus level, supramaxi-
mal responses are not always possible and the precise
site of stimulation is uncertain.30,32,112,116 However,
magnetic stimulation provides certain advantages in
some types of plexus lesions. For example, a
neurapraxic lesion of the upper trunk of the bra-
chial plexus cannot be detected by electrical stimu-
lization of Erb’s point, which is usually below the le-
sion. Accurate localization would require direct
electrical stimulation of the spinal roots through a
monopolar needle. This can be achieved noninva-
sively by magnetic stimulation. Eliciting a response
from the deltoid or biceps is clear evidence of nerve
continuity, and significant slowing of onset latencies
would indicate focal demyelination.35 MEP ampli-
tudes after magnetic plexus stimulation are variable
and one cannot comment as to the presence or ab-
sence of conduction block. Once there has been sig-
ificant axonal loss, needle EMG is the best method
of determining axonal continuity and reinnervation.
Stimulation of the lumbosacral plexus and cauda
equina is also possible with magnetic stimulation,
but, like stimulation of the brachial plexus, it some-
times fails to elicit reproducible, maximal re-
sponses.17,31,80 This again limits its value in the as-
sessment of lumbosacral radiculopathies and
plexopathies.31

Peripheral Neuropathies. As previously mentioned,
magnetic stimulation is presently limited with regard
to the peripheral nervous system because of lack of
focality and inability to elicit a potential of consistent
maximal amplitude. This precludes, amongst other
things, accurate detection of conduction block.
However, there are at least two situations in which
use of the coil is advantageous. In children who do
not tolerate electrical stimulation, magnetic stimula-
tion often allows measurement of conduction veloc-
ities sufficient to differentiate between a demyelinat-
ing and an axonal neuropathy. Secondly, in
demyelinating neuropathies, cortical stimulation
can reveal marked conduction slowing in the most
proximal nerve segments. The F wave can often do
the same, but when the neuropathy is severe it may
be absent.

CRANIAL NERVES

The intracranial portions of the motor cranial nerves
V, VII, XI, and XII are readily stimulated with a mag-
netic coil.6,21,129 To elicit responses from muscles
innervated through the cranial nerves at their intra-
cranial-extradural portion, the magnetic coil
should be positioned over the occiput ipsilateral to
the recording site. Evidence indicates that the nerves
are excited close or just distal to their exit foramina.
Because proximity of the stimulus to the surface re-
cording electrodes can be a problem, a concentric
needle electrode is often preferred for recording the
elicited muscle response. An intra-oral “permucosal”
recording device is also helpful to reduce artifact.

The central, crossed, corticopontine portion of the
motor cranial nerve conduction is more difficult
to assess. The coil is optimally placed 4 cm lateral to
the vertex on a line joining the vertex (Cz) and the
external auditory meatus. Activation of the target
muscle is usually required to obtain a response.

DIAPHRAGMATIC CONDUCTION

Diaphragmatic recording is used routinely to diag-
nose and monitor patients with impaired respiratory
function. Although electrical stimulation of the
phrenic nerve is well established, cervical magnetic
stimulation of the phrenic nerves is less painful and
achieves a more constant degree of diaphragmatic
recruitment.120,148 An unexplained phenomenon is
the greater transdiaphragmatic twitch pressure that
occurs with magnetic rather than electrical stimula-
tion. This may be due to coactivation of extradia-
aphragmatic muscles. Normal values for the latency
to the diaphragm using electrical stimulation in the
neck are between 7 and 8 ms, but data are less ho-
mogeneous for magnetic stimulation.

The diagnosis of impaired central respiratory
drive can often be accomplished by transcortical
magnetic stimulation of the motor cortex with re-
cording of the diaphragm and phrenic nerve responses. These studies are of particular value in critically ill patients in whom both central and peripheral lesions may impair respiration.\textsuperscript{140} Phrenic nerve pacing is becoming a more frequent substitute for positive pressure ventilation via tracheotomy in patients with high cervical cord lesions or central hypoventilation. Although its indications are infrequent, TMS may help to determine which patients may benefit from this treatment.\textsuperscript{120}

**INTRAOPERATIVE MONITORING OF MOTOR EVOKED POTENTIALS**

The ability to evoke MEPs during surgery has been a useful addition to the battery of neurophysiological tests that can be used to monitor and prevent the development of clinical deficits during surgery.\textsuperscript{5,20} MEP monitoring is particularly relevant in surgery that may damage the motor pathways independently of the sensory pathways. Examples of this include resection of spinal cord tumors, cross-clamping of cerebral blood vessels, and resection of tumors and arteriovenous malformations involving the motor cortex and subcortical motor pathways. However, intraoperative monitoring is expensive, requiring dedicated teams and equipment, and its cost-effectiveness needs to be considered.

Electrical stimulation of the cortex with recording over the spine (preferably using intradural electrodes) is the most reliable method because it is independent of the anesthetic used. However, it is possible to use magnetic stimulation with some anesthetics such as ketamine or fentanyl and obtain reasonably reliable results. If trains of stimuli are used rather than a single stimulus, the facilitation produced helps overcome the effects of some anesthetics.

**REFERENCES**


