Transcranial Magnetic Brain Stimulation: a Tool to Investigate Central Motor Pathways

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Transcranial magnetic stimulation allows the painless activation of cortical motor neurons and elicits responses in a wide range of muscles, termed “motor-evoked potentials.” Since its introduction in 1985, the technique has evolved as one of the most fruitful recent contributions to clinical neurophysiology.

This short review summarizes the technical principle and the basic physiology of the transcranial magnetic stimulation (TMS) method. Clinically, TMS is used to examine the function of the pyramidal tract in patients with central nervous system disorders. The technique allows calculation of the central motor conduction time. In healthy subjects, TMS can be utilized to painlessly monitor excitability changes of corticospinal and spinal motor neurons. Some of the experimental results highlighting mechanisms of cortical and spinal excitability changes during movements will be summarized. The short overview will also address TMS data on influences of cognition on the motor system and on adaptive mechanisms after lesions (“plasticity”). Finally, a new method will be presented that gives insights into the generation of motor-evoked potentials (MEPs). This “triple stimulation technique” (TST) allows a quantification of the proportion of spinal motor neurons discharging in response to the transcranial stimulus by use of collisions with peripherally induced nerve action potentials. In clinical studies, the TST has dramatically increased the diagnostic yield of TMS.

Technical principle and physiology

The technical principle of TMS is to pass a brief surge of current through a coil of copper wires, which induces a rapidly changing magnetic field. This magnetic field passes into the surrounding medium, where it again induces an electrical field (Fig. 1A). Applied over the human scalp, it may excite cortical neurons. The stimulus evokes multiple descending volleys in corticospinal neurons. The initial volley [the direct (D-) wave] is thought to arise from excitation of the pyramidal cell itself in the region of the axon hillock. The D-wave is followed by a number of indirect (I-) waves at 1.5- to 2-ms intervals for up to 10 ms. I-waves possibly stem from transsynaptic excitation of corticospinal cells by different sets of intracortical neurons, but their exact origin is not known. Weak magnetic stimuli do not usually evoke a D-wave but only a succession of I-waves, as demonstrated by epidural recordings in monkeys and in patients undergoing spinal surgery. The onset latencies of MEPs may be decreased in patients with losses of corticospinal cells, such as in stroke or in amyotrophic lateral sclerosis. However, due to the size variability of MEPs, normal limits for MEP amplitudes or areas are broad such that size parameters are more difficult to judge.

Clinical application of TMS

TMS is painless, and serious adverse effects have never been described. It was therefore easily accepted as a routine method in many clinical neurophysiology laboratories. In the clinical setting, it is often used to assess corticospinal conduction in patients suffering from diseases affecting the pyramidal tract. It is then useful to determine the central motor conduction time (CMCT) by subtracting the peripheral from the corticospinal conduction time. The peripheral conduction time is derived from electrical or magnetic stimulation of the motor root (a stimulation usually considered more unpleasant than TMS) or from F-wave studies. The CMCT is often prolonged in demyelinating diseases of the central nervous system. As mentioned above, the CMCT may also be prolonged in diseases affecting the number of functional corticospinal neurons, since the time requirements for summation may be increased. The size of MEPs may be decreased in patients with losses of corticospinal cells, such as in stroke or in amyotrophic lateral sclerosis. However, due to the size variability of MEPs, normal limits for MEP amplitudes or areas are broad such that size parameters are more difficult to judge.

The size of MEPs: MEP facilitation by voluntary activity

In healthy subjects, the size of MEPs is influenced by excitability changes of cortical and spinal motor neurons. Hence the method can be used to probe the excitability of
these neurons under various settings. For example, slight voluntary activation of the target muscle facilitates the MEP size dramatically (9). The MEP size is also facilitated by contractions of muscles other than the target muscle, and this effect is greater for neighboring muscles than for remote muscles. It is probable that the mechanism responsible for this facilitation resides at the spinal level, since epidural recordings show a similar number of descending volleys (D- and I-waves) during muscle relaxation and during voluntary contraction (5). Thus voluntary contraction raises the excitability of the spinal motor neurons such that they can be accessed more easily by the TMS-induced descending activity. The MEP facilitation by voluntary contraction varies between muscles. In small hand muscles, the MEP size rises sharply at small forces and levels off at forces above some 5% of the maximum (Fig. 2A). In more proximal muscles (biceps brachii and flexor carpi radialis), the MEP size increases continuously, with forces increasing to some 25–30%. These differences have been explained by the differences in motor unit recruitment in proximal vs. distal muscles.

Task-dependent facilitation differences were observed by a number of investigators with (at first glance) somewhat conflicting results. In clinical practice, it is a common observation that the MEP size is more facilitated at the beginning of a fast contraction than during a steady isometric contraction. We have experimentally confirmed this observation in a proximal

![FIGURE 1. A: technical principle of magnetic stimulation. B: comparison of compound muscle action potential of abductor digiti minimi after peripheral nerve stimulation and after transcranial magnetic brain stimulation. Twenty-four consecutive transcranial magnetic stimulation (TMS) responses were obtained with a threshold stimulus and during a voluntary contraction of 20% of the maximal voluntary contraction. The initial trace of each TMS response (including the stimulus artifact) is omitted to allow a better appreciation of the size variability. Note that the TMS responses are smaller than the response to peripheral stimulation and variable from one stimulus to the next.](http://physiologyonline.physiology.org/)

![FIGURE 2. A: facilitation of the motor-evoked potential (MEP) by voluntary background activity of the target abductor digiti minimi muscle. At low background forces, there is a steep increase of the MEP size, which levels off at greater background forces. CMAP, compound muscle action potential; Erb, stimulation point for the brachial plexus. B: facilitation of the MEP by a cognitive paradigm. The subject is alternately asked to concentrate on the target hand or to think of something else.](http://physiologyonline.physiology.org/)
middle
responding MEPs (middle) serve to interpolate isoamplitude lines (right). Output maps can be generated using amplitudes, areas, thresholds, or MEP probabilities. A variety of interpolation paradigms have been proposed (here, Microsoft Excel was used for calculation).

![Diagram of a motor output map](image)

**FIGURE 3.** Construction of a “motor output map.” Stimulation performed using a focal figure 8 coil at predetermined coordinates (left). The amplitudes of the corresponding MEPs (middle) serve to interpolate isoamplitude lines (right). Output maps can be generated using amplitudes, areas, thresholds, or MEP probabilities. A variety of interpolation paradigms have been proposed (here, Microsoft Excel was used for calculation).

muscle (deltoid) but not in a distal muscle [abductor digiti minimi (ADM)] (1). Subjects were asked to either maintain a constant force output of the target muscles (i.e., steady contraction) or to gradually increase their contraction force, with an automatically triggered TMS when the force level reached comparable values (i.e., dynamic contraction). The dynamic contraction facilitated the deltoid MEP considerably more than the steady contraction, whereas both facilitated the ADM MEP similarly. The same difference in task-specific deltoid MEP facilitation was observed when TMS was replaced by magnetic brain stem stimulation and when the isometric contraction was replaced by a isotonic contraction. Hence the mechanism of this type of task-specific facilitation is likely to be localized at the spinal segmental level and is independent from afferent input from the periphery. Other investigators have found compelling evidence for a cortical source of task-specific facilitation. The subjects of Flament et al. (6) had to perform a variety of simple and complex hand movements while the facilitation of MEPs of the first dorsal interosseus (FDI) was measured, with the level of ongoing FDI EMG activity adjusted to be equal during the tasks. Complex tasks (such as turning a knob) facilitated the MEP considerably more than simple tasks (abduction of the index finger). To differentiate between a cortical and spinal localization of this difference, Flament et al. repeated the experiment using electrical instead of magnetic brain stimulation. Electrical stimulation excites the pyramidal neurons directly without involving much of the intracortical network and resulted in a much smaller amount of task-dependent extra facilitation, thus suggesting that cortical networks were involved in the facilitation during complex tasks. Together, the data are consistent with the notion that cortical facilitation occurs predominantly during controlled precision movements but not during simple movements of the hands, whereas spinal facilitation is particularly enhanced during dynamic movements of proximal muscles. The difference in spinal facilitation between distal and proximal muscles may be explained by the different mechanisms of force gradation, which in proximal muscles use augmenting of the firing frequency of a subset of motor neurons (frequency principle), whereas in distal muscles, force increases are primarily achieved by recruiting additional motor neurons already at low forces (recruitment principle). Consequently, in proximal muscles only a fraction of the motor neuron pool may be active over a wide range of force, leaving much play during dynamic tasks for additional recruitment and thus MEP facilitation (1).

**MEP facilitation by cognitive tasks and by motor training**

MEPs are not only facilitated by muscle contractions but also by changes of overall arousal and attention. This is shown in Fig. 2B, which illustrates a subject asked to “concentrate on the target hand” or to “think of something else” (17). The facilitatory effect of directing the attention to the target hand is quite obvious because it appears and disappears within seconds. Similar attentional effects may underlie the observation of enhanced MEPs during eye movements or during the preparatory phase just before starting a movement. Thinking about moving or even watching someone else move may be sufficient to facilitate MEPs in the observer (18). The H-reflex (used as a measure of spinal excitability) remains unchanged, suggesting a cortical mechanism of the facilitation. This type of facilitation is less powerful than that of true contractions, but it is specific for the imagined movements since it concerns predominantly the muscles involved in that movement. Hashimoto and Rothwell found that in imagined repetitive wrist flexion and extension movements at 1 Hz the MEPs in flexor carpi radialis were larger during the phase of imagined flexion and those in extensor carpi radialis were larger during the phase of imagined extension (8). These observations indicate that systems involved in the efferent motor path may be activated in the absence of descending activity, causing an actual movement. Accordingly, functional imaging studies using positron emission tomography or functional magnetic resonance imaging have shown activation of the cortical primary motor areas during imagined movements, confirming that the cortical excitability changes observed with TMS are similar in space to those occurring in actual movements. Compared with functional imaging, the TMS studies have the advantage of a much better time resolution and also reveal that the timing of the cortical excitability changes match those of real movements. Thus a fairly accurate programming of move-
ments appears to occur at a cortical level, which is not dependent on sensory feedback (8).

A number of studies have addressed the question of how motor learning affects MEPs. Pascual-Leone et al. (16) trained naive subjects to play a simple five-key melody on the piano and recorded both the acquired playing skill and the threshold stimulus strength for evoking a MEP in the FDI of the trained hand. After 5 days of piano training for 2 h each day, the number of errors (pressing the keys inaccurately or in the wrong sequence) decreased by ~90%; this was paralleled by a decrease of the threshold for evoking a FDI MEP in the playing hand. In the untrained hand and in two control groups (one group did not practice piano playing, one group played self-generated sequences of keys for 2 h/day), neither playing accuracy nor MEP thresholds changed. Thus the acquisition of the new skill was associated with a modulation of the cortical motor output to the muscles involved in the task. This was taken as evidence for an increase of synaptic efficacy of involved cortical circuits or for a disinhibition of existing connections (16). Most interestingly, in an additional control group, the effect of mental piano rehearsals (sitting in front of the piano for 2 h/day and trying to visualize the fingers performing the exercise and imagining the sound) was analyzed. The threshold for evoking an MEP decreased in the mental training group as much as it did in the physical training group; the actual piano playing skill increased significantly during mental training, albeit less than during physical training. At the end of the experiment, the mental trainees were given the opportunity for 2 h of physical training, which brought them to the same level of playing skill as the physical trainees. Thus the TMS data sheds light on the mechanism of mental rehearsal, which appears to provide a cognitive (cortical) model of the demanded motor act (8) and thereby accelerates the acquisition of a new motor skill.

Cortical motor output maps and plasticity

The size of MEPs depends not only on facilitatory maneuvers but also on the positioning of the stimulating coil over the head. Using coils designed to deliver comparatively “focal” stimuli (a figure eight coil is usually used, consisting of two circular coils side by side and with opposing current directions),
it is possible to determine the motor area from which a given muscle can be activated. In general, the points of optimal stimulation follow the known somatotopy of the primary motor cortex and they are colocalized with the respective cortical activation points seen in functional imaging studies. By systematic stimulation at predetermined points over the scalp, a cartography of MEP amplitudes (or thresholds) can be obtained. It is then relatively simple to derive a “cortical motor map” by interpolation of isoamplitude or isothreshold lines (Fig. 3) or to calculate the maps’ center of gravity (“hot spots”). The size of a motor map quickly increases concentrically when the overall excitability of the corticospinal system is increased. Such concentric map enlargements were shown in the subjects concentrating on their hands and practicing piano (see above). Because of their rapid occurrence, concentric map enlargements may not be taken as evidence of structural cortical motor reorganization (e.g., by axonal sprouting). “Use-dependent” plastic changes are reduced by dextrometorphan [an N-methyl-D-aspartate (NMDA) receptor blocker] and by lorazepam [an agonist of γ-aminobutyric acid (GABA) type A receptors], thus suggesting as possible mechanisms NMDA receptor activation and intracortical GABAergic disinhibition (3), with unmasking of preexisting connections. Many studies have shown their rapid transient occurrence and disappearance in a number of paradigms (see above). However, motor maps may also change their position in response to the functional demands, suggesting the possibility of adaptational structural cortical changes. It is principally here that magnetic stimulation mapping has reproduced earlier observations obtained by invasive experiments in animals. For example, after limb amputation in patients, cortical motor representations of neighboring muscles have been shown to expand into the area that formerly represented muscles of the amputated limb (7). Relocation of motor maps have been observed in patients with complete arm palsy due to root avulsion that had received a nerve anastomosis from the intercostal to the musculocutaneous nerve. Four to six months after surgery, motor unit potentials could be found in the biceps muscle during inspirations. During the following 2–3 yr, these unit discharges became independent of respiration, and in parallel the motor output maps to the reinnervated biceps gradually moved toward that of the arm area (12). These data therefore suggest a true structural reorganization of the motor output following peripheral nerve anastomosis.

It remains a matter of debate whether adaptational changes during the functional recovery after cortical injuries can be assessed using TMS. In monkeys, shifting positions of motor maps have been observed following cortical lesions, when adjacent unlesioned areas begin to control the function of the previously ablated areas. Similar changes have been observed using TMS in patients with strokes affecting the motor output to the hands (4). In these patients, however, the relationship between the relocation of the “hot spots” and the clinical findings was not straightforward. Thus it remained unclear if these changes were related to plasticity involved in the functional recovery. In some patients with unihemispheric strokes, ipsilateral MEPs have been demonstrated i.e., MEPs from a muscle of the hemiparetic side of the body on stimulation of the unaffected hemisphere (14)]. In adult patients, these ipsilateral responses are probably not significant for recovery, since they do not correlate with clinical improvement (14). They rather suggest unmasking of preexistent but functionally irrelevant uncrossed corticospinal projections. This may be different if the brain lesion occurred in early childhood. We observed a teenaged patient who had suffered a perinatal unilateral brain injury. As the only clinical sequel, mirror movements persisted, but the muscle force was symmetrical. MEPs on both sides of the body were only obtained by stimulation of the unaffected hemisphere, with identical corticomuscular latencies. Hence recovery during early infancy resulted in motor control by the healthy hemisphere using direct ipsilateral corticospinal projections (15).

**Back to basic physiology: improvement of MEP size assessment**

Measurement of MEP size is the basic method of all studies presented above. Yet in all of these studies, averaging of several MEPs was necessary to account for the observed stimulus-to-stimulus size variability. Besides their size variability, MEPs are characterized by the fact that they are usually smaller than responses to maximal peripheral nerve stimulation (Fig. 1A). What are the reasons for these characteristics? Theoretically, the reduced MEP size could result from an inability of TMS to drive all spinal motor neurons to discharge, due to insufficient stimulus strength (“submaximal stimulation”). This possibility is challenged by the observation of Marsden et al. (13), who showed that the force of the TMS-induced muscle twitch may be equal to or even greater than that of the twitch evoked by maximal nerve stimulation and that the size of the MEP is still smaller than the peripheral nerve electrical response. The situation is complicated by the unknown number of multiple discharges of some spinal neurons to the cortical stimulus. In peripheral nerve stimulation, there exists a linear relationship between size of the CMAP and the number of activated muscle fibers. Clearly, a similar relation must exist for MEPs, but it must be altered by some factor(s).

A possible mechanism that reduces the size of a compound action potential is desynchronization of the action potentials from which it is composed. Summation of “out of phase” action potentials induces phase cancellation phenomena, reducing the size (amplitude and area) of the compound potential. If the desynchronization would vary, then the compound action potential would change its shape from one stimulus to the next. In fact, in single-fiber EMG studies and studies in patients with severe peripheral nerve diseases leaving only one or two functioning motor units in the range of the recording electrode, a considerable latency variability of single motor units has been observed after TMS (Fig. 4A and Ref. 11). To test how important desynchronization of spinal motor

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**“Summation of ‘out of phase’ action potentials induces phase cancellation phenomena...”**
neuron discharges influenced the shape and size of MEPs, Magistris et al. (11) developed a technique that can serve to “resynchronize” the descending activity. The principle of this TST is depicted in Fig. 4B. Applied in healthy volunteers, the method proved that nearly 100% of all motor neurons supplying the target ADM could always be brought to discharge, thus demonstrating that desynchronization of action potentials caused the small size of the conventional MEP. Moreover, the trial-to-trial variability of the response size decreased dramatically by use of the TST, proving the importance of varying degrees of desynchronization for the observed variability of MEP shape. The method was recently adapted for use with a foot target muscle, in which it confirmed the ADM data (2). We have used the TST routinely in patients to measure central conduction deficits, and a marked increase in the diagnostic sensitivity was found (2, 10). Thus the TST appears to be a promising tool for the assessment of the TMS response size in future studies.

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References


