Chapter 3.5

Applications of magnetic cortical stimulation

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Introduction

At the beginning of the 1980s, in Cambridge, UK, a special stimulator able to elicit contralateral muscle twitches by discharging electric pulses to the scalp overlying the motor cortex was developed (Merton and Morton 1980a,b). Such responses – thereafter named motor evoked potentials (MEPs) – were elicited after a brief latency (~20 ms to the hand muscles, and ~30–40 ms to the leg and foot muscles), utilising the paucisynaptic, fast-propagating corticospinal tract. The required intensity was painful and not well tolerated. However, it was shown very soon that this technique could open new frontiers in research and clinical contexts concerning motor behaviour (Rossini et al. 1985). A further refinement employing a pericranial cathode and a stimulating anode was developed in the following years. This allowed obtaining MEPs with significantly lower amounts of current. However, the real impetus to transcranial stimulation came from the introduction of the magnetic stimulator (Barker et al. 1985). Since then, brain stimulation has become a frequent procedure in clinical neurophysiology. Details concerning physiological and technical aspects are given in another section of this Book (Rothwell et al.). By employing commonly used circular coils (for example with an inner diameter of about 10 cm) absolute latencies of MEPs, excitability threshold for a given muscle as well as silent period duration and central conduction time can be measured. However, studies concerning interhemispheric differences of the examined parameters and mapping of the motor output from each hemisphere cannot be reliably done due to the possibility of contralateral stimulation and non-focal brain activation. To avoid this problem, in recent years, figure-of-eight coils that allow more focal stimulation were introduced. Moreover, double stimulators able to discharge paired stimuli or triplets within

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the same coil or within two independent coils applied on two separate scalp areas were also developed, for investigating the recovery curves, the interaction of a subthreshold conditioning with a suprathreshold test stimulus as well as the analysis of interactions between different brain areas (Kujirai et al. 1993).

Most frequently measured routine parameters

Central conduction time

Central motor conduction time (CCT) can be calculated by subtracting the conduction time in peripheral nerves from the total latency of MEPs, both measured at the onset of the initial deflection. Depending on the method of peripheral conduction time measurements it might also include the time taken for at least one synaptic delay at the spinal level and the time in the proximal root to the intervertebral foramen. Peripheral motor conduction time is currently measured through two methods: (1) F-wave recordings for the measurement of spine-to-muscle conduction time and (2) direct stimulation of the efferent roots and nerves over the spine.

Both electric and magnetic stimulation on the posterior neck or the back activates spinal roots at the level of the intervertebral foramina. The cervical roots are excited about 3 cm away from the anterior horn cell; this distance is longer for the lumbar sacral cord and suggests that magnetic stimulation of roots is not entirely precise for CCT measurements and – in a clinical context – might miss a partial or complete block of impulse propagation along the most proximal root segment.

F waves are elicited in the relaxed state by delivering supramaximal stimulation (cathode proximal) to peripheral motor fibres at a site near the muscle under examination. The stimulus produces an orthodromic volley in the motor nerves, which gives rise to a short latency response in the muscle (M wave). In addition, an antidromic volley is back propagated to the spinal motoneurones. When this antidromic volley reaches the cell body, it may induce excitation of the spinal α-motoneurone (α-MN) and an efferent volley orthodromically along the motor nerve causing a late excitation of the muscle known as ‘F wave’ (Kimura 1983). These late responses are usually small in amplitude, since excitation – which occurs in the whole α-MN population – is only propagated in a small fraction of the motor axons. Large diameter, rapidly conducting motor-axons tend to show more F waves than small diameter axons. Following Kimura (1983) the peripheral motor conduction time is therefore estimated at: 0.5 × (F − M − 1) + M (where M is the latency of the motor response to peripheral nerve stimulation, F is the shortest latency of a reliable F wave with minimal latency, after having collected at least 20 responses, and 1 is the time due to the central delay at the level of the α-MN). Consequently, the CCT can be obtained as follows: Latency of MEP − [0.5 × (F + M − 1) + M] (Rossini et al. 1987a,b).

There are two main sources of error in this estimation: (1) the turn-around time of 1 ms at the -MN cell body is a rough approximation, and (2) the F wave, especially in its proximal course, travels along a partially refractory axon, and its velocity may be slowed down by an unknown amount.

CCT is partly dependent upon the subject’s height, particularly for the lower limb and pelvic muscles. It is therefore advisable to have either sufficiently large control groups to draw a normogram, or to gather 2–3 separate subgroups of progressively greater height. It is of importance to calculate interside differences of CCTs to limb muscles; this would allow tracking lateralised prolongation of CCT even if the absolute value is still normal.

In children CCT linearly declines with age \( r = -0.836, \ P < 0.001 \). CCT measurements mature during childhood in parallel with increase of axon diameter and myelin thickness, reaching adult unless at the age of 2 or 3 years ( Muller 1991); on the other hand, absolute latencies increase with age due to the increase of body size and limb length.

The latency jump between MEPs obtained at rest and with background contraction has a value of about 2–4 ms in the adult. In children this jump is longer than in adults (up to 10 ms) and progressively decreases with age, reaching the adult value with adolescence. MEPs during contraction
(contracted-MEPs) are shorter in latency and larger in amplitude than MEPs obtained during relaxation (relaxed MEPs); maximal facilitation is exerted in the muscle(s), which act as prime mover(s) for the voluntary movement. The latency jump between relaxed- and contracted-MEPs is also remarkably influenced by the amount of tonic cutaneous input from the skin overlying the target muscle. It is, therefore, advisable to know whether the examined muscle belongs to a region with abnormal sensory perception either due to peripheral or to central nervous diseases.

Magnetic fields pass unattenuated through high resistance body structures including skull and scalp. Stimulus threshold for the elicitation of MEPs in a given muscle during complete relaxation can be defined; the procedure for threshold measurement has been reviewed by a panel of international Experts and defined as the intensity which elicits reproducible MEPs in about 50% of a cascade of 10 to 20 stimuli (Rossini et al. 1994). Motor threshold reflects the global excitability of fast-conducting corticospinal pathways, including large pyramidal neurones, but also cortical interneurones and spinal motoneurones. Motor threshold measured in the fully relaxed target muscle is about 25% higher than when the muscle is activated voluntarily. Minimal muscle activation produces a large reduction of threshold; therefore, visual inspection and acoustic EMG feedback are advisable to ensure complete relaxation. To ensure that the whole system is brought to its maximal excitability, it might be preferable to measure motor thresholds both in complete relaxation and under slight isometric contraction. Interhemispheric threshold differences are not significant provided that a ‘biphasic’ stimulus and a lateralised coil positioning is employed in order to avoid bihemispheric stimulation with the lateral wings when the coil is centred on Cz; this parameter is remarkably less variable than absolute threshold values, and, therefore, it is useful in testing patients with monohemispheric lesions of various aetiologies. Interhemispheric excitability threshold differences are more reliably measured with a ‘focal’ figure-of-eight coil than with a large, circular coil. Excitability threshold can physiologically vary because of brain ageing, and changes with the content of alpha activity in the background EEG.

Threshold abnormalities encountered in various neurological illnesses are summarised in Table 1.

Silent period

Besides early excitatory effects, TMS also produces negative phenomena, the most evident being the presence of a long period of EMG silence (SP) during a sustained voluntary contraction; this SP follows the early excitation as reflected by the MEP (Fuhr et al. 1991). It has been shown that the SP induced by TMS is largely a cortical phenomenon. Its precise origin (i.e. cortical inhibition of descending excitatory inputs or activation of inhibitory descending or spinal pathways) remains uncertain. The magnitude of the Cortical SP is not the same for all muscles: for a given stimulus intensity, adjusted as a function of motor threshold, SPs are longest in hand muscles and less prominent in proximal arm or leg muscles, suggesting that the relative importance of muscle representation within the motor cortex plays a role. In normal subjects, the level of background EMG activity does not influence the duration of the SP but it increases for higher stimulus intensities. Thus, SP measurements should be made under precise control of stimulus intensities, with respect to individual motor threshold values.

Paired transcranial stimulation.

Paired TMS allows exploring the function of intracortical inhibitory interneurones (Kujirai et al. 1993). It has been used to investigate the possible role of central mechanisms for epilepsy and antiepileptic drug action, as well as in the genesis of chronic fatigue reported by MS patients.

Magnetic stimulation of spinal roots and peripheral nerves

Due to their physical properties, magnetic stimulators can be used to activate peripheral nervous structures, even when they are located some distance away from the skin. For example, the sciatic nerve can be readily stimulated in the thigh, where it is inexorable by conventional non-invasive electrical stimuli. Except for measuring the conduction time within otherwise inaccessible
TABLE 1

SUMMARY OF MEP ABNORMALITIES MOST OFTEN OBSERVED IN VARIOUS SPINAL CORD DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>Threshold</th>
<th>CCT</th>
<th>Amplitude</th>
<th>Silent period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>N/+</td>
<td>++</td>
<td>N/-</td>
<td>+</td>
</tr>
<tr>
<td>Motor neurone disease</td>
<td>++</td>
<td>N/+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cervical spondylotic myopathy</td>
<td>N/+</td>
<td>+</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis</td>
<td>N/+</td>
<td>N/+</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>Degenerative atactic disorders</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>?</td>
</tr>
</tbody>
</table>

*CCT, central conduction time; N: normal; +, prolonged CCT or silent period, increased threshold; −, reduced amplitude, shortened silent period; ?, no data available.

parts of the peripheral nervous system, this new technique has not replaced conventional nerve conduction studies. With large circular coils, which are most efficient to stimulate deep structures, the precise site at which nerve excitation actually occurs remains difficult to determine while more focal eight-shaped coils often lack the necessary power to ensure that stimulation is supramaximal. Thus, the presence of a conduction block in a proximal root or deep nerve can seldom be ascertained. Finally, except with specially designed coils (Maccabee et al. 1996), magnetic stimulation cannot activate the intradural portion of motor roots, for example within the cauda equina; the large stimulus artefacts usually render nerve conduction studies time-consuming. Nevertheless, there are some clinical indications in which magnetic stimulation of roots or nerves seem to be of interest and we will briefly review some of them.

Estimation of peripheral motor conduction time

As previously noted, magnetic stimulation over the cervical and lumbar spine activates the motor roots at the vertebral foramina and produces muscle responses with similar latencies as percutaneous electrical stimulation over the same region. In most subjects, the largest responses are obtained in hand muscles when the lower half of a large diameter circular coil is placed over the lower cervical spine while the opposite is usually observed for proximal muscles. This is probably because upper cervical roots (C4,5,6) leave the spine in a downwards direction while the lower roots (C8/T1) leave in an upward direction. Thus, in the above mentioned positions, the windings of the coil are best following root orientation. There are marked interindividual variations of the optimal coil positioning, although, for a given coil position, responses are reproducible and latency measurements present no major difficulties. Amplitudes of evoked CMAPs are seldom maximal, i.e. equal to those obtained by supramaximal electrical stimulation of the corresponding nerve. Moreover, magnetic spinal stimulation simultaneously activates several roots, so that responses recorded in a given muscle can be contaminated by those elicited in nearby muscles innervated by other nerves. This is particularly true for forearm and arm muscles. In this case, calculation of peripheral motor conduction time could give abnormally short values if responses recorded in a given muscle are contaminated by those of other muscles innervated by faster conducting nerves. This difficulty can be overcome by comparing the shapes of responses elicited in a given muscle by spinal magnetic and peripheral electrical stimulation, which should be similar or by employing coaxial recording needles inserted in the muscle(s) of interest. Some normal values of MEPs are reported in Table 2.

Magnetic stimulation over the lumbosacral spine can also be used to assess conduction time within peripheral nerves and roots. However, with conventional circular coils, excitation only occurs at the vertebral foramina, omitting the conduction within the cauda equina. In this case, alternative methods should be proposed: F-wave measurements described above (Rossini et al. 1987a,b), magnetic stimulation over the conus medullaris with specially designed coils (Maccabee et al. 1991) or
TABLE 2
NORMAL VALUES OF DIFFERENT MEP PARAMETERS

<table>
<thead>
<tr>
<th>Muscle</th>
<th>n</th>
<th>Threshold (% max)</th>
<th>Latency (ms ± SD)</th>
<th>Interhemispheric difference</th>
<th>CCT (ms ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deltoid</td>
<td>50</td>
<td>51 ± 7</td>
<td>9.5 ± 1.5</td>
<td>0.6 ± 1.7</td>
<td>4.1 ± 0.7</td>
</tr>
<tr>
<td>Biceps</td>
<td>89</td>
<td>42 ± 7</td>
<td>11.4 ± 0.7</td>
<td>0.4 ± 0.4</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>A.D.M.</td>
<td>50</td>
<td>47 ± 8</td>
<td>21.8 ± 0.8</td>
<td>0.8 ± 0.7</td>
<td>7.1 ± 1.1</td>
</tr>
<tr>
<td>F.D.I</td>
<td>89</td>
<td>38 ± 6</td>
<td>20.7 ± 0.8</td>
<td></td>
<td>6.5 ± 0.7</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>50</td>
<td>55 ± 9</td>
<td>21.0 ± 1.5</td>
<td></td>
<td>12.4</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>89</td>
<td>53 ± 11</td>
<td>26.7 ± 2.6</td>
<td>0.7 ± 0.5</td>
<td>14.8 ± 1.4</td>
</tr>
<tr>
<td>Soleus</td>
<td>50</td>
<td>70–90</td>
<td>26.6 ± 2.7</td>
<td>0.7 ± 0.7</td>
<td>13.3 ± 1.9</td>
</tr>
<tr>
<td>Abductor hallucis</td>
<td>50</td>
<td>55–75</td>
<td>35.9 ± 3.3</td>
<td>0.6 ± 0.5</td>
<td>12.9 ± 0.8</td>
</tr>
<tr>
<td>Bulbo-cavernous</td>
<td>50</td>
<td>75–100</td>
<td>19.4 ± 3.5</td>
<td></td>
<td>13.2 ± 2.7</td>
</tr>
<tr>
<td>Anal-sphincter</td>
<td>50</td>
<td>75–100</td>
<td>22.8 ± 3.6</td>
<td></td>
<td>13.3 ± 2.3</td>
</tr>
</tbody>
</table>

*These values are taken from the laboratories of A. Maertens de Noordhout and P.M. Rossini. n, number of patients; CCT, Central Conduction Time.

Percutaneous electrical stimulation over the same region (Maertens de Noordhout et al. 1988). The latter two methods offer the advantage of allowing measurement of conduction time within the cauda equina.

Conduction studies within deeply situated nerves and roots

As stated above, large magnetic coils are able to excite deeply situated nerves. Some authors (e.g. Chokroverty et al. 1991) have suggested that this method could be useful in the lumbar radiculopathies. However, since nerve excitation takes place distally to the most common sites of compression (e.g. disk herniation), there must be a marked axonal damage to induce significant latency prolongation or amplitude reduction of CMAPs. Due to marked interindividual variations of CMAP amplitudes evoked by magnetic root stimulation and to the fact that responses are seldom maximal even in normal subjects (Fig. 1), the presence of a definite conduction block within a plexus or root segment is unlikely to be demonstrated if usual criteria are to be applied. Nevertheless, this technique can be of some help in special situations, for example in localising a gross lesion of deep nerves such as the sciatic nerve in the thigh, or for early evaluation of brachial plexus function after severe trauma. In the latter case, patients are often unconscious so that co-operation for needle EMG examination is lacking, and conventional nerve conduction studies may remain normal for a few days. Provided the

Fig. 1. Responses evoked in tibialis anterior of a normal subject by magnetic stimulation of the motor cortex (upper set of traces), magnetic stimulation over the low lumbar spine (second set of traces), magnetic stimulation over the posterior thigh (third set of traces, lower edge of large circular coil 15 cm above the popliteal fossa) and conventional supra-maximal electrical stimulation of the peroneal nerve at the fibular head (bottom set of traces). Responses to cortical, spinal and thigh stimulations are clearly smaller than those to conventional superficial nerve stimulation. Thus, although responses are very well defined in this example, the presence of a conduction block, for example within the thigh, could never be ascertained.
The cervical spine is intact, magnetic stimulation over this region with multiple recordings can help establish the extent of root or plexus damage. Simultaneous recordings from proximal and distal muscles with different myelomeric innervation can be of help in localising the level of abnormal motor impulse propagation within the spinal cord.

**Facial nerve stimulation**

Careful studies conducted on patients who underwent posterior fossa surgery have indicated that magnetic stimulation over the mastoid region activates the facial nerve in the labyrinthine part of the facial canal, i.e. proximally or very close to the site where nerve injury usually occurs in Bell’s palsy (Rössler et al. 1991). In this case the coil should be positioned on the parieto-occipital region ipsilateral to the nerve. In Bell’s palsy, while the facial nerve often remains partially excitable by electrical stimulation at the stylomastoid foramen, it is usually inexcitable upon magnetic stimulation. In Guillain-Barré syndrome with facial nerve involvement, latencies of responses to magnetic stimulation are usually prolonged but responses remain present. The technique seems very sensitive to detect clinically silent contralateral lesions. The facial nerve of patients having suffered from Bell’s palsy often remains inexcitable to magnetic stimulation for long periods, even after clinical recovery.

**Mapping of motor output**

A surface map of the topography of human cortico-motor projection can be generated by TMS which is in some way related to the representation of the muscle in the motor cortex (Wassermann et al. 1992). Since TMS preferentially activates fast-conducting cortico-spinal fibres, TMS maps are likely to be related to the origin and the distribution of the most directly projecting and fast conducting output fibres of the motor cortex. It is possible to quantify the centre of the map, based upon curve fitting approaches or by a weighted sum of the MEP amplitude at each stimulus site. There are at least two mechanisms that explain the rate of fall-off in MEP amplitude as the centre of the coil is moved away from the centre of the map. Firstly, with increasing distance from the map centre either density or excitability of fast-conducting cortico-spinal fibres could decrease. Secondly, the distribution of excitable cells could be confined to a small region and the decline in MEP amplitude be caused by decreased stimulation efficacy due to current spread.

Changes in the cortico-motor representation associated with altered sensory input, associated with immobilisation, voluntary activation, motor learning, limb amputation and ischemic nerve block, dystonia, stroke, and facial palsy have elucidated basic mechanisms of neuronal ‘plastic’ reorganisation.

**TMS in clinical practice**

The examination should be performed in a well-lighted environment, the subject should be asked to maintain the eyes open and the state of wakefulness should be monitored.

Whenever possible, the examiner should try to define the normative values of his/her lab (or at least to compare a small sample of ‘in house’ controls with the reference tables available in the literature, Table 2), and it would be better if normal values are subdivided by age and height. The more precise the electrode localisation on the target muscle and the lower the skin-electrode resistance (≤10 kΩ), the more distinct the MEPs will be. Skin cleaning with ether, alcohol or sandpaper, as well as a brief massage in the contact area, facilitates the penetration of the conductive jelly and impedance lowering. The active (exploring) electrode should be placed in the area between proximal third and middle of the muscle belly (where the motor point is usually located), while the inactive electrode should be placed on the muscle-tendon junction (= so-called belly-tendon montage). Interelectrode distance should never be too long (usually in the order of 2 to 5 cm depending upon the muscle length) in order to avoid excessive contamination or cross talk from adjacent muscles. Sterile, coaxial needles can be employed whenever recordings from an individual muscle without cross-talk contamination are needed (i.e. from an atrophic muscle, from pelvic floor muscles etc.). The ground electrode should be positioned as close as possible to the
For brain stimulation:
(a) Place the coil with the appropriate side in contact with the skull (Fig. 2). The side of contact is very important for monophasic stimulators, while its influence on MEP amplitude is less with biphasic stimulators. In fact, for the former, the appropriate side is chosen on the basis of the orientation of the current circulating in the coil and the hemisphere to be stimulated. By knowing that the current flow most appropriate for motor area stimulation is from posterior (= inion-nasion direction) and that induced current direction is opposite to the one of the current circulating in the coil, seen from the above, then clockwise current circulation in the coil activates primarily the right hemisphere and vice versa.
(b) Search for the ‘hot spot’, i.e. the scalp position where the stimulus elicits the MEP of largest amplitude and minimal latency (Fig. 3). To do this, a distinctly suprathreshold intensity of stimulation should be used (i.e. 60–70% of stimulator’s output for upper limb muscles). Once the ‘hot spot’ is localised, then progressively decrease the stimulus intensity in steps of 1% until MEPs are present on only about 50% of trials and define it as the excitability threshold.
(c) Acquire 2–3 MEPs during complete relaxation and, if possible, during contraction at roughly

![Fig. 2. Position of eight-shape focal coil. The right position is over the motor area, with the coil making an angle of 45° versus Cz and the handle of the coil posteriorly oriented.](image)

![Fig. 3. TMS delivered in different scalp sites. MEPs are recorded from ADM muscle of the right hand in relaxed condition (on the left) and during contraction. Note that during relaxation, MEPs are elicited only when the stimulus is delivered over the appropriate scalp site above the motor area. During contraction, MEPs are elicited from several points, testifying that there is an increase of cortical excitability.](image)
30% of maximal strength. The precise amount of contraction is not critical. If voluntary contraction is not possible (i.e. uncooperative patient, hemiparesis, comatose etc.) other types of facilitating techniques are available which include:

- ask the subject to activate the homologous muscle on the opposite side (this is useful for hemiplegic patients);
- electrical prestimulation of the sensorimotor peripheral nerve fibres innervating the target muscle (interval suggested around 20 ms for upper limb and around 60 ms for the lower limb);
- vibration of the target muscle (usually around 80 Hz);
- noxious stimulation of the region including the target muscle.

As a general rule, interstimulus intervals of 3 s or longer should be used throughout the examination. Usually a consistent result can be achieved with about 5 to 10 stimuli. In normals there is no evidence for side effects with this low-frequency stimulation. If necessary, TMS can be repeated in different recordings sessions for follow-up purposes. In very rare patients seizures have been induced by this technique, but only when an underlying disease such as stroke or epilepsy predisposes to seizures.

For elicitation of ‘F waves’, the motor nerve innervating the target muscle should be supramaximally stimulated (i.e. 20% intensity above the one producing the largest M wave), with the cathode proximal, in order to avoid anodal block of the antidromically propagated motor impulses. At least 15–20 ‘F waves’ should be collected; the latency of the earliest and reproducible one should be taken for calculation of the CCT formula (Section 2.1).

Whenever possible, measurements should be performed on both sides, trying to replicate exactly the same technique (i.e. the interelectrode distance). This will be maximally helpful in detecting minor interside differences which – in the healthy – are small and quite stable (Table 2).

In a separate chart, the pharmacological treatment should be listed, considering that several neuroactive drugs, particularly sodium channel blockers can influence absolute CCT and threshold values, but do little affect their interhemispheric differences.

**How to measure the various parameters**

Absolute latencies of MEPs are measured at the onset of the initial, repeatable deflection, regardless its polarity, whenever a multiphasic morphology is obtained. Be aware of long, positive initial phases of MEPs which might be due to volume conduction from muscles different from the one under examination. In case the onset is difficult to define (i.e. due to background EMG) then the initial peak latency might be taken. Absolute amplitudes are taken as the difference between the two peaks of opposite polarity. Silent period duration can be measured either from the onset of MEP to the return of EMG bursting or from the end of MEP (defined as its return to baseline) to the return of EMG.

It is recommended to prepare a checklist to be submitted for careful consideration and signature by the referring physician and the patient, enquiring whether metallic objects are present in the body, especially in the region of the head. There has been, however, no systematic study if TMS may be performed safely in patients with cervical myelopathy and cervical implants for stabilising the cervical spine. It is further important to know, whether the patient is suffering from epilepsy, whether craniotomies have been previously performed (this is particularly important for electrical stimulation, since the current usually tends to focus below bone discontinuities), whether electronic devices are worn (i.e. cardiac pacemakers, brain or spinal cord or nerves or bladder stimulators, or portable pumps for drug administration etc.). Finally, both the patient and the examiner should remove mechanical watches, magnetic cards or other electronic devices (portable computers, electronic notebooks, cellular phones) putting them at least 1 m away from the stimulating coil. Some authors recommend that the Examiner (especially if working for several hours with TMS) should wear earplugs. First-aid facilities should be available for assisting in case of a seizure.

During an ‘ideal’ routine TMS session the following should be performed:

1. Check-list for safety
2. Explanation of the purposes and methods
3. Take a note about the age, height, current therapy, and relevant clinical information.
4. Electrode application on the appropriate sites, and with optimal skin-electrode impedance.
5. Patient lying supine (this facilitates full muscular relaxation) or seated, with open eyes in a relatively soundproof environment (any sudden noise can modify threshold parameters).
6. Demonstrate a few stimuli in the air or on the examiner at wrist in order to familiarise the subject with stimulus.
7. Stimulate the brain, scanning the appropriate scalp area in search for the ‘hot spot’.
8. Define the excitability threshold during relaxation and contraction.
9. Collect and superimpose 2–3 MEPs during relaxation.
10. Collect and superimpose 2–3 MEPs during contraction.
11. Perform sustained contraction for silent period measurements, collect and superimpose 2–3 traces.
12. Collect M wave of maximal amplitude during supramaximal peripheral nerve stimulation and calculate the M/MEP amplitude ratio.
13. Collect and superimpose 2–3 MEPs during spinal root stimulation.
14. Collect and superimpose the ‘F waves’ during supramaximal nerve stimulation.
15. Repeat – if required – for other body areas (i.e. lower limb, pelvic floor etc.).
16. Repeat on the other side and note the interside differences of the measured parameters.
17. Ask and take a note for any side effect.

**Clinical studies**

In the following sections we report the major findings and some practical instructions in performing TMS in some clinical conditions where they are often required by referring physicians.

**Stroke**

MEPs are often absent in most severely affected patients whereas in less affected patients they show longer latency and smaller amplitude. The presence of MEPs in the earlier stages of disease correlates with a good recovery (Heald et al. 1993a,b). Abnormalities of Central Conduction Time (CCT) are observed in more than 50% of cases with minor cerebral ischemia of lacunar type. While prolonged CCTs correlate with the level of weakness, the increase of threshold correlates with the presence of brisk tendon reflexes. The mechanism for CCT prolongation is probably multifactorial: loss of fast-propagating corticospinal neurones, slowing at the lesioned site, the contribution of direct cortico-motoneuronal connection from non-primary motor areas, loss of tonic facilitatory sensory feedback from the hand, and involvement of new cortico-cortical connections (not contributing to normal MEPs).

Robust muscle contraction in paretic arm shortens the duration of the SP; this represents a bad prognostic sign when observed in the acute stage of the disease, being associated with poor functional recovery and with the appearance of spasticity. Serial TMS performed for up to 2 years after stroke has showed a decrease of the SP duration paralleling the clinical amelioration.

A significant correlation between reorganisation of cortical motor output, and clinical recovery in a subacute post-stroke epoch has been described. An increased output from the Unaffected Hemisphere (UH) is found in subacute stroke patients, which decreases during follow-up, associated with an increased Affected Hemisphere (AH) output. Inter-hemispheric balancing of contracted MEP amplitude may represent a ‘marker’ of clinical recovery (see Rossini and Rossi 1998 for a review).

The recovery of MEP latency is highly correlated with return of muscle strength and hand function. Ipsilateral responses can be found (mainly from more proximal muscles) during stimulation of the Unaffected Hemisphere (UH). Some authors consider them extremely important for recovery, while others have identified them prevalently in the poorly recovering patients, therefore suggesting that the underlying mechanism may not be beneficial for recovery.

In normals, the cumulative effect of active contraction and vibration of the target muscle is less than the summation of the two facilitatory
effects considered individually. On the contrary, when voluntary contraction and vibration are combined in a muscle affected by spasticity a cumulative facilitation is obtained. In spastic muscles it is also possible to record a SP in the absence of a MEP.

Multiple sclerosis

In multiple sclerosis (MS) there is a prolonged – either bilateral or unilateral – CCT which is consistent with demyelinating lesions of the corticospinal tracts. Similarly to other evoked potential modalities MEPs also vary considerably in latency, amplitude and shape when they are measured in consecutive trials. In fact, while the onset latency fluctuates between 0.27 and 0.86 ms in controls (mean 0.59 ms) during 10 to 50 consecutive trials, this index ranges between 0.5 and 5.9 ms (mean 1.49 ms) in MS patients. One possible drawback of this technique is represented by the fact that onset latency of contracted MEPs is sometimes hardly discernible from the background EMG. Increased onset latency variability correlated significantly with impairment of fine finger movements and pathological finger jerks, while the latter symptoms correlated with abnormally prolonged CCT. Slower conduction and increased refractoriness to repetitive trains may be the causes for late ‘I waves’ to be much smaller in amplitude than the earlier ones with insufficient excitatory effect to raise the motoneuronal threshold to activation threshold. Peristimulus time histograms of a motor unit in the first interosseus muscle triggered by TMS in MS patients show that the primary peak is either absent, or delayed in its latency onset; moreover, increased intermodal intervals separate subpeaks. Frequency-dependent blocks of impulse propagation across demyelinated plaques and differential thresholds to successive ‘I waves’ have been postulated amongst the probable causes of descending impulses desynchronisation leading to less effective temporal summation of EPSPs at the spinal motoneurone. A significantly increased excitability threshold for relaxed MEPs elicitation is frequent. In a population of MS patients, average motor thresholds in resting or pre-activated hand muscles are moderately increased. This finding may seem surprising, as spinal motoneurones are known to be hyperexcitable in spastic patients and thus undoubtedly reflects a loss of excitability of central motor pathways. There is a positive correlation between CCT prolongation and threshold values, and a negative correlation between MEP amplitude and motor thresholds.

TMS in movement disorders

In patients with Parkinson’s disease the corticomotoneurone conduction is normal whereas it can be abnormal in other types of parkinsonism. Similarly, in Huntington’s chorea, primary dystonia, essential tremor and myoclonus, the corticomotoneurone conduction is normal whereas it can be abnormal in patients with secondary forms. The analysis of the SP and of the suppression of the test response after a conditioning shock has demonstrated altered cortical excitability in patients with movement disorders. In Parkinson’s disease, the SP is shorter and can be prolonged after dopaminergic therapy. Cortico-cortical inhibition tested at short conditioning-test intervals and with the muscle at rest is reduced in Parkinson’s disease. On the other hand, suprathreshold conditioning stimulation and long conditioning-test intervals during contraction increases intracortical inhibition. Again, dopaminergic stimulation reverses this abnormality. Studies conducted to assess the effect of TMS on the execution of rapid movements in Parkinson’s disease have noted that a single magnetic shock given over the motor cortex before a movement improves the reaction time and the EMG pattern associated with the movement. This observation is compatible with the increased inhibition of the test response reported with the paired shocks at long interstimulus time intervals (Berardelli et al. 1996). In Dystonia mild shortening of the duration of the SP is a common finding (Rona et al. 1997). In a study of cortico-cortical inhibition, performed at rest and with short interstimulus time intervals, Ridding et al. (1995) reported a decrease of intracortical inhibition. Conversely, Rona et al. (1997), using the paired shock technique, during contraction and testing longer conditioning-test intervals, demonstrated an increased inhibition of MEPs.

In Huntington’s disease the SP has been reported
to be prolonged in duration in some patients. On the other hand, studies of the cortico-cortical inhibition performed at rest and during contraction and testing short and long interstimulus time intervals did not show modification of the intracortical inhibition. In patients with essential tremor the SP and the MEPs elicited by the paired shock technique tested at short and long conditioning-test intervals behave similarly to normal subjects (Romeo et al. 1998). This suggests that patients with essential tremor have normal cortical motor excitability. TMS in patients with myoclonus has been used for studying the excitability of the motor cortex and the site of origin of myoclonic jerks. Briefer SP and abnormalities of cortico-cortical and transcallosal inhibition have been found.

Various attempts have been made to detect abnormality of MEPs threshold in patients with movement disorders. In Parkinson’s disease threshold measurements have produced inconsistent results. Some authors have found a decrease, others an increase and others no change. Conditioning of brain excitability threshold via pre-stimulation of peripheral nerve fibres is lost in parkinsonian patients who have depressed frontal somatosensory evoked potentials. Patients with Huntington’s disease, dystonia and essential tremor have all been reported to have a normal threshold for evoking the MEPs.

*Transcranial magnetic stimulation in spinal cord diseases*

Prolongation of CCT can be encountered in a broad spectrum of spinal cord diseases including cervical spondylotic myelopathies or spinal tumours, syringomyelia, spinocerebellar ataxia and hereditary spastic paraparesis. A careful analysis of some other parameters of responses to TMS, such as threshold measurements, latency variability of response to cortical stimulation or TMS-induced silent periods can sometimes help distinguishing between these entities. Subjects with cervical spondylotic myelopathy often have normal CCT to proximal cervical cord while it is usually prolonged to lower cervical segments, reflecting the fact that spondylotic changes are most often encountered at C5/6 and C6/7 levels.

In the majority of cases, CCT to lumbar roots is also prolonged but, due to increased variability of normal range of values, this parameter is less reliable than CCT to lower cervical segments. In cervical spondylosis, responses to TMS are usually polyphasic, desynchronised, but such response shapes can occasionally be observed in lower limb muscles of normal subjects. From a technical point of view, simultaneous recording from multiple muscles, with different myelomeric innervation, is helpful for a better localisation of partial or total block of impulse propagation.

In patients with traumatic spinal cord injury relaxed-MEPs might be absent; however, combined stimulation of peripheral afferents and of corticospinal fibres impinging upon the same spinal MNs often enable eliciting MEPs revealing preserved corticospinal innervation despite absent MEPs to TMS alone. A train of impulses to the medial sole can be used for MEPs conditioning in tibialis anterior muscle. Therefore, when TMS and conditioning stimuli are combined, MEPs clearly show up in some cases, demonstrating the presence of surviving corticospinal fibres to lower limb.

*Amyotrophic lateral sclerosis (motor neurone disease)*

Loss of corticospinal cells in the typical motor neurone disease (MND) would be expected to result in decrease of amplitude of MEPs to TMS and also to cause prolongation of CCT, by both dropout of larger, faster conducting axons and reduction in the amount of descending impulses impinging upon anterior horn cells, thus increasing the time necessary for excitation to exceed their firing threshold. The MEP/M-wave amplitude ratio is normal in patients with MND without hyperreflexia, while it has been reported decreased in those with brisk tendon reflexes. Significantly briefer SPs have been found in MND, while this index is longer when the MND is combined with dementia. Primary lateral sclerosis (PLS) patients show significantly increased values of excitability threshold and longer CCT for both upper and lower limbs. On the contrary, threshold for relaxed-MEPs elicitation is often lower than normal in ALS especially in muscles with relatively
preserved muscular bulk and rich of fasciculations. In this case, MEPs with lower than normal thresholds are indistinguishable in shape from spontaneous fasciculations (Fig. 4). Spastic limbs, with an advanced muscular atrophy, often show higher than normal threshold for relaxed-MEPs elicitation. The shorter duration of the SP in patients with corticospinal tract involvement either reflects a reduced central inhibitory effect, or a hyperexcitability of spinal motoneurones. Motor threshold measurements can also be useful in other diseases of central motor pathways and can sometimes bring clues about their pathophysiology. For example, it has been elegantly shown that motor thresholds are usually normal or even slightly reduced in early motor neurone disease, while later in the course of the illness, thresholds are usually very high, often to the point that no responses to TMS can be evoked (Fig. 4). In several patients, no responses at all can be recorded upon maximal TMS.

**Intraoperative monitoring**

In intact humans, electrical or magnetic stimulation of cortical motor areas evokes a complex descending volley that can be recorded with electrodes placed in the epidural space or directly on the spinal cord. Investigators have concluded that both the early and later waves are similar to the D and I waves recorded in animal experiments after direct stimulation of motor cortex. The descending volley consists of an initial wave, followed by later and smaller waves (similar to the D and I waves of animal experiments), which are transmitted along the corticospinal axons.

Recording the descending volley evoked by cortical stimulation is an important tool for monitoring the integrity of the corticospinal paths during neurosurgery. The experimental conditions yielding reliable recordings included a bipolar montage for transcranial electrical stimulation, epidural recording of the descending volley at two spinal levels, a high-pass filter of 500 Hz, and stable anaesthesia. In patients with spinal cord lesions the descending volley evoked by electrical stimulation of cortical motor areas can be recorded from a site above a lesion but not below. An alternative way of monitoring spinal cord function is to record the motor potentials from the muscles after transcranial stimulation. A reduction in the amplitude of the motor evoked potentials elicited by transcranial stimulation could indicate the neurological outcome in patients with spinal cord lesions. However, one of the problems of this method is the effect of anaesthetic agents on the MEPs. Commonly used inhalational and intravenous anaesthetics cause an attenuation of transcranial magnetic and electrical MEPs therefore limiting the clinical usefulness of transcranial stimulation for intraoperative monitoring. Stimulation of cortical motor areas with short trains of high-frequency electrical stimuli may elicit MEPs of large amplitude that are less attenuated by anaesthesia. A further method is direct electrical stimulation of the spinal cord, able to record stable MEPs in the presence of a balanced anaesthetic technique. Deterioration of MEPs have been demonstrated in a number of patients with this method. As a methodological point it should be pointed out that anaesthetic agents, muscle relaxants and body temperature all affect speed of propagation of the neuronal impulse as well as synchronisation along

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**Fig. 4.** Responses evoked in the first dorsal interosseous muscle of the hand of a patient with classic amyotrophic lateral sclerosis by TMS (upper traces) and magnetic stimulation over spinal roots (bottom traces). While the latter show normal shape and latency, responses to TMS have very variable and slightly prolonged onset latencies, small amplitudes and relatively short duration (compared to responses to spinal stimulation). TMS responses recorded under slight isometric contraction.
fibres of various calibre and the amount of muscle evoked-twitching. Therefore, measurements of baseline values should begin only when the patient is in a stabilised anaesthesiological condition (including BP and HR). Maximal cooperation with the anaesthesiologist is needed in order to monitor and maintain stable conditions throughout the various stages of the surgical procedure. Latency prolongation of about 1 ms and amplitude reductions beyond 50% of baseline are considered signs deserving attention; if maintained in time (i.e. in 3 consecutive records) the surgeon should be alerted for possible spinal cord damage. Special attention should be paid to false amplitude reductions; in fact, physiological and draining liquids might reach the recording electrodes (especially the epidural ones) and produce their short-circuiting.

Epilepsy and drugs

Several TMS parameters such as motor threshold (MT), MEP size or intracortical excitability are altered in epilepsy. MT was reported to be elevated in a number of partially conflicting studies (overview in Ziemann et al. 1998). It has become clear that sodium channel blockers elevate MT whereas GABA Agonists do not (see below). So far it is still unclear if epilepsy itself changes MT or if the many alterations reported in the literature are caused by the concomitant medication (see Cracco and Rossini 1998 for a review).

A reduction of MEP size has been reported when TMS was triggered during the slow wave of the Spike-and-Wave EEG complex. In progressive myoclonic epilepsy a marked increase in MEP amplitude could be shown after conditioning the test stimulus by a peripheral electrical stimulus 20–60 ms earlier. The SP in epilepsy is reported to be bilaterally prolonged. In general, intracortical (cortico-cortical) inhibition has been found to be reduced in all diseases studies so far. In epilepsy this has been confirmed for patients with juvenile myoclonic epilepsy, cortical myoclonus, temporal lobe epilepsy, epilepsy partialis continua, and focal epilepsy. In the latter study the reduction of intracortical inhibition was confined to the motor cortex ipsilateral to the epileptic focus. Intracortical facilitation was reported to be normal in patients with myoclonus and increased in patients with focal epilepsy ipsilateral to the epileptic focus. Transcortical inhibition was normal in the subgroup with focal cortical myoclonus, while it was abolished in the subgroup with generalised myoclonus.

Attempts to use TMS for seizure induction and focus localisation have been disappointing. Instead, with lower stimulation frequencies, a reduction in epileptic activity has been observed. At present no strong applications are indicated in the diagnostics of epilepsy. The epileptic focus cannot be localised with sufficient resolution. Reduced cortico-cortical inhibition is a nonspecific finding in many other diseases.

TMS studies on the acute effects of CNS active drugs in normals

Antiepileptic drugs (AEDs) with a main mode of action onto sodium channels (carbamazepine, phenytoin, lamotrigine) increase motor threshold. In contrast, AEDs or other drugs supporting the action of GABA such as lorazepam, diazepam, vigabatrin, baclofen and ethanol have no significant effect on MT. Inconsistent results have been reported on the SP which was lengthened by carbamazepine and shortened by diazepam (overview in Ziemann et al. 1998).

None of the tested sodium channel blocking AEDs have significant effect on intracortical inhibition, where most of the GABA-supporting drugs enhance intracortical inhibition and suppress intracortical facilitation. Glutamate antagonists reduce intracortical facilitation. Intracortical inhibition is increased by dopamine agonists such as bromocriptine and pergolide and reduced by neuroleptic drugs such as haloperidol. Haloperidol also increases intracortical facilitation. I-Wave generation is transiently suppressed by the GABAAergic drugs lorazepam, vigabatrin, phenobarbital and ethanol, whereas the GABA-B receptor agonist baclofen, the antiglutamate drugs gabapentin and memantine and the sodium channel blockers carbamazepine and lamotrigine have no effect.

Miscellaneous

In patients affected by hereditary spastic para-
plegia from 17 kinships including Type I, Type II and intermediate forms, MEPs, when present, are very often delayed. No correlation has been found with hyperreflexia or Babinski sign. Two generations (19 members) of a family affected by hereditary motor and sensory neuropathy with pyramidal signs (HMSN Type V) showed a normal CCT to the hand muscles, while that to biceps was slightly prolonged in 3 cases. CCT to lower limbs was normal in all the non-affected members, while all the affected ones showed both CCT prolongation as well as low voltage, small MEPs. CCT was abnormal to thenar muscles in 91% of patients with Friedreich’s ataxia, and 70% in patients with early onset cerebellar ataxia and 38% with late onset cerebellar ataxia. Abnormal thenar and soleus muscles latencies were found in all out of 20 cases of Friedreich’s ataxia investigated. Pathological conduction times in all patients with Friedreich’s ataxia and spinocerebellar ataxia, more accentuated to the lumbar spine and in about half of the patients with olivopontocerebellar atrophy and non Friedreich’s ataxia. In spinocerebellar ataxia type 1, 8/8 patients had either prolonged latencies or absent responses, whereas this was only found in 2/11 patients with SCA2 and in 5/18 SCA3 patients. Distinctly, higher rates of abnormalities in SCA1 were found (see Rossini and Rossi 1998 for a review).

MEPs to magnetic TMS have been recorded from bulbocavernous and anal sphincter muscles. CCT have been calculated by direct stimulation of the sacral roots. Abnormally prolonged CCTs to pelvic muscles have been calculated in patients suffering from dorsal and lumbosacral myelopathies of various aetiologies (herpetic myelitis, MS etc.) The combined use of motor and somatosensory evoked potentials together with sacral reflex recordings has been encouraged in the evaluation of patients with urinary and sexual dysfunctions.

In conclusion, brain and spinal root stimulation represents a relatively new field of clinical neurophysiology undergoing a rapid evolution. The method is safe, clinically suitable and extremely useful in determining propagation and excitability characteristics of the central motor tracts and along the proximal portion of spinal roots and nerves.

References


