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Hands-on course 1

Transcranial magnetic stimulation

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1. Summary

Transcranial magnetic stimulation (TMS) is used clinically to detect lesions in the corticospinal tracts. Following TMS of the motor cortex motor potentials can be recorded from the target muscles. Magnetic stimulation is also used in special applications for diagnostic assessments of certain parts of the peripheral nervous system that are inaccessible to conventional electric stimulation. TMS was introduced in 1985 by Barker and colleagues as a new method for painless and non-invasive stimu-

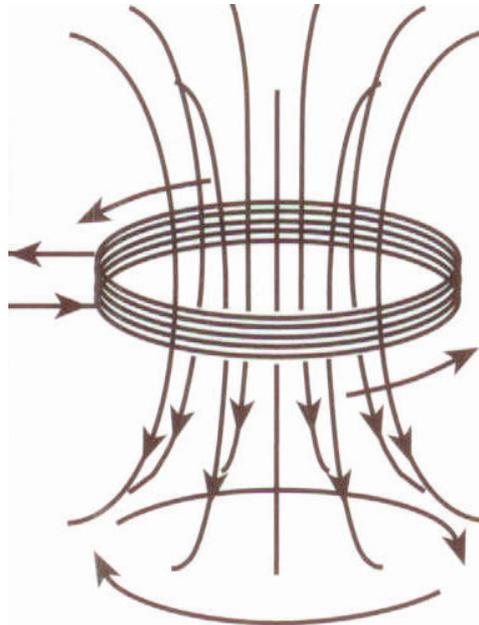


Fig. 1: Principle of electric magnetic induction. A capacitor is discharged through a copper coil. A magnetic field is induced perpendicular through the direction of the windings. By rapid change of the magnetic field an electric current is induced in parallel through the magnetic coil, whose direction is opposite to the current direction in the magnetic coil.

lation of the human motor cortex. TMS is used in Europe in the routine diagnostic assessment of neurological disorders. In contrast it is less popular in other parts of the world including North America. TMS is also of eminent significance beyond its clinical utility as a scientific method, by the use of which a host of scientific questions in relation to central motor control has been successfully addressed. TMS is also increasingly being used to generate lasting changes of excitability both in research settings as well as with a therapeutic intention. These latter applications cannot be dealt with in the following sections for space reasons.

2. Anatomy and Physiology

2.1. Physical Foundations

TMS is based on the principle of electromagnetic induction. A capacitor is discharged through a magnetic coil placed over the motor cortex of the subject, the brief pulse generates a large current of several 1000 Ampere. A magnetic field (about 2 Tesla) is induced perpendicularly to the plain of the coil. The magnetic field is not attenuated by the skull or any other tissue. The dynamically changing magnetic field, in turn, induces an electric field which is oriented in parallel trough the current induced in the coil (yet in the opposite direction). The current induced by the changing electric field depolarises the cortical neurons causing them to fire an action potential.

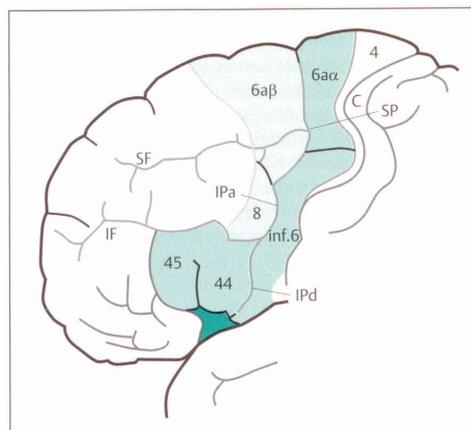


Fig. 2: Human motor areas.

The frontal agranular cortex can be parcelled in different regions according to its afferents and its cytoarchitecture. The largest and functionally most significant part of the corticospinal tract which projects monosynaptically through the spinal motor neurons arises from Brodmann Area 4. Further motor regions are the pre-motor cortex (Area 6 a) and the supplementary motor cortex (Area 6 a β), the frontal eye-field (Area 8), the Broca-Region (Area 44 and Area 45).

2.2. Anatomy

The motor cortex consists of a mosaic of several different areas, of which each holds an independent somatotopically organized representation of movements. Each motor area plays a specific role in the organisation of movements. This role is determined by the type of its cortical afferents and descending projections. In this mosaic of motor areas the primary motor cortex which is located in the pre-central gyrus is of particular importance. This area correspond

cytoarchitecturally to area 4 of Brodmann. Below the cortex are a host of complex partially hierarchically organised motor systems at the level of the brain stem and the spinal cord. Cortical, medullar and spinal motor systems, in turn, are modulated by the basal ganglia and the cerebellum. As all motor cortices, so is the primary motor cortex organised somatotopically. The lower extremity is represented medially and the facial muscles laterally with respect to the representation of the upper extremity. Within the upper extremity there is a mediolateral gradient for the representation of more proximal or more distal movements.

The primary motor cortex harbours unusually large pyramidal tract cells, the Betz cells. These giant Betz cells send fast conduction, large calibre axons travelling in the corticospinal tract to the alpha-motor neurons of the spinal cord. The conduction velocity of the fastest axons in the corticospinal tract is 50 - 70 m/s. TMS over the primary motor cortex stimulates mainly, indirectly, the Betz cells. Disproportionally many Betz cells project to motor neurons subserving distal muscles of the extremities. Apart from the corticospinal tracts the primary motor cortex sends off cortico-cortical fibres and fibres projecting to the basal ganglia, the pontine nuclei and the cerebellum, the red nucleus and the reticular formation which are all inaccessible by TMS techniques. Roughly 50 percent of all fibres travelling in the corticospinal tract arise from the primary motor cortex. The axons of the large Betz cells travel through the posterior limb of the internal capsule, the cerebral peduncle and the decussatio pyramidum where their majority cross to the contralateral side, and then descent in the lateral corticospinal tract to the anterior horn of the spinal cord. The axons synapse particularly with the spinal motor neurons projecting to the distal extremity muscles monosynaptically. After exciting the spinal motor neurons, an action

potential travels along the peripheral motor axon to the muscle fibres generating an action potential and contraction.

2.3. Physiology

A large suprathreshold magnetic pulse released over the primary motor cortex generates a series of descending action potentials. The first of these waves, which is not present in every case is termed the D-wave (direct wave) (Fig. 3) because it corresponds to the activation of the axons of the corticospinal tract at the axonhillock or a proximal internodes.

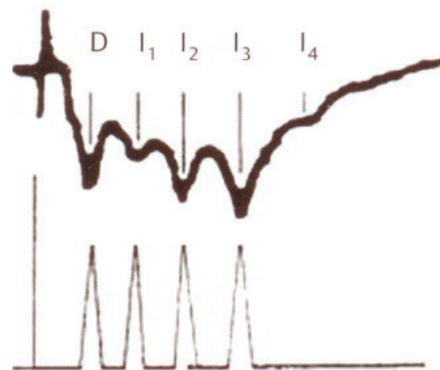


Fig. 3: Principle of D- and I-waves. Magnetic stimulation of the cortex releases a series of descending action potentials. In order to raise the membrane potential of the spinal motor neuron above the level required to release an action potential, several descending action potentials must arrive at the spinal motor neuron if it is at rest. If the membrane of the spinal motor neuron is depolarised by voluntary activity,

the threshold of action potential release is reached earlier and receiving signals from descending corticospinal tract can be sufficient to release several action potentials. Earlier release of spinal activity is reflected in shortening of the latency until recording of a motor unit potential or a compound action potential (after Amassian, *Clinical Neurophysiology*, 1989).

Several I-waves (indirect waves, Fig. 3) follow the D-wave in intervals of a little less than 2 ms. The I-waves are thought to be generated by the activity of excitatory intracortical inter neurons. With magnetic stimulation the threshold of releasing of indirect waves is lower than that of direct wave. Under most conditions, therefore, exclusively indirect activation of pyramidal tract cells of the corticospinal tract is induced. This implies that responses recorded after TMS are influenced by factors modulating the cortical excitability “up stream” of the pyramidal tract

cell as well as by factors that influence the membrane potential of the pyramidal tract cell and those that influence segmental spinal excitability.

Action potentials reaching the anterior horn of the spinal cord trigger excitatory post-synaptic potentials (EPSP) at the spinal motor neuron. If they follow each other rapidly enough they can summate (“temporal summation”). If the spinal motor neuron is sufficiently depolarised then an action potential is released which is transmitted via the axon and leads to excitation of the muscle fibre membrane. The term “spatial summation” refers to the fact that pulses from different cortical motor neurons converge on to the same spinal motor neuron. The potential that can be recorded from the target muscle is the result of the synchronous activation of several motor units.

The resting membrane potential of the spinal motor neurons is influenced by several mechanisms on the spinal level. For this reason identical descending action potentials lead to quite different effect at the motor neuron. A single (D- or I-) wave will not, as a rule, depolarise the membrane of the resting spinal motor neuron. Facilitation occurs if the target muscle is contracted while the magnet stimulation of its cortical representation is performed (Fig. 4).

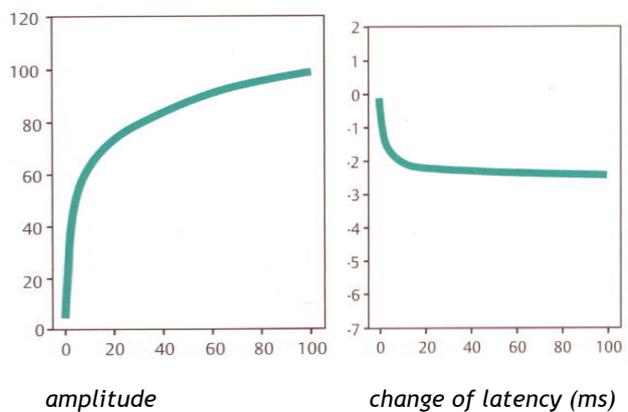


Fig. 4: Influence of pre-innervation on amplitude and latency of the MEP. At constant magnetic strength the MEP-amplitude increases and the latency until the beginning of the MEP decreases with increasing voluntary activity. Above a contraction level of about 20 percent of the maximal

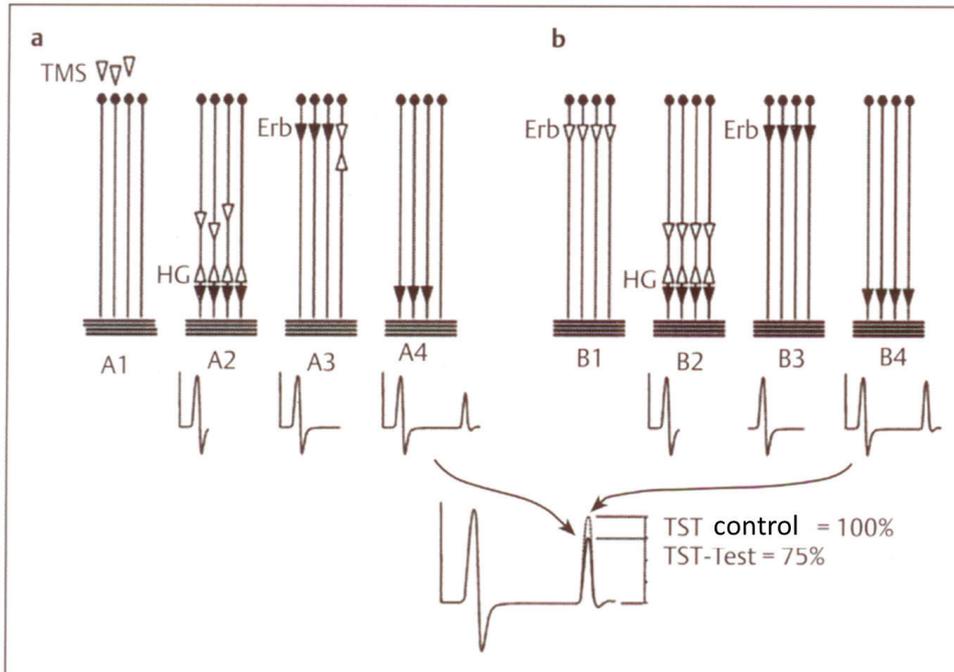
contraction the amplitude increase is relatively small. Similarly, the latency stays nearly constant above 20 percent of the maximal voluntary force (modified after Meyer 1992).

The MEP-amplitude increases and the latency until the beginning of the potential decrease (by some 2 - 4 ms) by voluntary contraction. These phenomena are generated by physiological mechanisms on a spinal as well as cortical level. Pre-activation leads to depolarization of the membrane potential of the spinal motor neuron. Compared to a resting state a smaller number of incoming I-waves will be sufficient to release a supra threshold excitation. Furthermore, with low voluntary force small spinal motor neurons conducting more slowly, will be recruited first - fast conducting larger motor neurons will be recruited only with strong pre-innervation. Pre-innervation also influences the membrane potential of cortical pyramidal tract cells and excitatory interneurons. This will lead to a stronger activation of descending D- and I-waves causing earlier supra threshold excitation compared to the resting state.

TMS is capable of stimulating all alpha-motor neurons projecting to an intrinsic hand muscle if sufficient stimulation strengths are used. The compound motor action potential, however, is markedly smaller after TMS than after stimulation by peripheral electric nerve stimulation at supramaximal intensity. The discrepancy between cortically evoked and peripherally evoked compound motor action potentials arises from the fact that motor unit potentials following TMS are not exactly synchronized. Because of their desynchronization they can partially cancel each other when recorded from the surface. The portion of the spinal motor neurons that can be excited by cortical stimulation can be exactly quantified by the so called triple stimulation technique (Magistris et al. 1998). This technique allows to eliminate the influence of desynchronization on the size of the compound muscle action potential and the influence of repetitive discharges of motor neurons. One cortical and two peripheral stimuli collide at two sites on the peripheral nerve. As

a result all cortically induced action potentials of spinal motor neurons become synchronized.

Fig. 5



2.4. Fractionated stimulation

The latency between the time of release of the magnetic pulse until the beginning of the compound muscle action potential recorded from service electrodes is influenced by both the central and the peripheral nervous system. This is also true for the MEP amplitude. For example the amplitude can be diminished by a lesion to the muscle, arising for instance as a consequence of an axonal motor neuropathy. Similarly, the amplitude can be diminished by an insufficient activation of spinal motor neurons as a result of a lesion to the central motor pathway. To distinguish between central and peripheral lesions of the motor pathways, the peripheral segment is examined separately (principal of fractionated stimulation, Fig. 6). The central motor latency (CML) is given by the entire latency from the release of the magnetic pulse to the beginning of the muscle compound action potential, diminished by the conduction time needed for

the peripheral motor conduction (peripheral motor latency, PML). Several methods exist how to establish the peripheral motor latency. Of these the most accurate is by using the F-wave-latency. For this we have

$$PML = \frac{(F + M - 1)}{2}$$

where F is the shortest latency of about 10 - 20 F-Waves, M the shortest M-wave-latency and 1 the estimated delay (in ms) at the alpha-motor neuron for the antidromic activation. Because the F-wave-latency requires some experience and skill, frequently the peripheral motor conduction time is determined by magnetic stimulation of the nerve roots. Using this method one has to be aware that the axons of the spinal motor neurons will be excited by the magnetic pulse only when passing through the foramen intervertebrale, i.e. distally from the exit from the spinal cord. This distance is short in the cervical region, hence the resulting error is only some 1.5 ms. However, in the lumbar region the nerve roots travel intraspinally a long distance. Hence the peripheral conduction time is underestimated by some 3-4 ms by magnetic root stimulation. As a result the central motor latency is overestimated particularly for the central motor pathway leading to the lower extremities. The resulting error is even larger when nerve roots are locally afflicted by inflammatory or compressive lesions. In this case local excitation in the foramen can be impossible and the site of excitation will be proximally or distally instead.

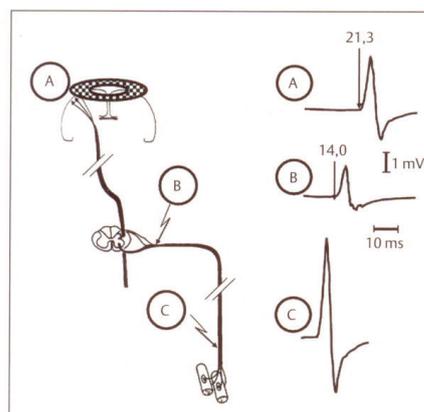


Fig. 6: Fractionated stimulation for determination of a central motor latency and relative amplitude of the MEP.

a) Transcranial magnet stimulation of the motor cortex. The cortico-muscular latency (recording from first dorsal interosseus muscle) is 21.3 ms, the MEP amplitude is 9 mV.

b) Magnetic stimulation of the proximal nerve roots at the level of the foramen intervertebrale. The peripheral motor

latency (PML) is 14.0 ms. Then central motor latency is determined as 7.3 ms.

c) The peripheral electric stimulation of the ulnar nerve is followed by an M-response with an amplitude of 16 mV. With an MEP amplitude of 9 mV the relative MEP amplitude is 56 %.

2.5. Contralateral “silent period”

Apart from excitatory effects, which result in an evoked muscle potential, TMS can also induce inhibitory phenomena. When TMS is applied while the target muscle is being contracted a silent period can be recorded after the MEP (Fig. 7) during which there is absence of electrical muscle activity. The late part of the silent period is generated exclusively at a cortical level. The silent period reflects the activity of cortical inhibitory interneurons. It is largely independent from excitatory responses as evidenced by the fact that, occasionally, a silent period can be observed in a pre-contracted muscle without a preceding MEP. The duration of the silent period increases with the intensity of the magnetic pulse. However, unlike the amplitude of the MEP, the duration of the silent period is largely independent of the pre-innervation of the level of pre-innervation except for very weak force levels.

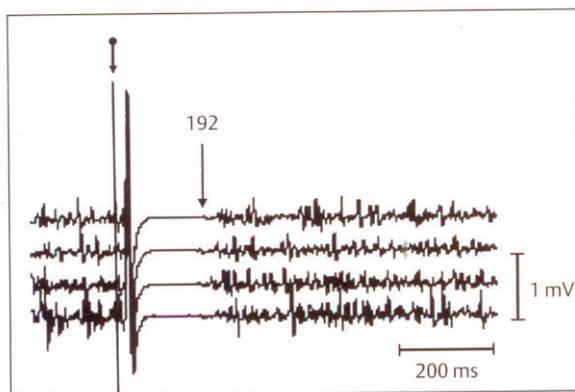


Fig. 7: Contralateral silent period with slight preactivation. A silent period can be seen after the MEP which follows the magnetic stimulus. The duration of the silent period as measured from the time of the release of the magnetic pulse until the re-appearance of the voluntary muscle activity is

192 ms. 4 trials are shown to demonstrate reproducibility of the silent period. Arrow, time of release of the magnetic cortical stimulation.

2.6. Ipsilateral “silent period”

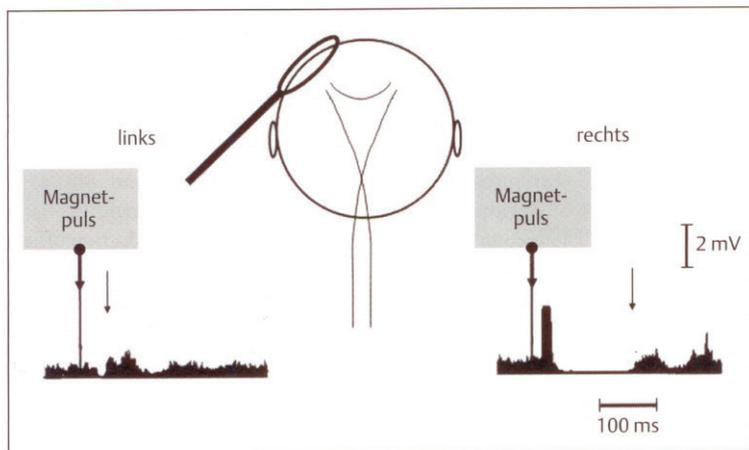
A similar inhibitory phenomenon can be observed ipsilaterally of the stimulated hemisphere. The ipsilateral silent period has typically a latency of some 30 ms and a duration of 14 ms. After stimulation of the left hemisphere action potentials are conducted over the corpus callosum onto inhibitory interneurons in homologous regions of the motor cortex in the right hemisphere. The ipsilateral silent period requires focal magnetic stimulation. Although it can be elicited with a conventional round magnetic coil usage of a “focal” figure eight coil is recommended.

A number of inhibitory and facilitatory cortical phenomena can be studied by application of double pulses of the same or different intensities. Such phenomena have not entered clinical routine.

TMS is also capable of stimulating corticobulbar pathways. In this case compound muscle action potentials can be recorded from muscles contralateral to the cortical stimulation but also from muscles located ipsilaterally to the stimulated hemisphere. The facial nerve can be stimulated at the entry of the facial canal by appropriate positioning of the magnetic coil. Because electrical facial nerve stimulation stimulates the nerve at the exit from the canal a fractionated diagnostic stimulation of the facial nerve can be accomplished by combining magnetic and electric stimulation.

Fig. 8: Ipsilateral silent period. In the figure a left hemisphere stimulation is demonstrated with recordings taken from the activated first dorsal interosseus muscle ipsilateral and contralateral to the stimulated hemisphere. Mean of 10 trials after rectification. The silent period contralateral to the stimulated hemisphere lasts approximately 170 ms. Ipsilateral to the stimulated hemisphere the silent period is much shorter, about 15 ms.

↓: time of release of a magnetic cortical stimulation. ↓: end of the silent period.



3. Pathophysiology

Lesions to the corticospinal tract can show as a prolongation of the CML, a decrease of the MEP amplitude and dispersion of the compound muscle action potential. To correctly interpret the results of an investigation of the motor system by TMS it is essential to understand that diverse lesions of the central motor pathways can lead to similar patterns of TMS studies. Complete axonal interruptions of the corticospinal tracts lead to a complete loss of contralateral responses at short latencies. In contrast partial axonal interruptions are followed by a diminished temporal and spatial summation at the spinal motor neuron. Therefore, fewer motor neurons are activated later and this shows in a prolongation of the CML and the reduction of the relative MEP amplitude.

3.1. Demyelinating processes

If the delay by demyelination leads to a strong dispersion of action potentials at the alpha-motor neuron the excitatory post-synaptic potentials do not summate or reach supra threshold values at a delay. In this case, importantly, the contralateral MEP can be lacking although continuity of the corticospinal tract is retained. If different motor neurons are excited asynchronously the phases of single motor units can cancel each other, thereby reducing the amplitude despite excitation of a large proportion of the spinal motor neurons. If, however, the synchronicity of descending action potentials is retained in spite of strong central conduction delay, the MEP will appear at substantial (< 5 ms) delay. Only in this case will the type of pathological change tell the demyelinating nature of the underlying pathology. Especially with demyelinating lesions there will be abnormal variability of central motor latencies with consecutive cortical stimulation. With severe lesions of the corticospinal tract either by complete conduction block or axonal damage the threshold for eliciting motor evoked potentials is enhanced.

3.2. Localisation of lesions

The site of the lesion can be narrowed down by fractionated stimulation and recording of the central motor latency to target muscles on different segmental levels and across sides. This is because potentials recorded from target muscles above the lesioned segment are normal where they are pathologically altered below the site of the lesion. Changes to CML or to the relative MEP amplitude correlate poorly with clinical pyramidal tract signs (enhancement of reflexes, Babinski sign, disturbance of fine motor skills, pareses). In contrast, the central conduction deficit as determined by the triple stimulation technique highly correlates with the presence and the degree of a weakness in the target muscle.s