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Review

Transcranial magnetic stimulation: review of the technique, basic principles and applications

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Abstract

Transcranial magnetic stimulation is rapidly developing as a powerful, non-invasive tool for studying the descending motor tracts in humans. The applications of the test in animals are for the moment restricted to small animals. However, this non-invasive, sensitive and painless technique appears promising as a test of motor tract function in horses where the neurological examination is mainly restricted to clinical evaluation and some ancillary tests, such as radiography, cerebrospinal fluid analysis and electromyography. In this review, we want to discuss the history, basic principles, technique and applications of transcranial magnetic stimulation in humans and small animals and indicate the possibilities for its use in horses. Since the great portion of this review is based on human studies, it is worthwhile to mention that the reports being described are from humans unless otherwise specified.

Keywords: Review; Principles; Technique; Transcranial; Magnetic

1. History

Electromagnetic induction, i.e., the induction of an electrical voltage in a circuit subjected to a changing magnetic field, was first discovered in 1831 by the English physicist Michael Faraday. This was the first experimental observation of magnetic stimulation and the term “magnetic field” was born. A relationship between magnetism and electricity was reported at the beginning of this century by d’Arsonval who found that the brain could be magnetically stimulated by a coil carrying a high current. The induced eddy currents in the retina, when placing one’s head in a coil driven from an alternating 110 V supply at 30 A, produces magnetophosphenes or flashes of light (D’Arsonval, 1896).

The MEP, or motor evoked potential, comprises a class of tests of conductivity in central nervous system pathways. The technique of stimulating the motor cortex and recording the muscle twitch or surface potential responses in the periphery was established by the work of Merton and Morton, who showed in 1980 that it was possible to stimulate the motor cortex of the human brain through the intact scalp by using very short duration and large amplitude *electrical* pulses, delivered through a pair of surface electrodes (transcranial electrical stimulation, TES). After stimulation a relatively synchronous muscle response, the electric motor evoked potential (EMEP) is produced. It was immediately clear that this would be useful for many purposes. The required intensity, however, was very high (in the order of 1–1.5 kV), uncomfortable and poorly tolerated (Merton et al., 1982). The major problem with this form of stimulation is that only a small fraction of the applied current actually flows into the brain. Much of the electric current flows between the electrodes on the scalp and produces local discomfort and contraction of the scalp muscles. In the mid-1980s, however, Barker and colleagues demonstrated for the first time that stimulation of the human motor cortex and peripheral nerves can be performed using a brief and strong external *magnetic* field. The magnetic stimulator works by

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discharging a charge on a capacitor through a circular wire coil. The subjects reported that the muscle twitches were produced "without causing distress or pain". Transcranial magnetic stimulation (TMS) is now routinely used in humans for a variety of clinical and scientific applications, including testing of motor function, vision, language and studying the pathophysiology of brain disorders (Mills and Murray, 1985; Rossini et al., 1987a,b; Fehlings et al., 1989; Hess et al., 1987a; Boniface et al., 1991; Cantello et al., 1991; de Noordhout et al., 1998; Berardelli, 1999; Kohara et al., 1999; Naka and Mills, 2000). It may even be useful for therapy, particularly in psychiatry (George et al., 1997; Feinsod et al., 1998; Klein et al., 1999; Hasey, 2001) and is especially useful as a monitoring tool for anaesthetised patients undergoing spinal surgery (Shields et al., 1989; Bartley et al., 2002; Aglio et al., 2002).

While routinely used in humans, application of TMS in other species is rare. The unique features of TMS are particularly useful in evaluating spinal cord injury and recovery (Fehlings et al., 1987, 1988; Magnuson et al., 1999) and anaesthesia (Ebert and Ziemann, 1999; Ghaly et al., 1999) in animal models. The methodology for reproducible assessment of motor potentials evoked by TMS has been characterised in different animal studies on rodents, cats and dogs (Heckmann et al., 1989; Linden et al., 1990; Van Ham et al., 1994, 1995, 1996a,b; Nakatoh et al., 1998; Luft et al., 2001). Several studies have demonstrated its safety (Russell et al., 1994; Post et al., 1999; Van Ham et al., 1994, 1995, 1996a,b). In horses, Mayhew and Washbourne (1996) have shown that transcranial magnetic stimulation is able to induce magnetic motor evoked potentials (MMEPs) in unanaesthetised normal ponies. We have also demonstrated the diagnostic usefulness of the technique in horses with cervical cord lesions (Nollet et al., 2002).

2. Technique and basic principles of magnetic stimulation

2.1. Basic principles

Magnetic stimulation is a technique for stimulating peripheral nerves and cerebral cortex in order to help quantify the integrity of the motor nervous system, especially to measure conduction times. Its purpose is to create a pulsed electric current, induced by the time-varying magnetic field (Barker et al., 1985), that will momentarily depolarise the nervous system. It is important to acknowledge that the actual pathways being investigated are not known; however, they incorporate the fastest conducting fibres which presumably include the pyramidal tracts (Corthout et al., 2001).

A magnetic field is generated by passing an electric current through a coil of wire, called the magnetic coil (Fig. 1), which is placed above the scalp. Faraday's law

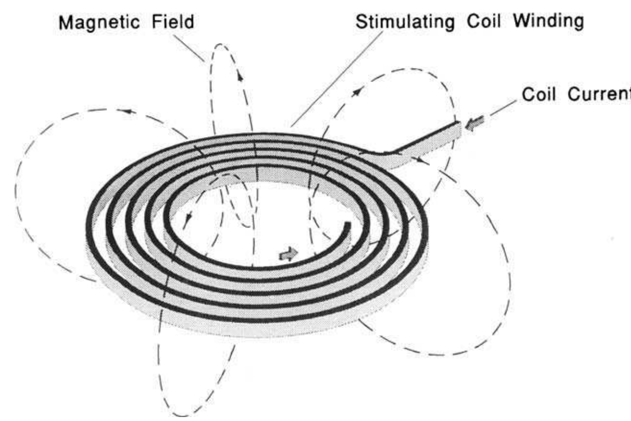

Fig. 1. A magnetic field is produced by passing an electric curent through a coil of wire. In an air-core winding the magnetic field intensity is directly proportional to the current flowing through the coil (with permission of R. Jalinous; Magstim).

(Faraday, 1839) says that whenever a magnetic field changes there is an induced electric field which impedes the changing magnetic field. The magnetic pulse produced from an electric current pulse will thus induce in turn a current in an electrically conductive region, such as the human or animal body. This induced electric current flows perpendicularly to the magnetic field and circulates up to a few centimetres away from the coil's external edge, and with a direction opposite to the current flowing in the coil and an intensity proportional to the magnetic field.

The intensity of the magnetic field can be represented by flux lines around the coil (Fig. 2) and is measured in Tesla (T). The magnetic field is oriented perpendicular to the coil and, for currently available devices, can reach values of up to 4 T (Barker et al., 1985). The precise stimulating characteristics depend upon the model of stimulator used. For example the Magstim 200 stimulator (used in our experiments) produces a magnetic field which rises to peak within about 150 μs and then decays slowly to zero over the next millisecond. Such a rapidly changing magnetic field induces electric eddy currents in any conductive structures nearby. Because the skull presents a low impedance to magnetic fields of this frequency, eddy currents are produced in the brain, and these currents can stimulate neural tissue. Currents induced on the scalp by magnetic stimulation are much weaker than those produced by transcranial electrical stimulation, because they crossed the extracerebral layers (scalp, skull and meninges) with minimal or no activation of the pain receptors and resulted in a well tolerated procedure (Rossini and Rossi, 1998). Therefore, the sensation produced by magnetic stimulation is very slight (Jalinous, 1991).

In a homogenous medium, the electric field will cause the current to flow in loops parallel to the plane of the coil. The loops with the strongest current will be near the circumference of the coil itself. The current loops

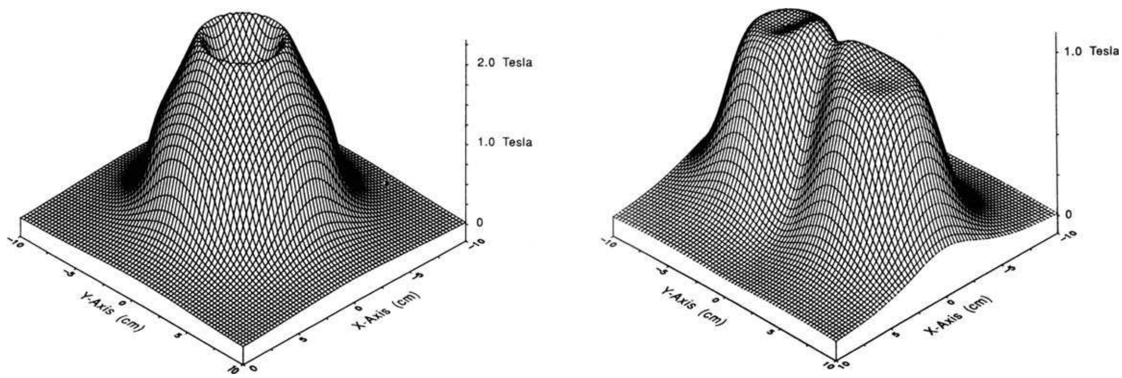

Fig. 2. A three dimensional representation of the peak magnetic flux produced on the surface by the 90 mm circular coil (left) or 10 mm below the surface of the double 70 mm coil (right). For the circular coil (left) the field distribution is symmetrical about the central axis and the maximum magnetic field strength normally occurs next to the innermost turn. Double, butterfly or figure of eight coils (right) consist of two windings placed side by side producing a maximum electric field under the point where the two windings meet (with permission of R. Jalinous; Magstim).

become weak near the centre of the coil, and there is no current at the centre itself. The magnetic field decreases rapidly with increasing distance from the coil: with a typical 12 cm diameter round coil the strength falls by half at a distance of 4–5 cm from the coil surface (Hess et al., 1987b). Since the cerebral cortex can be 1–2 cm from the surface of the scalp, and since the central sulcus itself can be 2 cm deep in man, this means that stimulation is severely attenuated at deep sites such as basal ganglia or thalamus. The magnetic motor evoked potential (MMEP) testing can be regarded as a counterpart of the longer-established procedure of somatosensory evoked potential (SSEP) monitoring, where small "cortical" potentials are recorded over the scalp in response to peripheral nerve stimulation.

2.2. Technical requirements

When magnetic stimulation is performed on the motor cortex, electromyographic responses (MMEPs, magnetic motor evoked potentials) can be recorded in contralateral, particularly distal, appendicular muscles. However, large pulses of magnetic field need to be generated in order to induce electric fields in the body of sufficient amplitude and duration to cause stimulation of the neural tissue in its vicinity. Therefore, magnetic stimulators consist of a coil of wire connected to a large electrical capacitance. A *magnetic stimulator* works by charging one or more energy storage capacitors and then rapidly transferring this stored energy from the capacitor(s) to the stimulating coil as it discharges. Current (with a peak value of 5000 A or more) flows thus from the capacitor through the stimulating coil generating the required magnetic field.

The difficulty in producing magnetic nerve stimulators is related to the high discharge currents, voltages and power levels involved in producing the brief magnetic pulse. Typically 500 J of energy has to be transferred from the energy storage capacitor into the stimulating coil in around 100 μs. Power, measured in watts, is equivalent to joules per second. From this, the power output of a typical magnetic stimulator during the discharge phase is 5 MW (5,000,000 W) – adequate to provide the electricity necessary for 1,000 homes for 1/1000th of a second. During the discharge, energy initially stored in the capacitor in the form of electrostatic charge, is converted into magnetic energy in the stimulating coil in approximately 100 μs. This rapid rate of energy transfer produces a time varying magnetic field build-up which induces tissue currents in the vicinity of the coil in the order of 1–20 mA/cm^2 (Jalinous, 1991). However, the amount of thermal energy deposited in tissue due to magnetic stimulation is very small. At maximal output, assuming a maximal stimulus repetition rate of one pulse every 3 s, the average power deposited in the brain is calculated to be less than 2 mW. This represents less than 0.01% of the heat generated in the adult brain due to the normal basal metabolism. Heating of the brain is of the order of 10^{-6} °C/pulse and unlikely to cause deleterious effects (Barker, 1991). Similarly, international standards suggest that the continuous thermal energy deposited in tissue by electromagnetic radiation should not exceed 0.4 W/kg to avoid thermal stress. For a typical human adult brain mass of 1.5 kg, this limit is 300 times greater than the average thermal energy deposited by the magnetic stimulator at maximal output, even if stimulation is carried out continuously (Barker et al., 1987).

The *stimulating coil*, normally housed in moulded plastic covers, consists of one or more tightly wound and well insulated copper coils together with other electronic circuitry, such as temperature sensors and safety switches. At the present time, most commercial magnetic stimulators are supplied with a circular coil of 5–10 cm diameter. Different coil types are nowadays available each with their advantages and disadvantages. Large coils cannot produce very focal stimulation of the brain, but have the advantage that a reasonable depth of

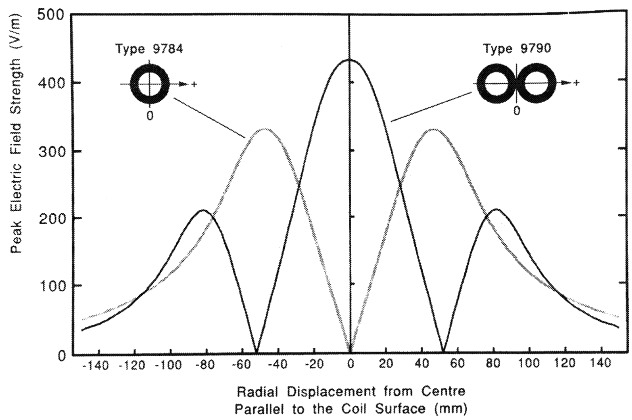

Fig. 3. The induced electric field profile of single circular and double circular coils differ widely because of their geometry. The induced electric field of a circular coil is zero directly under its center and rises to a maximum in a ring under the mean coil diameter. In the case of double coils the field is a maximum directly under a coil centre and has two smaller characteristic peaks on either side. These are less than one half the amplitude of the central peak (with permission of R. Jalinous; Magstim).

penetration can be achieved. Although the circular coil is a very useful general purpose coil the site of stimulation is not well defined. For example, with a standard round coil, the induced current in the brain flows in an annulus, underneath the coil, which is usually some 8–12 cm in diameter. Clearly a large volume of neural tissue may be activated by such a device. Increases in the focality of stimulation can be achieved by tilting these circular coils so that they lie at an angle to the skull. The greater the angle between the skull and the coil, the more focal the stimulation. Unfortunately, increased focality of stimulation is offset by a decrease in the effectiveness of stimulation. Recently, coils wound in a figure-of-eight shape (also termed butterfly or double coil) have been used, and in these, the induced electric field (Fig. 3) under the junction region of the 8 is twice as large as that under the two wings (Rothwell, 1997). These coils have a lower induction than circular coils of the same number of turns, and hence larger currents can flow in them. However, the hypothesis that the double coil only stimulates under its centre should be viewed with caution. There are also smaller peripheral peaks of approximately half the amplitude of the central peak on either side of the winding.

2.3. Difference with electrical stimulation

Like magnetic stimulation, electric stimulation of the motor cortex evokes electromyographic responses in contralateral, particularly distal, appendicular muscles. Motor evoked potentials resulting from either transcranial electric or magnetic motor cortex stimulation may be used to demonstrate the functional integrity and conduction properties of the descending motor nervous system (Merton and Morton, 1980; Rothwell et al., 1987).

Magnetic stimulation has three main advantages over conventional electrical stimulation. First, the primary benefit of magnetic stimulation is its ability to penetrate all body structures without attenuation. Because this increased field penetration compared to surface electrical stimulation, it allows to stimulate regions below layers of bone, for instance the brain. The cells are still activated by electric currents, but the magnetic field penetrates the tissue more efficiently and induces current within the brain itself. The mechanism of stimulation at the neural level is thought to be the same for both magnetic and electrical stimulation, namely current passes across a nerve membrane and into the axon, resulting in depolarisation and the initiation of an action potential that then propagates by the normal method of nerve conduction (Barker et al., 1987). Although the magnetic field and hence the induced electric field theoretically should be unaffected by the bone of the spine, there is however a stimulation of the nerve roots at their spinal exit but not the spinal cord when the magnetic coil is placed over the spine. Machida et al. (1992) showed that magnetic stimulation could excite the thoracolumbar spinal cord after laminectomy and pediculotomy in dogs. It is suggested that the bony structure surrounding the spinal cord interferes with the spread of magnetically induced eddy currents to the spinal cord. The current induced by the magnetic coil is theoretically maximum in the annulus under the coil. The charge buildup on the bone at the points where the induced current loops enter and leave the spine will reduce the current in the spinal cord. Therefore, the bony vertebrae act as an insulator between the spinal cord and the external tissue and the current probably tends to flow around the spinal cord rather than through it. Hence stronger magnetic fields are needed for spinal stimulation and novel coil geometries may be able to improve the coupling between the induced currents and the anatomy of the spine (Barker et al., 1989).

Second, the electrical field induced with a coil (of 100 mm in diameter) decreases significantly less with increasing distance into the body than a field induced by currents applied via surface electrodes (Barker et al., 1987). Electrical stimulation injects current into the body via surface, needle, or implanted electrodes. The charge from an electrical stimulator is carried by electrons flowing in the wires to the stimulating electrodes and is transferred to an ion flow at the electrode-tissue interface. A small percentage of these ions will flow into nearby axons, resulting in membrane depolarization. Magnetic stimulation differs from electrical stimulation in that it uses a pulse of magnetic field to cause an electric field (a voltage difference between two points) in the tissue and results in stimulation. Hence the magnetic field functions as the vehicle that causes ion flow (or electric current) in the body and does not itself stimulate the nerve (Barker, 1991). The primary circuit is the stimulating coil, through which the stimulator drives current pulses, but which is not the electrical contact with the tissue. The magnetic field generated by the current flow in the coil is proportional to the rate of change of the magnetic field with respect to time. At the frequencies used in magnetic stimulation, the magnetic field is not affected by the electrical properties of the body and passes through both bone and soft tissue (and even clothing and air) without being affected by them and without causing large electrical fields at the surface. An additional factor that may contribute to the difference between the two forms of stimulation is that the electric field induced by magnetic stimulation has quite a different distribution to the field produced by transcranial electrical stimulation. In the latter the current flows beneath the electrodes in all directions away from the anode both radially and tangentially to the cortical surface and will tend to stimulate structures close to the surface in this orientation. The electric field resulting from magnetic stimulation is much more homogeneous and is parallel to the surface of the coil at all points and hence will tend to stimulate structures with a different orientation (Tofts, 1990). These two facts were thought to explain the lack of pain associated with magnetic stimulation and its ability to stimulate, without discomfort, deep structures such as the lumbar roots, the brachial plexus, and the sciatic, radial, and femoral nerves in humans (Krain et al., 1989; Mills et al., 1987). However, the depth of penetration depends on anatomical factors, coil size, coil geometry and the intensity of the applied stimulus. In the simple homogeneous model, the volume within which straight nerves can be stimulated, for both circular and figure-of-eight coils, is shaped roughly like an egg. Its maximum dimensions are at the surface and it decreases in cross-sectional area to zero at the maximum depth at which the stimulation threshold is reached (Barker, 1999).

Third, magnetic stimulation does not require either physical or electrical contact with the body. Hence, no skin preparations are required, and clothing need not be removed at the stimulation site. Although the coil is normally placed in contact with the body for convenience, stimulation can be achieved with the coil held some millimetres away from the body. This could be valuable in situations such as the stimulation of traumatized regions where physical contact may cause further damage or infection. The stimulating coil can be moved freely over the area of interest, which makes the location of the optimal stimulation site rapid and easy (Barker et al., 1987).

Ever since the introduction of TMS, there has been considerable debate over which structures within the cerebral cortex are activated. The first hypothesis was proposed by Day et al. (1989) on the basis of single motor unit studies in the hand. His statement was that direct electrical stimulation through the skull preferentially activates corticospinal fibres directly within a few millimetres of the cell body. This is referred to as direct activation, and results in D-waves conducted down the pyramidal system. Further studies (Di Lazzaro et al., 1998a,b) revealed that pyramidal neurones could be activated trans-synaptically only at higher intensities. In contrast, the lowest threshold form of TMS over the hand area of the motor cortex tends to preferentially activate corticospinal neurones trans-synaptically, resulting in I-waves in the pyramidal tract. With higher stimulus intensities both direct (D-wave) and trans-synaptical (I-wave) activation occur (Day et al., 1989; Kaneko et al., 1996; Di Lazzaro et al., 1998a,b). The result is that the EMG responses that are recorded at threshold in response to transcranial magnetic stimulation often occur 1–2 ms later than those recorded following transcranial electric stimulation of the brain (Rothwell et al., 1991). Why there should be this difference between electrical and magnetic forms of stimulation is unclear at the present time. However, it is presumed to be related to the fact that TMS induces electrical current that flows parallel to the surface of the brain. In contrast, electrical stimulation causes current to flow in all directions both parallel and radial to the surface. The result is that radially oriented neurones will have a higher threshold for magnetic and electric stimulation (Rothwell et al., 1999). The response of lower limb muscles has a similar latency with electrical and magnetic stimulation. This suggests that both techniques have the same activation site in the initial segmental or proximal nodes of pyramidal axons as they leave the cortex and readily produce D wave activity (Rothwell, 1997).

2.4. Safety

Since 1985, many thousand subjects have been examined using low-repetition-rate magnetic stimulators to assess motor function of the peripheral and central nervous systems. There is now a considerable volume of data supporting the safety of magnetic stimulation. There have been no ill effects reported with magnetic stimulation of the peripheral nervous system, and, in the case of cortical stimulation, the incidence of side effects has been very low and within that expected by available statistics for various patient groups (Kandler, 1990; Hufnagel et al., 1990).

The main area of concern has been the triggering of epileptiform activity in individuals at a high risk for epilepsy. Since TMS has been successfully used in the study of epilepsy and the determination of the site of the epileptic focus, there have only been a few reports of seizures occuring at or shortly after the magnetic stimulation (Homberg and Netz, 1989; Hufnagel et al., 1990; Classen et al., 1995). However, the more recently used repetitive TMS (rTMS) can, depending on the stimulation parameters, evoke seizures in normal subjects and in patients with neurological disease (Wassermann, 1998).

The presence of pacemakers and other electronic implants is also considered as a contraindication because of damage of the internal electronics due to the induced electric fields and currents resulting from the magnetic pulse.

Since implanted metal structures in the brain will have mechanical forces exerted on them due to induced currents, they also should be regarded as a contraindication (Barker et al., 1989).

2.5. Procedure and measured parameters

2.5.1. Procedure

Stimulation of the motor cortex is in most cases achieved via a circular coil hand-held over the scalp. The subject feels only a moderate tapping sensation on the scalp, and the limb twitch. Recordings in humans are made from surface EMG electrodes attached to the skin overlying peripheral muscles using an EMG machine. In some animal studies needle electrodes were inserted in the muscle (Young et al., 1994; Van Ham et al., 1994, 1995, 1996a,b; Mayhew and Washbourne, 1996; Nollet et al., 2002). The stimulator triggered the sweep of a standard electromyogram (EMG) machine, enabling the latency between the stimulus and the onset of the response to be measured. Measurements include the threshold, latency, amplitude and configuration.

2.5.2. Measured parameters

Threshold reflects the global excitability of the motor pathway and is often defined as the strength of stimulation that produced an identifiable MMEP of 50–100 μV in 50% of 10–20 consecutive occasions (Hufnagel and Elger, 1991; Ellaway et al., 1998). Threshold in human adults is independent of age, gender and hemisphere, but varies with different target muscles (Mills and Nithi, 1997; Wasserman et al., 1992). A lower threshold is observed in thoracic (51%) than in pelvic (73%) limbs. Even in upper limbs the threshold is lowest for hand muscles and highest for proximal arm muscles. This may reflect the larger cortical motor areas controlling the hand muscles (Tabaraud et al., 1989; Rothwell et al., 1987; Furby et al., 1992).

Amplitude refers to the recorded voltage of the response. It may be measured from the baseline to the negative peak or from the negative to the positive peak (peak-to-peak amplitude). Mostly amplitude is expressed in absolute terms, as μV or mV. Sometimes it is expressed as a percentage of the maximal response after stimulation of the appropriate peripheral nerve.

The amplitude can have a high degree of inter-trial as well as intra-individual variability (Hess and Ludin, 1988; Amassian et al., 1989), especially when stimulating at slightly suprathreshold level. With increasing stimulus intensity (Kiers et al., 1993) or when a subject makes a voluntary effort in a muscle (Nielsen, 1994) MMEPs are increased and become less variable in their amplitude presumably as a consequence of moving to a flatter region of the stimulus/response curve. The variability appears to be generated spontaneously and may be explained, at least in part, by differences in the state of relaxation of the muscles (Dimitrijevic et al., 1992). As will be discussed below under facilitation, even mild muscle contraction will increase the amplitude and it is difficult to state whether the response was elicited with the muscle relaxed or not, especially in animals. Also, small alterations in the position of the magnetic stimulating coil over the surface of the cranium can result in large changes in variability of MMEP responses to TMS which may reflect fluctuations either in the proportion of available target corticospinal neurones close to threshold (Brasil-Neto et al., 1992) or in the magnitude of the induced current under the coil (Kraus et al., 1993). However, clamping the coil relative to the head in studies done by Ellaway and co-workers (1998), failed to affect the variability of MMEP-amplitude. The same authors suggested that at least some of the observed variability in amplitude is likely to result from spontaneous changes in the size of the descending volley from the cortex and hence reflect fluctuations in the excitability of the motor cortex.

Latency is the interval between the delivery of the stimulus and the resulting response and reflects total motor conduction time from cortex to the target muscle. The latency may be measured to the onset of the action potential and is expressed in milliseconds (ms).

MMEP latency is affected by the size of the fibre, the abundance of myelin, and the number of synapses the impulse must cross (Sylvestre et al., 1993). Physiological and clinical studies have focused on the shortest latency responses to provide an estimation of conduction velocities in the fastest descending spinal tracts. Much of the signal is dominated by conduction in a few large fibres. Those fastest descending tracts have been shown to connect monosynaptically to spinal motor cells (Cheney et al., 1985; Porter, 1987; Dimitrijevic et al., 1992). However, there have been reports of longer latency responses being recorded from extensor and flexor carpi radialis muscles of the thoracic limbs and from tibialis anterior and triceps surae muscles of the pelvic limbs in healthy human subjects (Holmgren et al., 1990). In addition to the fastest descending corticospinal fibres, there exist other indirect descending corticospinal pathways with fibres that terminate on the spinal interneurons in the intermediate zone of the spinal gray matter (Kuypers, 1981). These descending pathways to spinal motor cells via polysynaptic networks may mediate MMEPs with longer latencies.

One single cortical stimulation is able to produce multiple descending volleys in the pyramidal tract (Hess et al., 1987a). Both spatial and temporal summation of impulses reaching the spinal motoneuron are necessary before it fires; therefore, reduction in the descending volley due to conduction block in some fibres or to loss of the fastest conducting fibres by degeneration and use of slower ones will lead to delay in excitation of the anterior horn cell, resulting in latency lengthening.

The *configuration* of the MMEPs evoked in the muscles of the hand is in most instances bi- or triphasic (Maertens de Noordhout, 1998). A polyphasic configuration (more than five phases) has to be considered as abnormal in those muscles, whereas a polyphasic configuration is more frequently seen with MMEPs evoked in more proximal muscles and muscles of the leg, even in normal subjects.

In children however, MMEPs are generally polyphasic in early childhood and gradually become triphasic, reaching adult levels at the age of 13 years (Nezu et al., 1997).

Researchers also describe an influence of the stimulation intensity on the configuration of MMEPs. At just suprathreshold levels, cortical stimulation produces EMG responses which are generally quite simple and comparable with those following stimulation of peripheral nerves. However, at higher intensities, the cortical responses (whether after electrical or magnetic stimulation) become polyphasic, due to the multiple descending volleys set up by moderate to high levels of cortical stimulation. Motor units may fire on receipt of any one of several EPSPs (excitatory postsynaptic potentials) which these volleys release. This gives rise to an asynchronous activation of motor units in muscle. The EMG responses from each unit interfere, reducing the maximal amplitude of response and increasing its duration (Rothwell and others, 1991).

The typical waveform of a MMEP recorded in the extensor carpi radialis muscle of a horse, with latency and amplitude parameters identified, is shown in Fig. 4.

2.6. Factors influencing the latency and amplitude of MMEPs

2.6.1. Effect of voluntary contraction: facilitation

Slight voluntary contraction of the target muscles (Fig. 5) shortens the onset latency, lowers the threshold, and increases the amplitude (Barker et al., 1986, 1987; Hess et al., 1987b; Rothwell et al., 1987; Berardelli et al., 1990; Thompson et al., 1991; Di Lazzaro et al., 1998a). The underlying mechanisms for facilitation are not entirely understood. Some researchers suggest that the effect would be caused by changes in cortical excitability: voluntary contraction increased the size and number of descending volleys evoked by a given stimulus. In the voluntary contraction state, the summation of descending voluntary impulses from cortical areas, afferent impulses from muscle spindles and descending potentials secondary to magnetic brain stimulation can activate the spinal motor neurons earlier than under resting conditions and shorten the MMEP onset latency (Claus et al., 1988; Rossini et al., 1987a,b; Kaneko et al., 1996; Di Lazzaro et al., 1998a). Experiments done by Kaneko and co-workers (1996) demonstrated that the latency shortening can range from 2 to 3.5 ms, and that the amplitude during voluntary contraction can be increased to 150–500% of that recorded during the resting state. They also showed, by recording of the evoked responses at the epidural space of the spinal cord and at the muscle simultaneously, that the shortened latency

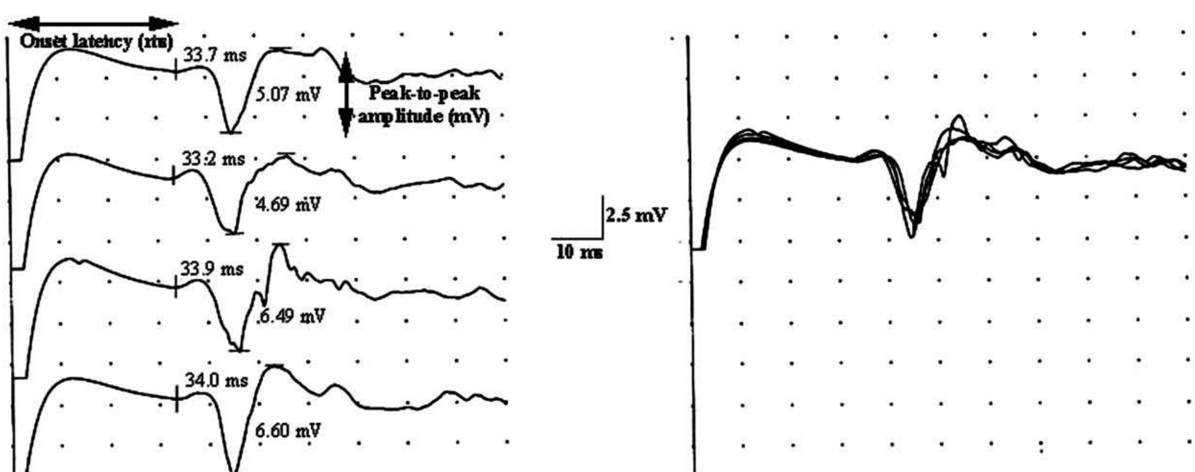

Fig. 4. MMEPs recorded in the cranial tibial muscle of a 4-year-old mare (height at withers 151 cm) after transcranial magnetic stimulation. Stimulation started at the beginning of the sweep (vertical line). Onset latency and peak-to-peak amplitude of each recording is marked. On the right, the four superimposed potentials are presented.

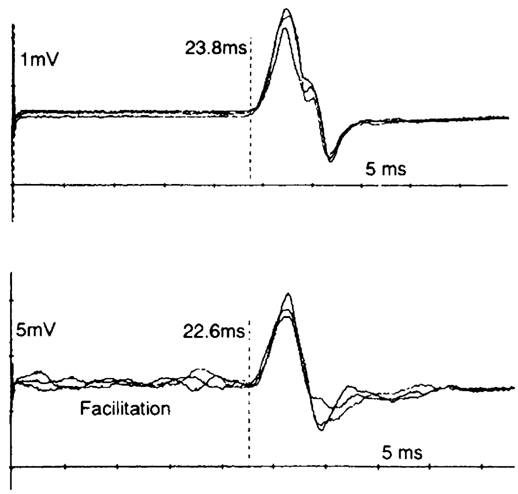

Fig. 5. Waveforms recorded over the left first dorsal interosseus after stimulation of the motor cortex with 90 mm circular coil placed centrally on the vertex – three superimposed responses each. Responses in the lower tracings are facilitated by slight pre-activation of the target muscle. Note the different scale for the two tracings (with permission of R. Jalinous; Magstim).

and increased amplitude of the MMEPs during voluntary contraction originated more in changes in spinal than supraspinal (cortical) excitability. Presumably the effect of voluntary activation raises the resting potential of spinal motoneurones closer to their discharge threshold and therefore the initial descending volley is capable of discharging at least some motoneurons. This can explain the predominant role of spinal excitability (Di Lazzaro et al., 1998a). Furthermore response latency shortening during voluntary contraction is likely to reflect application of the size principle of Henneman: the first corticomotoneuron cells to fire during a voluntary contraction are those that conduct most slowly and with increasing contraction, larger, faster conducting spinal neurons are recruited (Henneman et al., 1965), thus shortening the onset latency (Weber and Eisen, 2002).

Facilitation can be used when muscle responses are small because of central nervous system pathology (e.g., spinal cord trauma, multiple sclerosis, ...). In this situation, the ongoing muscle activity of a facilitatory contraction may make precise measurement of onset latency impossible. Therefore complete relaxation of the muscle, but moderate contraction of the same muscle on the opposite site (contralateral facilitation), will result in the same degree of latency reduction and amplitude increase (Hess et al., 1987c).

In animals, no data are available in literature concerning the influence of facilitation on MMEPs. Many animal studies are carried out under general anaesthesia where a conscious muscle contraction is impossible to perform. However, because of ignorance, some awake or sedated animals also contract their muscles during transcranial magnetic stimulation, but this facilitation is not controllable (own experience in horses).

2.6.2. *Effect of coil position*

In the majority of subjects, the lowest threshold for stimulation occurs when induced current in the brain (which is the opposite direction to that of the coil) flows from posterior to anterior at an angle approximately perpendicular to the line of the central sulcus (Mills et al., 1992).

As a general rule, when the coil is placed over the scalp, maximum and shorter responses could be elicited on the right if the stimulating current in the coil flows counterclockwise. To obtain the largest and shortest response on the left the current flow had to be reversed. The reasons for this difference are poorly understood but presumably reflect differences in the direction and distribution of current flow within the brain produced by the two orientations of the coil. This findings are most obvious at threshold. However, during voluntary contraction, about 20% of the MMEPs were maximum (amplitudes) on the left when the current flowed counterclockwise and vice-versa (Furby et al., 1992).

The most stable responses were obtained from muscles of respectively the thoracic or pelvic limb with the round coil centered respectively on the vertex or slightly anterior to the vertex (Terao et al., 1994; Kaneko et al., 1997). For a given stimulus intensity, responses always are largest in distal, particularly hand muscles (Thompson et al., 1989).

In veterinary medicine however, no influence of the coil current could be observed in dogs (Van Ham et al., 1994) and horses (Nollet et al., submitted for publication in *The Veterinary Journal*).

2.6.3. *Effect of age, height and gender*

The latency time is strongly correlated with height. No statistical difference was reported between gender for threshold and amplitude. The statistical difference found between gender for latency seems to result from the correlation between latency and height (Barker et al., 1987; Chu, 1989; Furby et al., 1992). It is concluded that height is an important variable in defining the MMEP normality. Most studies however have concentrated on the 20–50-year range and there has been no comprehensive description of the normative results of hand and leg MMEPs over a wide range of ages in a substantial sample of male and female subjects. Some authors described a linear increase in latency with increasing age, but with a very weak correlation (Eisen et al., 1990). Tobimatsu and colleagues (1998), who examined persons from 19 to 74 years old observed a significant gender difference in the MMEP latencies of the leg, but not in those of the hand. Both height and age had a significant effect on the leg MMEP latencies. An interesting finding is the different effect that was seen regarding age on the hand and leg MMEP latency. In the cortical motor area, 75% or more of Betz cells showed age-related morphological changes, while changes of small pyramidal neurons were less severe than those of Betz cells (Scheibel et al., 1977). The study by Lassek (1940) showed that 75% of Betz cells were in the motor area supplying the leg, 17.9% in the arm region and only 6.6% in the hand area, despite the dedication of far more extensive cortical areas to the head and arm than to the leg. These results thus suggest that physical variables are important in defining normal MMEPs, especially in the lower limbs. In young children, latency of the MMEP, however, does not attain adult values until about age 11 years (Koh and Eyre, 1988).

3. Indications and results

3.1. Magnetic stimulation of the human nervous system

3.1.1. Diagnosis

A diagnostic test should be sufficiently accurate and should have specified clinical indications. Several authors (Eisen and Shtybel, 1990; Di Lazzaro et al., 1999; Mills, 1999) reported that the overal accuracy of MMEPs is high. The high accuracy makes MMEPs efficacious in evaluating corticospinal tract functionality. The corticospinal tract function can be assessed with reliability by a rigorous clinical examination, therefore, only if the test can demonstrate abnormalities not revealed by an accurate clinical evaluation will it assume a definite clinical value. The ability of MMEPs in documenting a subclinical involvement of central motor pathways has been documented by Di Lazzaro et al. (1999) who found a high rate of subclinical abnormalities in motor neuron diseases, muscle disorders, multiple sclerosis and spinal cord diseases.

In patients with spinal cord disorders, MMEPs may be useful in demonstrating the site of spinal cord lesion and also to monitor the disease, as for example in cervical spondylotic myelopathy. Serial MMEP recording might be useful in ascertaining progressive forms and for selection of patients who may benefit from surgical treatment.

Next to its application in spinal cord lesions, the technique is also extremely useful in multiple sclerosis (MS). Multiple reports (Rossini et al., 1985; Snooks and Swash, 1985; Eisen and Shtybel, 1990) suggest that the technique is more sensitive than other evoked potentials in MS, but this should not imply there is specificity.

In Parkinson's disease (Eisen and Shtybel, 1990; Mills, 1999) MMEP latency have been shown to be normal. Sometimes an increased amplitude is reported (Eisen and Shtybel, 1990).

Presently, electrophysiology is the only means of confirming suspected amyotrophic lateral sclerosis (ALS) (Eisen, 2001). In addition to electromyography performed to determine lower motor neuron involvement, the introduction of transcranial magnetic stimulation has allowed the assessment of central motor pathway function (Urban et al., 2001). A common finding is that TMS fails to evoke a muscle response or evokes a response with a reduced amplitude, despite high intensity stimulation (Mills, 1999). The MMEP latency is only modestly prolonged (Mills, 1999). This can be attributed by the degeneration of the corticomotor cells or reduced firing frequency in corticospinal fibres with consequent impaired temporal summation at the motoneuron (Mills, 1995). Moreover, it provides a sensitive means for the assessment and monitoring of upper motor neuron involvement in motor neuron disease (Triggs et al., 1999).

3.1.2. Prognosis

Especially in human medicine, it is worthwile to have early indicators of significant motor recovery, especially for the patient's motivation. Furthermore, obtaining early and reliable indications of the final degree of motor function recovery would also be useful for optimizing rehabilitation strategies and evaluating their costs. The quality of motor recovery after stroke is difficult to predict on the basis of only clinical data. Since 1989, studies have been conducted to assess the value of MMEPs in patients with stroke. The application of TMS has yielded contradictory results (Macdonell et al., 1989; Arac et al., 1994; Timmerhuis et al., 1996; Escudero et al., 1998), probably because of the great variability of patients included and differences in the methodologies used. However, most authors agree that the evoked potentials measured in the acute stage had predictive value (Timmerhuis et al., 1996; Rapisarda et al., 1996; Pennisi et al., 1999). For instance, Pennisi et al. (1999) reported that the absence of responses to TMS in the first 48 h is predictive of absent or very poor functional hand motor recovery.

The use of TMS as a predictive test in patients with traumatic cervical spinal cord injury does not provide more useful information regarding motor recovery than the physical examination, but may be of benefit in uncooperative or incomprehensive patients (McKay et al., 1997; Kirshblum and O'Connor, 1998). Meyer and Zentner (1992) reported that TMS is a valuable diagnostic tool for detection of lesions along the spinal cord, but found no linear correlation between the clinical motor status and the electrophysiological changes.

For facial nerve outcome after acoustic neuroma surgery, Wedekind and colleagues (2000) reported no prognostic significance of preoperative TMS.

3.1.3. Monitoring

There are two clinical indications for monitoring neurological function during surgical procedures: to detect inadvertent damage early when the resulting dysfunction might still be reversible, and to guide the surgeon with regard to the extent of safe operative resection (e.g., in tumor resection) or curve correction (e.g., in scoliosis surgery). For these purposes, the ideal neurophysiological technique should: (a) have high sensitivity and specificity,

(b) provide real-time feedback, (c) not intrude physically into the operative field, (d) not hinder access for the anesthetist, (e) not prolong the operation unduly, (f) not be subject to artifactual changes that could be misinterpreted as incipient or actual neural dysfunction (i.e., there should be a low incidence of "false-positives") and (g) be equally useful in patients with and without preexisting neurological deficits.

Since the introduction of TMS, MMEPs as well as SSEPs are recorded routinely in many centres, for more complete information on both the descending corticomotoneuron tracts and ascending sensory pathways during major spinal surgery (Shields et al., 1989; Bartley et al., 2002; Aglio et al., 2002). However, in animal experiments, motor pathways have been reported to be more susceptible than sensory pathways to spinal cord trauma and ischaemia (Machida et al., 1988; Fehlings et al., 1989; Kai et al., 1995); therefore, identifiable motor dysfunction commonly might be expected to precede sensory dysfunction and a technique to monitor conduction in the corticospinal pathways (e.g., TMS) is advisable.

In addition to spinal cord monitoring during spinal operations, other potential roles for the technique may be sciatic nerve function during hip replacement (Schoenfeldt et al., 1987), peripheral nerve and brachial plexus integrity during hand surgery (Kaplan et al., 1984; Schmid et al., 1990), facial nerve function during surgery (Hatem et al., 2001) and spinal cord status during aortic surgery (Friedman et al., 1987).

3.1.4. Therapy

Transcranial magnetic stimulation is able to modify neuronal activity locally and at distant sites when delivered in series of trains of pulses: repetitive TMS (rTMS). Data from stimulation of the motor cortex suggest that the type of effect on the excitability of the cortical network depends on the frequency of stimulation.

Studies with rTMS for the treatment of psychiatric disorders (depression, schizophrenia, etc.) (Feinsod et al., 1998; Klein et al., 1999; Hasey, 2001) and motor disorders (Parkinson's disease, task-related dystonia (e.g., writer's cramp) tic disorders and epilepsy) were promising for the future and the authors concluded that the technique may possess tremendous potential as a treatment for these disorders (Hallett, 1998; Tergau et al., 1999; Shimamoto et al., 2001; Wassermann and Lisanby, 2001). However, much research is still needed to optimise the technical considerations, such as stimulus frequency, intensity, and magnetic coil position, and to investigate the neurophysiological changes.

3.2. Magnetic stimulation of animal nervous system

While routinely used in humans, application of TMS in other species is rare and few data are available on the characteristics of animal MMEPs. In recent years rodent studies have elucidated TMS mechanisms (Wang et al., 1996), demonstrated its safety (Russell et al., 1994; Post et al., 1999) and have demonstrated the effect of spinal cord injury (Magnuson et al., 1999) and anaesthesia (Ebert and Ziemann, 1999; Van Ham et al., 1995, 1996a,b). Mainly because magnetic transcranial stimulation is not invasive and painless, clinical studies on dogs and cats have increased over the last few years. In 1987 (Konrad et al., 1987) MMEPs were described in dogs and the influence of ischaemia of the spinal cord on the responses was examined. Heckmann and colleagues (1989) described the technique in awake dogs and in dogs awaking from general anaesthesia. In 1993, Sylvestre and co-workers reported TMS for assessing spinal cord integrity in dogs with thoracolumbar intervertebral disc disease. They concluded that MMEPs were very sensitive to lesions of the spinal cord in dogs, as indicated by the significant changes in the waves in patients with mild or no neurological deficits and in the loss of response in dogs that still demonstrated purposeful movement. There was a significant attenuation of the amplitudes in all clinical cases, even if the dogs demonstrated back pain alone. Significantly prolonged latencies were associated with neurological deficits. In contrast to the results published by Owen et al. (1988), significant lateralization, even when clinical signs indicate one side of the spinal canal in which the extruded disc material was located, was not shown by TMS. Recently, Poma and co-workers (2002) noted the potential of TMS to become a useful screening tool for cervical spinal cord disease in large-breed dogs. Impairment of the functional integrity of the spinal cord, regardless the severity of the neurological signs, was revealed by TMS. Of special interest is the group of dogs with neck pain only and no other neurological abnormalities, where in all dogs MMEP latencies and peak-to-peak amplitudes were significantly abnormal and in 5 of 7 dogs cervical spinal cord lesions were confirmed by myelography. Despite the lack of a significant difference among dogs in the three neurological categories, a linear association was observed when the mean latencies and peak-to-peak amplitudes of all affected dogs were correlated with severity of neurological deficits.

The effects of different forms of anaesthesia and sedation on MMEPs elicitated in dogs have been described (Sylvestre et al., 1992; Young et al., 1994; Van Ham et al., 1994, 1995, 1996a,b). The sedative combination of droperidol and fentanyl was reported to be the best to record MMEPs with shortest onset latency and highest amplitude (Van Ham et al., 1994). Sylvestre and others (1992) reported that TMS could be accomplished in normal dogs sedated with oxymorphone, midazolam or acepromazine and did not find a significant difference between the three drugs.

At surgical levels of anaesthesia, Van Ham and co-workers (1995, 1996a,b) only could elicit MMEPs when using sufentanil in combination with midazolam or either fentanyl or sufentanil with nitrous oxide. No MMEPs were obtained when propofol, thiopental, diazepam and ketamine, and halothane were used in dogs. Young and colleagues (1994) demonstrated that MMEPs can be reliably recorded under methohexital anesthesia. In horses, the sedative combination of detomidine and buprenorphine (Nollet et al., 2003 accepted for publication in The Veterinary Record) has no significant influence on MMEP recordings.

The effects of coil orientation of a figure-of-eight coil was described in rats and cats in 1998 (Kamida et al., 1998; Nakatoh et al., 1998). In 2001, the rodent motor evoked potentials to TMS were characterized and a methodology for reproducible assessment of motor excitability was developed in the rat (Luft et al., 2001). In 1996, Mayhew and Washbourne reported that TMS was possible in unanaesthetized or minimally sedated (acetylpromazine) normal ponies. In 2002, the usefulness of MMEPs in horses with cervical cord lesions was described (Nollet et al., 2002).

These few reports are already promising concerning the diagnostic value of TMS in veterinary medicine. However, the extensive evaluation of the technique will certainly expand the diagnostic impact of magnetic stimulation in neurological veterinary practice in the near future. Especially for revealing subclinical lesions of the central motor pathways in several neurological disorders in dogs and horses or for investigating complaints of back pain in performing horses, TMS may be an additional diagnostic tool. The technique may open new areas for assessing the central motor pathway function in disorders as equine motor neuron disease.

Studying the effect of TMS as a therapeutic tool would also be very interesting. Neurostimulation therapy for epilepsy in humans is growing in popularity. Reduced seizure frequency has been reported in human patients treated with transcranial magnetic stimulation at varying low-frequency stimulus rates. For the moment, no such data are available in veterinary patients. Epilepsy is very rare in horses. In dogs, however, the condition is often seen. To study the effect of rTMS would be indeed interestingly, since the common antiepileptic medications have important sedative side effects. First, however, safety studies, the effect of high and low-frequency stimulus rates and different parameters (stimulation frequency, stimulation period, coil position) have to be tested in these animal species.

4. Conclusions

In order to use transcranial magnetic stimulation in horses, we have described the basic theory and some practical applications of the technique in human beings and some animal models. We can conclude that the technique will provide reliable information about the functional integrity and conduction properties of the corticospinal tracts and motor control in animals and hope that it will be a complementary diagnostic test in the neurological examination, especially in the horse, where the information from clinical examination, as well as other tests are limited due to the animal's size and often poor cooperation.

We have already published an application of the technique in horses with cervical cord lesions (Nollet et al., 2002) and preliminary results in other neurological conditions look promising.

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