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TRANSCRANIAL MAGNETIC STIMULATION OFFERS NEW POSSIBILITIES FOR THE STUDY OF MOTOR CONTROL

TRANSKRANIALNA MAGNETNA STIMULACIJA ODPIRA NOVE MOŽNOSTI ZA RAZISKOVANJE KONTROLE GIBANJA

Abstract

Since its introduction in 1985, transcranial magnetic stimulation has been used as a tool for non-invasive exploration of motor control in humans. This paper reviews transcranial magnetic motor cortical stimulation as a revolutionary research tool in neurophysiology and its wider application. Historical facts on the development of magnetic nerve stimulation are first presented, followed by the basic physical and physiological mechanisms underlying this stimulation. The core of the paper provides an overview of the methods and measurements of transcranial magnetic stimulation paradigms, such as (i) central motor conduction time, (ii) threshold and amplitude of the motor potentials evoked by transcranial stimulation, (iii) input-output properties of the corticospinal tract, (iv) cortical brain mapping using transcranial stimulation, (v) cortical silent period, and (vi) intracortical inhibitory and facilitatory mechanisms tested by paired pulse paradigms. Finally, there is a discussion of the current knowledge of the application of transcranial magnetic stimulation in relation to neuromuscular potentiation, central fatigue, neural plasticity and sensorimotor integration. Proposals are put forward for potential novel applications of magnetic stimulation in sports science.

Key words: motor control, brain stimulation, transcranial magnetic stimulation, corticospinal excitability, plasticity, central fatigue.

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Izvleček

Transkranialna magnetna stimulacija se od iznajdbe leta 1985 uporablja kot neinvazivna metoda za raziskovanje kontrole gibanja pri človeku. Ta članek podaja pregled transkranialne stimulacije možganske motorične skorje, ki se kot inovativno raziskovalno orodje uporablja v nevrofiziologiji ter njej sorodnih raziskovalnih področjih. Najprej je navedenih nekaj zgodovinskih dejstev o razvoju magnetne stimulacije živcev, čemur sledi razlaga fizikalnih in fizioloških mehanizmov stimulacije. Opisana so anatomska področja in prevodne poti, ki jih s to stimulacijsko tehniko testiramo. Jedro članka predstavlja pregled najpogostejših merilnih tehnik, pri katerih uporabljamo transkranialno magnetno stimulacijo. Kratko so pojasnjeni: (i) centralni motorični prevodni čas; (ii) prag in amplituda motoričnih potencialov vzbujenih s transkranialno stimulacijo; (iii) vhodno-izhodne lastnosti kortikospinalnega trakta; (iv) določanje topografskih možganskih map z uporabo transkranialne stimulacije, (v) obdobje tišine možganske skorje in; (vi) znotrajmožganska inhibicija in facilitacija, ki ju testiramo s tehniko parnih magnetnih dražljajev. Skozi živčno-mišično potenciacijo, centralno utrujenost, plastičnost živčnega sistema in senzomotorično integracijo, sklenemo uporabo transkranialne magnetne stimulacije na področju športne znanosti. Na koncu so podane nekatere sugestije za bodočo uporabo transkranialne magnetne stimulacije pri proučevanju kontrole gibanja.

Ključne besede: kontrola gibanja, možganska stimulacija, transkranialna magnetna stimulacija, kortikospinalna vzdražnost, plastičnost, centralna utrujenost.

Introduction

Motor evoked potentials (MEPs) are established as diagnostic tests and research tools, providing objective measure of function in their related neural processing systems and conducting tracts. In neurophysiology, peripheral muscle and nerve stimulation was followed by stimulation of the central nervous system. Transcranial electrical stimulation (TES) (Merton & Morton, 1980) was preceded by direct stimulation of brain structures during surgery. TES, which uses high voltage electrical pulses of short duration applied to the scalp overlying the motor cortex, is an uncomfortable procedure, inappropriate for routine clinical use. In 1985 the technique of non-invasive transcranial magnetic stimulation (TMS) was introduced (Barker, Jalinous, & Freeston, 1985a), which led to a new era of research into motor control and cortical function. Since then, TMS has become a widely used diagnostic tool in neurophysiology, as attested by the volume of literature on the subject (for review see Bailey, Karhu, & Ilmoniemi, 2001; Cantello, Tarletti, & Ciravdi, 2002; Hallett, 2000; Lisanby, Luber, Perera, & Sackeim, 2000; Petersen, Pyndt, & Nielsen, 2003; Siebner, & Rothwell, 2003; Walsh, & Cowey, 2000; Weber, & Eisen, 2002).

The purpose of this paper is to present the technical, anatomical and physiological basis of TMS. Measurements of the magnetically evoked motor potentials (MEPs) are described. Emphasis is placed on research applications of TMS, such as brain mapping, sensorimotor integration, intra-cortical excitatory and inhibitory mechanisms and neuroplasticity. Potential new applications in sport science are proposed.

Basic principles and neurophysiology of TMS

The basic mechanism of nerve cell activation is identical for TES and TMS. Both techniques cause a change in the transmembrane potential, which, if the stimulus is strong enough, results in the initiation of a nerve action potential (Pascual-Leone, Davey, Rothwell, Wassermann, & Puri, 2002). However, apart from TES, TMS, based on the principle of electromagnetic induction, employs a pulse of magnetic field to cause current flow in the tissue. Switching the electrical current on or off in a primary (stimulation) coil will cause currents to be induced in a secondary coil placed near neural tissue, although the primary coil is not itself in electrical contact with target neural structures. The independence of electrical resistance of the skull enables non-invasive brain stimulation by TMS. For peripheral, spinal cord and transcranial magnetic stimulation, different shapes (circular, double circular, double cone), and sizes (Ø=50 to 100 mm) of magnetic coils are available. The main difference between the double-circular or figure-of-eight coil and the standard circular coil is that the former has a more focal area of effect.

When using TMS, it is necessary to be aware of the complexity of the structures and processes that are probed. Motor function in humans is served by several distinct, yet interconnected, neurofunctional components. For example, when voluntary movement of the hand is to be executed, numerous parallel, as well as sequential, integrative sensorimotor processes are involved. In the same way as perceptual skills reflect the ability of sensory systems to detect, analyse and differentiate certain physical stimuli, dexterity indicates the ability of the motor system to plan, co-ordinate and execute movements. In fact, these two systems are inseparable, operating in a complementary manner. All the three main categories of movements (reflexive,

rhythmic and voluntary) are complexly organized within the brain and spinal cord. Planning and setting of voluntary movement are organized in the cerebral cortex, with different areas communicating with subcortical areas, the cerebellum and the spinal cord. The initiation of a voluntary movement is driven by pyramidal cells in the primary motor cortex. The output of the motor system through muscle activity however depends on parallel processes and states of other serial components of the corticospinal tract. TMS similarly activates only a restricted part of the motor system, with the evoked MEPs being influenced by other functional elements of the sensorimotor system.

Pyramidal cells are not independent units that generate rudimentary neural activity autonomously, but rather are subject to excitatory and inhibitory input transmitted from other nerve cells. Different types of brain stimulation of the motor system are capable of activating pyramidal cells in different ways. Patton and Amassian (1954) were the first to measure direct and indirect volleys (D and I waves, respectively) following transcranial electrical stimulation using epidural electrodes (Figure 1). Lower intensities of stimulation evoked short latency D waves that were ascribed to direct activation of pyramidal cells at the axon hillock (Day et al., 1987; 1989). Increasing the intensity of stimulation evoked I waves, which were attributed to indirect or transsynaptic activation of the same corticospinal neurons. A time gap of 1.5 to 2 ms between D and I1 as well as between successive I2, I3, and I4 waves was observed.

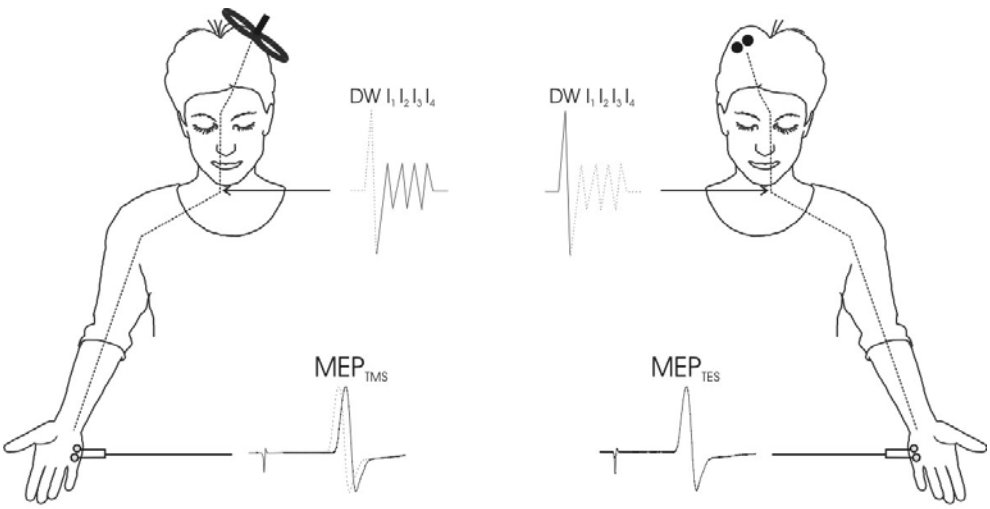

Figure 1: Comparison of TMS (left) and TES (right). Magnetic stimulation with a figure-of-eight coil oriented in a posterior-to-anterior direction activates pyramidal neurons predominantly transsynaptically. This causes multiple descending indirect volleys (I_1-I_4) of the cervical spinal cord and longer latencies of the MEPs detected by the EMG electrodes. Conversely, TES, or lateral-to-medial orientation of the TMS, causes direct activation of the pyramidal cells at the axon hillock. The MEP latency is therefore shorter as a result of a predominantly direct descending volley (DW).

Later studies (Amassian, Quirk, & Stewart, 1990; Burke et al., 1993; Di Lazzaro et al., 1999; Edgley, Eyre, Lemon, & Miller, 1990; 1997) have shown that TMS acts on the corticospinal neurons in a very similar way to high intensity electrical brain stimulation. Threshold in-

tensity TMS transsynaptically activates the motor cortex preferentially through excitatory cortical interneurons. Increasing the magnetic stimulation results in the appearance of D waves, which cause an approximate 2 ms shortening of the MEP latency. The orientation of the magnetic coil also affects the nature of activation and quantitative parameters of MEP (Brasil-Neto, Cohen, Panizza, Nilsson, Roth, & Hallett, 1992b; Mills, Boniface, & Schubert, 1992; Pascual-Leone, Cohen, Brasil-Neto, & Hallett, 1994b). Using a figure-of-eight coil, the lateral-to-medial orientation preferentially evokes D waves, while the posterior-to-anterior coil orientation causes transsynaptic activation. Furthermore, TMS activates other local intrabrain circuits that could be tested by other stimulation paradigms such as paired pulse stimulation, which is described in a later section.

The spinal motor neurons of the cord are the "final common pathway" of the motor system, with which the higher centres and pyramidal cells make direct or indirect connections via multiple descending tracts (Bernhard & Bohm, 1954; Landgren, Philips, & Porter, 1962; Kuypers, 1981). Anatomical studies (Kuypers, 1981; Schoen, 1964) have demonstrated that the majority of corticospinal fibres terminate in the ventral horn, where the spinal motor neurons are located. Although the estimation of conduction velocities of different sections of the corticospinal pathway is possible by the application of either TMS at different levels (Gandevia, Petersen, Butler, & Taylor, 1999; Nielsen, Petersen, Deutschl, & Bellegaard, 1993; Ugawa et al., 1991) or by measuring descending volleys evoked by TMS at different levels of the spinal cord (Burke, Hicks, Gandevia, Stephen, Woodforth, & Crawford, 1993; Di Lazzaro et al., 1998; Rothwell et al., 1994), this estimation is too imprecise to draw firm conclusions about the activated pathway.

Supportive evidence for the monosynaptic nature of the TMS-activated corticospinal projections comes from single motor unit studies considering their firing probability. Although reports on short rising times in post-stimulus time histograms are in favour of monosynaptic projections, no general agreement has been reached on this issue. The publications available (Burke, Gracies, Mazevet, Meunier, & Pierrot-Deseilligny, 1992, 1994; Burke, Gracies, Meunier, & Pierrot-Deseilligny, 1992; Nicolas, Marchand-Pauvert, Burke, & Pierrot-Deseilligny, 2001; Pierrot-Deseilligny, 1996; Pierrot-Deseilligny, & Marchand-Pauvert, 2002) provide neurophysiological evidence for the possible existence of a cervical propriospinal system, which is postulated to play a mediating role in the transmission of descending motor commands to cervical motor neurons.

TMS is much more than just a tool for testing the continuity of the corticospinal system. Since its introduction, it has been developed and many different diagnostic applications have been established. In the following section of this paper methods and measurements that employ motor cortex single- and double-pulse TMS paradigms will be presented. Consideration of other types of magnetic stimulation (high-frequency train TMS, and single TMS of other neuroanatomical regions) would make this review too large.

Methods and measurements

Central motor conduction time

The majority of today's clinical neurophysiology laboratories routinely apply TMS as part of their diagnostic procedure. Clinicians are mainly interested in central and peripheral con-

duction times, which can provide valuable insight into pathologically changed processes of neural signal propagation.

The time between TMS of the motor cortex and the EMG response in the target muscle is the result of the propagation of an action potential along the whole motor pathway – from the cortex to the spinal segment, synaptic transmission to spinal motor neurons, along peripheral nerves from the spinal cord to the muscle and neuromuscular synaptic transmission. Combinations of electrophysiological measures enable independent estimation of the central and peripheral motor conduction times. To calculate the central motor conduction time, conduction in the peripheral segment of the motor pathway is estimated and then subtracted from the onset latency of the TMS-elicited MEP. To measure peripheral motor delays, F waves or direct stimulation of the efferent roots and nerves over the spinal columns are mainly used (Barker, Jalinous, Freeston, & Jarratt, 1985b; Merton, Morton, Hill, & Marsden, 1982; Rossini, Marciani, Caramia, Roma, & Zarola, 1985; Zarola et al., 1989). Calculations of the central conduction time from root stimulation will give slightly higher values due to the distance between the anterior horn synapse and the point of stimulation (Maccabee, Amassian, Eberle, & Rudell, 1993).

During contractions, MEPs are both larger in amplitude and shorter in latency. The main shifts occur at the beginning of force gradation, with no further significant latency change being observed with volitional contraction above 10% of the maximal voluntary force (Rossini, Caramia, & Zarola, 1987). This contraction-dependent time change shortens in the process of biological maturation and reaches adult values during adolescence (Caramia, Desiato, Cicinelli, Iani, & Rossini, 1993). There is only a weak correlation between age and the central conduction time (Eisen, Shytbel, Murphy, & Hoirch, 1990; Mills & Nithi, 1997a). Values of central motor conduction times in women are slightly lower than those in men, due to the differences in height and arm length (Furby, Bourriez, Jacquesson, Mounier-Vehier, & Guieu, 1992; Mills & Nithi, 1997b). Clinical studies provide evidence for prolonged central conduction times under pathological conditions such as stroke (Abbruzzese, Morena, Dall'Agata, Abbruzzese, & Favale, 1991), multiple sclerosis (Rossini et al., 1987) and upper motor neuron diseases (Barardelli, Inghilleri, Craccu, Mercuri, & Manfredi, 1991).

Threshold and amplitude of the MEP

In neurophysiology, a threshold represents the minimal stimulus required to provoke a defined response (Reid, Chiappa, & Cros, 2002). The cortical motor threshold to magnetic stimulation is usually defined as the stimulus intensity required to elicit reproducible responses of 50 to 100 μV in about 50% of 10 to 20 consecutive trials (Rothwell et al., 1999). According to the two main recommendations, threshold intensity can be achieved by either increasing or decreasing (Rossini et al., 1994; Mills & Nithi, 1997b) the stimulation in steps of 1 to 5% of the maximum output intensity. However, when MEPs are recorded from pre-activated muscle, the required amplitude level ranges from 200 to 300 μV.

The TMS threshold is a complex measure that is influenced not only by the excitability of corticospinal cells, but also by the activity of the cortical cells that project to them, as well as by the excitability of spinal motor neurons, through which motor signals are conveyed to the periphery (Morita et al., 2000). Therefore, analytical approaches should be applied to selectively identify excitability levels at the intracortical, corticospinal, spinal and peripheral levels. In adults, the threshold is independent of age and gender. It is lowest for the hand muscles and

highest for more proximal muscles (Mills & Nithi, 1997b; Wassermann, McShane, Hallett, & Cohen, 1992).

The set-up for TMS conventionally employs electromyography for detecting evoked muscle responses. In acquired MEPs, amplitudes and rectified areas are the most common excitability parameters analysed (Figure 2). Either absolute or normalized values can be used. The maximal compound motor action potential, the M wave, is used for the purpose of normalization. Because of the variability of MEPs detected by the surface EMG, it is necessary to use averaged responses for final analyses. Statistical standards for reliable MEPs are available (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992a), however, the majority of researchers have used fewer (4 to 10) consecutive magnetic stimuli to compose the final MEP (Stedman, Davey, & Ellaway, 1998; Thickbroom, Byrnes, & Mastaglia, 1999). Although factors such as changes in coil positioning (Bohning, Denslow, Bohning, Walker, & George, 2003), background voluntary contractions, or phases of the cardiac or respiratory cycles should be considered, they are not of vital importance for the reproducibility of MEPs (Amassian, Cracco, & Maccabee, 1989). Recent studies employing the triple stimulation technique (Magistris, Rösler, Truffert, & Myers, 1998; Magistris, Rösler, Truffert, Landis, & Hess, 1999) have confirmed that the major MEP variability arises from phase cancellations. Additionally, evidence has been provided for the ability of a high intensity TMS to completely activate the goal muscle. This combined type of stimulation also has some pitfalls that prevent it simply replacing the conventional TMS application.

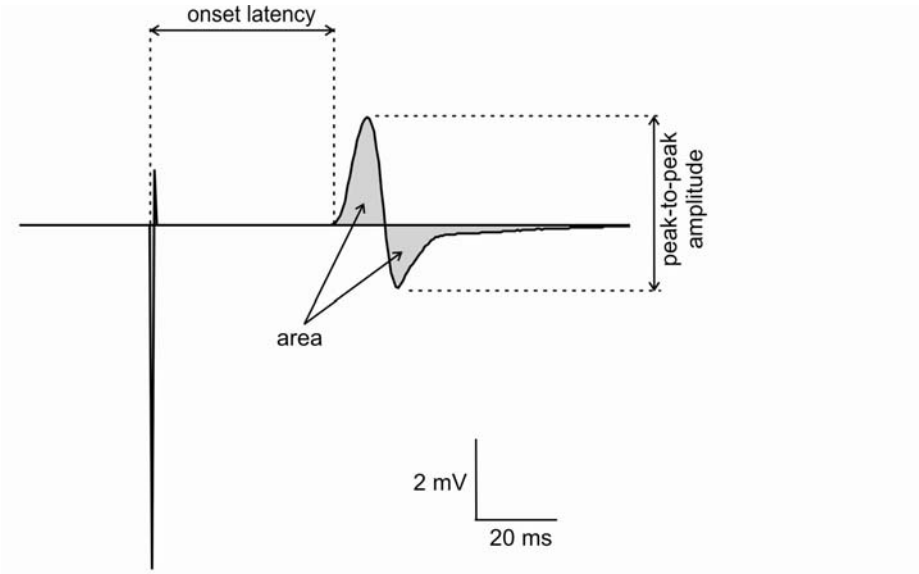

Figure 2: The average response of he first dorsal interosseus muscle of the hand composed of 20 consecutive magnetic stimuli. The most frequently measured parameters of the transcranially elicited MEPs include latency, area, and peak-to-peak amplitude.

Input-output curves

Spontaneous physiological oscillations in motor neuron excitability at both the cortical and spinal levels may play a role in fluctuations in the response size, while overall corticospinal

excitability may vary as a function of time. For further improvement in metric characteristics of MEPs, TMS is applied at different intensities and an input-output curve is composed. This was first performed by Devane, Lavoie, and Capaday (1997) in a report on the stimulus-response properties of TMS. They found the relationship to be sigmoidal and thus strongly non-linear (Figure 3). Additionally, it was independent of the behaviour of a single motor neuron. The most striking result was that the steepness, i.e. the gain of the relation, changes as a function of the level of motor activity of the same qualitative task. This output parameter, as well as the others measured in TMS input-output studies (Carroll, Riek, & Carson, 2001; Devane et al., 1997; Ridding & Rothwell, 1997), most likely reflects the excitability properties of the population of cortical interneurons, corticospinal neurons, and the motor neuron pool with interneuronal relays.

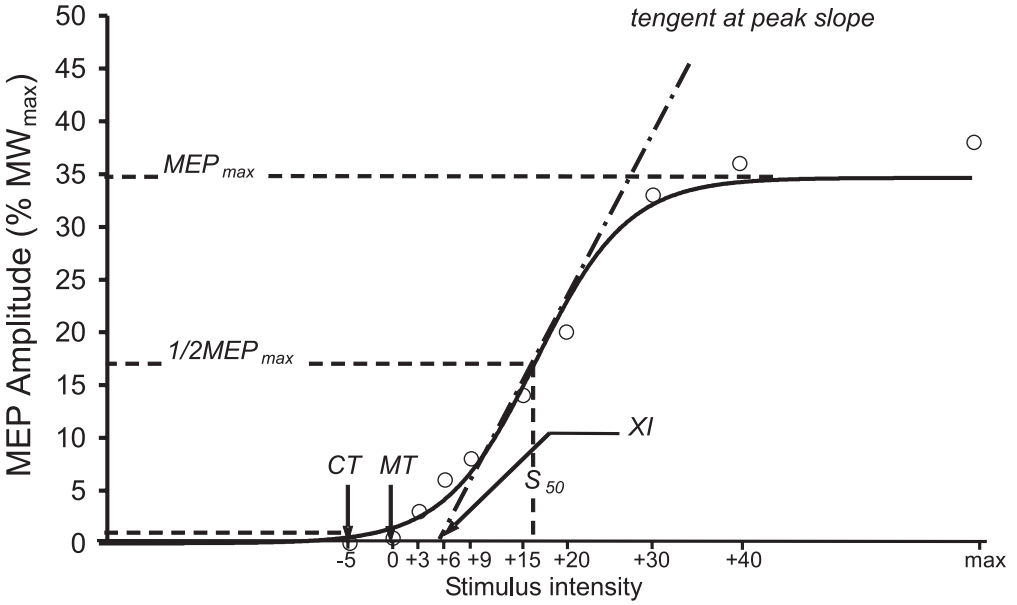

Figure 3: The TMS input-output curve for the first dorsal interosseus muscle. The following parameters are used as measures of corticospinal excitability: MT – measured threshold, CT – threshold calculated from the function, XI – x intercept of the tangent, MEP_{max} – maximal MEP defined by the function, S_{50} – stimulus intensity at which MEP size is 50% of the MEP_{max}, k – slope parameter of the function, k_{max} – maximal slope of the function. MEP amplitudes are expressed as percentages of the maximal M wave (MW_{max}).

To compose the function technically, MEP amplitudes are plotted against the stimulus intensity, and the data fitted with the Boltzmann equation:

$$MEP(s) = \frac{MEP_{\max}}{1 + e^{m(S_{50} - S)}} \qquad \text{(Equation 1)}$$

where MEP_{max} is the maximum MEP defined by the function; m, the slope parameter of the function; S_{50}, the stimulus intensity at which the MEP size is 50% of the maximal MEP. Besides the slope parameter, which is usually taken as a general measure of the excitability of

the pathway, a peak slope, which occurs at a stimulus intensity equal to S_{50}, is defined by the relationship:

$$\frac{m^{\star}\ MEP_{\max}}{4}. \qquad \text{(Equation 2)}$$

The purpose of fitting a mathematical function to the experimentally observed relationship between stimulus intensity and response magnitude is to provide a succinct description of the input-output properties of the corticospinal pathway (Carroll et al., 2001). The sigmoidal shape of the input-output relation is most likely due to a combination of factors. The experimentally measured curve, at least in part, reflects the well-known fact (Henneman, 1957) that stimuli of increasing strength recruit motor neurons with increasing motor unit potentials. Namely, sigmoidal input-output relations occur in systems composed of excitable elements with a wide distribution of spike amplitudes (Erlanger, & Gasser, 1937; Rall, 1955). Other relevant factors are related to modulating influences arising from the properties of the neural circuitry. Multiple components of the corticospinal volley and perhaps a greater tendency for synchronization of single motor unit discharges with increasing stimulus strength (Poliakov & Miles, 1994) additionally contribute to the non-linear input-output properties. Thus, all the parameters of the sigmoidal function are complex in origin. For example, the plateau value of the function is probably not the maximal response to a purely excitatory corticospinal volley. Inversely, it represents the balance between excitatory and inhibitory components, including recurrent inhibition of later-recruited motor neurons by those recruited earlier. However, test-retest reliability assessment of the input-output parameters of the corticospinal pathway has shown that TMS can be used in long-term studies (Carroll et al., 2001). Nevertheless, such repeatability does not apply to classical single-intensity TMS applications.

TMS brain mapping

Since the first brain mappings of the sensorimotor system (Penfield, & Boldrey, 1937; Penfield, & Rasmussen, 1950), several studies using transcranial electrical and magnetic stimulation, positron emission tomography or functional magnetic resonance imaging have confirmed the existence of functional representations in the brain. The motor cortex is organized in terms of movements rather than muscles, including complex convergence and divergence. Different regions of the brain are stimulated in TMS mapping of cortical motor areas; the consecutive motor effects are quantified and related to the stimulated scalp site (Thickbroom et al., 1999; Weber & Eisen, 2002). While the need for spatial resolution of the stimuli has been emphasised, the figure-eight coil is generally employed. The coil is systematically moved over the scalp using a co-ordinate system referenced to the vertex (Cohen et al., 1991; Wassermann et al., 1992). To achieve focal activation stimulation should be of low intensity, which however, increases the amplitude variability of MEP (Kiers, Cros, Chiappa, & Fang, 1993). In addition, there is no firm rule regarding coil positioning, although obvious discrepancies between anterior-posterior and lateral-medial orientations have been proved (Mills et al., 1992; Werhahn et al., 1994; Wilson, Day, Thickbroom, & Mastaglia, 1996).

A clear definition of TMS will provide a useful map of sites on the scalp from which responses can be obtained for each muscle of interest. The two most important parameters of such maps are the amplitude-weighted centre of the map (centre of gravity) and the point of maximum response. The area of the map is more difficult to estimate because of the non-focal nature

of the stimulation, especially when higher intensities are used (Levy, Amassian, Schmid, & Jungreis, 1991) or target muscles are voluntarily pre-contracted (Nielsen, 1994), although these conditions give higher MEP amplitude consistency.

An alternative to the use of the standardized TMS intensity of 1.2 motor threshold or a stimulation output 20% above the threshold intensity (Wassermann et al., 1992) was provided by Classen et al. (1998), who mapped the thresholds for evoking MEPs at particular scalp locations.

Cortical silent period

Inhibitory neural systems are essential for shaping and modelling of the flow of excitatory signals and maintaining synaptic stability. In addition to the excitatory response, TMS also has some inhibitory effects. When TMS is applied during voluntary muscle contraction, MEP is followed by a pause in the electromyographic activity, known as the cortical silent period (Ahonen, Jehkonen, Dastidar, Molnar, & Häkkinen, 1998; Bertasi, Bertolasi, Frasson, & Priori, 2000) (Figure 4). The early phase (0 to 50 ms) of this phenomenon is ascribed to spinal inhibitory mechanisms, while the later phase is mainly due to the activation of cortical interneurons acting over the neural output elements of the motor cortex (Ziemann, Lonnecker, Steinhoff, & Paulus, 1996a). These implicated interneuronal circuits are mediated by the inhibitory neurotransmitter GABA (Inghillieri, Berardelli, Cruccu, & Manfredi, 1993). There is also evidence that the silent period is a separate process to MEP (Wilson, Thickbroom, & Mastaglia, 1995).

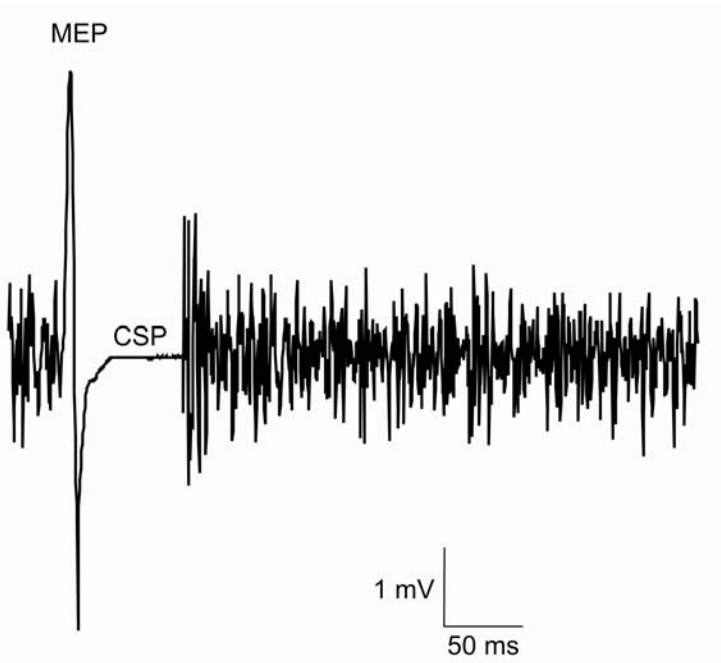

Figure 4: The cortical silent period (CSP) occurs when magnetic stimulation of the corresponding motor cortex is applied during an ongoing voluntary contraction. The potentiated MEP is followed by depression of the electrical muscle activity. After 80 to 300 ms the voluntary EMG signal rebounds.

A cortical silent period can last up to 300 ms and is basically divided into three phases: (i) the early phase that comprises approximately the first 50 ms after the MEP; (ii) the intermediate phase between 50 and 75 ms, and (iii) the late phase, more than 75 ms after the response. Increasing the intensity of TMS does not prolong the duration of the silent period after a plateau has been reached (Inghillieri et al., 1993). It has also been shown that the strength of the background contraction does not affect the silent period (Roick, von Giesen, & Benecke, 1993; Uozumi, Ito, Tsuji, & Murai, 1992), hence, proprioceptive mechanisms are unlikely to be involved in the generation of this phenomenon.

Paired TMS

Different combinations of two consecutive magnetic stimuli can provide a better understanding of the neural processes that are part of voluntary movement control. By modifying the intensities of the two stimuli and the time delay between them, cortical and corticospinal excitatory and inhibitory mechanisms can be probed. The following techniques are described in the literature (i) the paired pulse technique, using two equal suprathreshold stimuli at interstimulus intervals (ISIs) of 10 to 250 ms (Claus, Weis, Jahnke, Plewe, & Bruhnholzl, 1992; Valls-Sole, Pascual-Leone, Wassemann, & Hallett, 1992), (ii) the paired pulse technique, which employs a subthreshold conditioning stimulus followed by the suprathreshold test stimulus at 1 to 20 ms ISIs (Kujirai et al., 1993; Rothwell et al., 1991a; Ziemann, Rothwell, & Ridding, 1996b), (iii) the paired pulse technique, using an initial suprathreshold stimulus followed by a subthreshold stimulus at 0.5 to 6 ms ISIs (Tergau, Ziemann, Hildebrandt, & Paulus, 1997; Ziemann, Tergau, Wischer, Hildebrandt, & Paulus, 1998) and finally; (iv) the paired pulse techniques, in which the first and second stimuli are applied through different stimulating coils at separate stimulation sites (Ferbert et al., 1992; Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1995).

The general aim of all these protocols is to evaluate the effects of the conditioning stimulus on the size of the MEP elicited by the test stimulus as a function of ISI duration and stimulus intensity. If the test TMS is preceded by suprathreshold conditioning, facilitation of the control responses occurs at 10 to 40 ms ISIs, but inhibition at 50 to 200 ms ISIs (Roick et al., 1993; Triggs et al., 1993). This technique employs stimuli of equal intensity in the range from 120 to 160% of the resting motor threshold. Another method is to use a stimulus of only 80% of the threshold intensity to condition the test stimulus that follows, resulting in maximum inhibition at 1 to 5 ms ISIs and significant facilitation of MEPs at delays of 8 to 25 ms (Figure 5). Such interactions, which are universal for all muscles (Chen et al., 1998), are however dependent on coil orientation, stimulus intensity, and background muscle activity. Finally, very short ISIs are used in paradigms that combine the suprathreshold test stimulus followed by a conditioning subthreshold stimulus (Ziemann et al., 1998). The behaviour of MEPs under such conditions shows three facilitatory peaks at ISIs of 1.1 to 1.5 ms, 2.3 to 2.9 ms and 4.1 to 4.4 ms.

It is again obvious that the interaction between the effects of two stimuli could take place at the cortical, subcortical or spinal level. However, there is evidence that they are primarily caused by intracortical mechanisms. In all three listed stimulation techniques, researchers used complementary protocols to determine the exact sites and mode of interactions. They (i) used different intensities of TMS, (ii) systematically changed the coil orientation and replaced conditioning TMS with transcranial electrical stimulation, (iii) studied the effects of TMS on

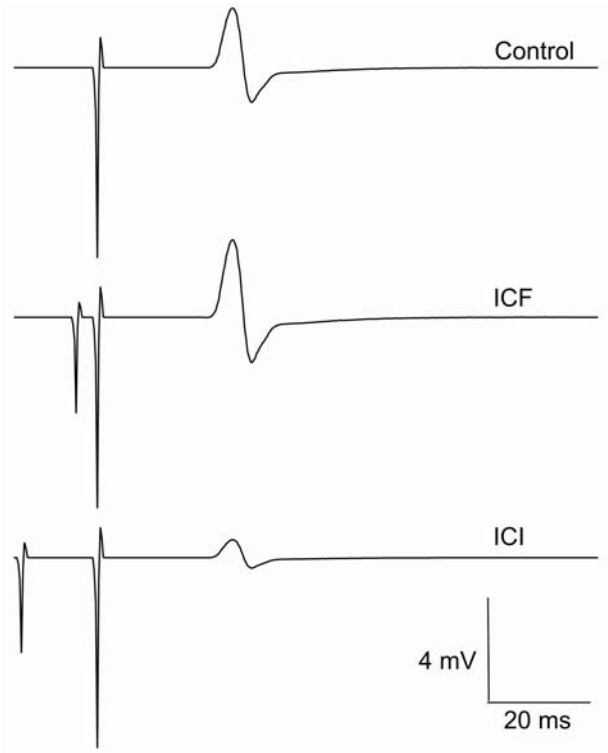

Figure 5: An example of the paired-pulse technique using subthreshold (80% MT) conditioning followed by the suprathreshold (130% MT) test stimulus. Averages of 20 consecutive MEPs are constructed for the control conditions, intracortical facilitation (ICF), and intracortical inhibition (ICI). The delays between the stimulation artefacts (left side of the traces) show the duration of the time interval between the two transcranial magnetic stimuli. ISIs of 1 to 5 ms result in ICI, while ISIs of 8 to 20 ms produce ICF. ICI is normally more prominent than ICF, as is also seen in this representative subject.

spinal excitability, and (iv) intraoperatively recorded descending volleys with epidural electrodes, and used neuroactive drugs. For the technique using two suprathreshold magnetic stimuli it is proposed that facilitation followed by a long-lasting (150-300 ms) inhibition of pyramidal cells is derived from supraspinal sites. Intracortical inhibition and facilitation, tested by the test stimulus preceded by a subthreshold stimulus, are also confirmed to be of cortical origin. Moreover, there is evidence that these neural characteristics are due to separate mechanisms, contradicting the view that facilitation is merely a rebound following inhibition. Finally, the interaction of the subthreshold stimulus that follows the suprathreshold stimulus is very likely to test the excitability of motor cortex circuits responsible for the generation of I waves.

The main and most commonly used measures of TMS have been presented. Undoubtedly, it is important to be aware of potential side effects of the technique. Single-pulse (<1 Hz) and paired-pulse TMS have been proved safe for use in normal subjects. However, it is interest-

ing that early reports on safety measures are from studies in humans (Bridgers & Delaney, 1989). Most of the research using animal models, which was conducted thereafter (Ravnborg, Knudsen, & Blinkenberg, 1990; Counter, 1993; Fleischmann, et al., 1996), examined the histological changes induced by prolonged exposure to TMS. Their only consistent finding was increased catecholaminergic activity following TMS in rats which had received direct deep brain stimulation because of their small head size. However, evidence on the depth of brain stimulation in human (Rudiak & Marg, 1994) argues against the possibility that this type of response could also occur in humans.

After exposure to prolonged single-pulse TMS, subjects have shown a transient increase in the auditory threshold (Pascual-Leone et al., 1992), hence the use of earplugs during TMS testing is recommended. Apart from its use in healthy subjects, single-pulse TMS has been reported to induce seizures in patients with large cerebral infarcts (Hömberg & Netz, 1989) as well as in epileptics (Classen et al., 1995; Düzel, Hufnagel, Helmstaedter, & Elger, 1996).

In summary, TMS does not appear to cause long-term adverse neurological, hormonal, motor, sensory or cognitive effects in healthy subjects. Current concepts even propose that Institutional Review Boards consider well-designed studies using single- and paired-pulse TMS protocols as being of minimal risk to children (Gilbert et al., 2004; Lin & Pascual-Leone, 2002). For further insight into TMS safety measures, including those of high-frequency repetitive TMS, the reader is referred to review articles by Anand and Hotson (2002), Bridgers (1991) and Wassermann (2000).

Possibilities for the use of TMS in sport science

TMS lends itself to many different research areas of particular interest to the sport science disciplines. Kinesiology-related research issues for which TMS has already been, or could potentially be applied, include: (i) post-exercise facilitation, (ii) central fatigue, (iii) sensorimotor integration and co-ordination, and (iv) neuronal plasticity. In the final section, some light is shed on applied studies that consider neurocontrol mechanisms in situations akin to those in sporting activities. Further proposals for the use of TMS in sport science research are put forward.

When a subject performs a weak voluntary contraction of a muscle, the corticospinal pathway to that muscle is facilitated (Rothwell, Thompson, Day, Boyd, & Marsden, 1991b). As already mentioned, most facilitatory effects occur at low contraction forces (Lim & Yiannikas, 1992; Stedman, Davey, & Ellaway, 1998). Additionally, higher MEP potentiation has been reported for precision movements as compared to general grip tasks (Datta, Harrison, & Stephens, 1989), presumably because of the larger involvement of pyramidal tract neurons in such tasks (Muir, & Lemon, 1983). A spread of facilitatory effects has also been shown during a voluntary contraction of neighbouring ipsilateral or homonymous contralateral muscles (Chiappa et al., 1991; Hufnagel, Jaeger, & Elger, 1990), but other reports give opposing results (Samii, Canos, Ikoma, Mercuri, & Hallett, 1997).

Besides the immediate influence of the voluntary motor activity, there are also prolonged post-exercise MEP potentiation effects (Brasil-Neto, Cohen, & Hallett, 1994; Samii, Wassermann, Ikoma, Mercuri, & Hallett, 1996). These authors found that 10-second activation could lead to post-exercise facilitation, which decayed to the baseline over 2 to 4 minutes. Researchers

have postulated that these effects are due to intracortical plastic changes, as they were not present after transcranial electrical stimulation. It has been shown (Balbi, Perretti, Sannino, Marcantonio, & Santoro, 2002) that the intensity of muscle contraction does not play a significant role in eliciting post-exercise facilitation. However, the maximum increase in MEP was present at the shortest and strongest muscle contractions.

Acute potentiation manoeuvres are incorporated into sport training and competition routines. These short-term conditioning procedures include: (i) explosive strength exercises are performed prior to speed and agility training, (ii) joint stability exercises are combined with foot work co-ordination, (iii) pliometrics is carried out just before sprint starts, and (iv) in resistance training, maximal and submaximal loads are combined in the same training session. Although peripheral electrophysiological and mechanical measures have been well evidenced (Enoka 1994), there are few studies that explain the acute response of the CNS to such active manipulations. Therefore, TMS could be effectively used to elucidate the precise nature of such procedures and possibly help in their optimisation.

If a subject performs many consecutive muscle contractions or sustains a constant muscle contraction for a longer time, this will result in depression of MEP responses (Sacco, Thickbroom, Byrnes, & Mastaglia, 2000) (Figure 6). During prolonged muscle activity a reduction in voluntary activation can significantly contribute to muscle fatigue, a phenomenon termed

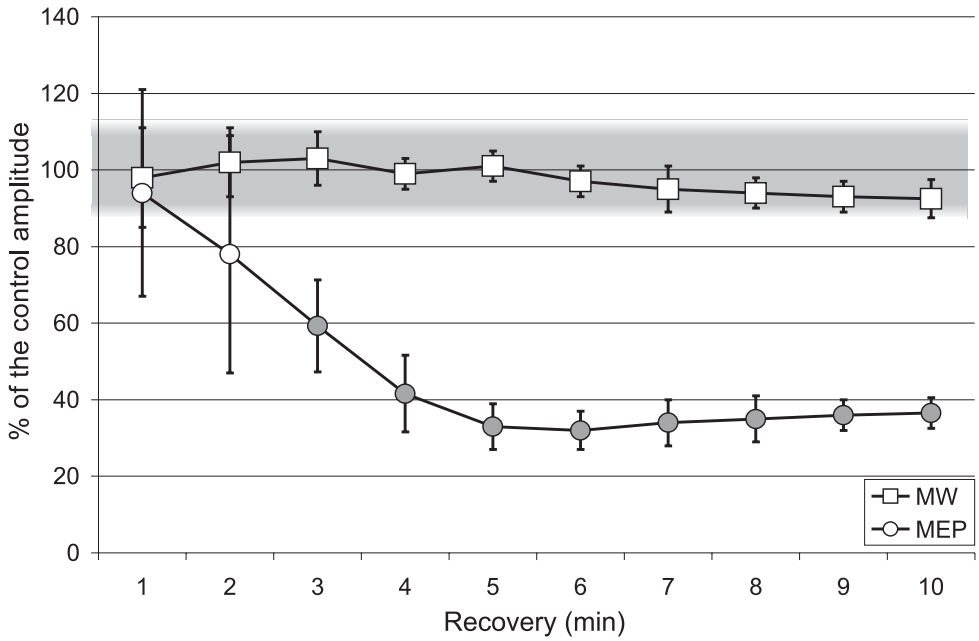

Figure 6: Mean relative changes (10 subjects) in evoked responses (±SEM) for the biceps brachii muscle after a 60-second maximum voluntary contraction. The pre-exercise control range is shaded. The motor evoked potentials (MEPs) elicited by TMS are significantly depressed from the third minute onwards (filled circles, P<.05). Maximal muscle potentials evoked by the peripheral nerve point stimulation (MW) remain unchanged. (Adapted after Sacco et al., 2000).

central fatigue (Gandevia, Allen, & McKinzie, 1995; Gandevia, Allen, Butler, & Taylor, 1996; Löscher, Cresswell, & Thorstensson, 1996). In the past fifteen years some investigators have used TMS in relation to corticospinal mechanisms of fatigue. Central fatigue and motor cortical excitability have been studied during different types of muscle contractions (Löscher & Nordlund, 2002). During fatiguing isometric contractions there is an increase in MEP size and a concomitant increase in the duration of the silent period (McKay, Stokic, Sherwood, Vrbova, & Dimitrijevic, 1996; Sacco, Thickbroom, Thompson, & Mastaglia, 1997; Taylor, Butler, Allen, & Gandevia, 1996), suggesting a simultaneous increase in excitability levels of inhibitory and facilitatory neural structures. Thus, the relationship ratio between the two systems determines the actual state of the corticospinal tract and in turn modulation of MEPs during and after muscle activity. It seems that plastic changes at cortical sites are responsible for the changes in MEP, since there are no significant changes at spinal and cortical levels.

There are fewer reports on TMS and fatigue in sports-specific motor activities. The first study to show the possible use of TMS in sports and various kinds of everyday exercise was undertaken by Hollge et al. (1997). They evaluated changes in MEP size and central motor conduction time after various, predominantly aerobic (climbing stairs and jogging), and anaerobic (press-ups, dumb-bell holding, and 400 m run) exercises. Exhausting strength exercises resulted in a significant reduction in MEP amplitudes, while no significant change was elicited by aerobic exercises. In addition, Tergau et al. (2000) investigated the modulation of intracortical mechanisms (ICI and ICF) following pull-up exercise until exhaustion. After exercise, ICF was significantly reduced, while ICI remained unchanged. ICF changes were limited to the muscles performing the task and tended to normalize within 8 min. Both the baseline ICF level and ICF reduction after exercise were significantly correlated ($r = 0.63$ and $r = 0.73$ respectively) with the overall lifting work accomplished by the subject before complete exhaustion. Another study (Fulton, Strutton, McGregor, & Davey, 2002) examined fatigue-induced change in the corticospinal drive to back muscles in elite rowers compared to an untrained group. Each subject completed two exercise protocols on a rowing ergometer (i) light rowing at submaximal intensity for 10 min and (ii) intense rowing at maximal output for 1 min. The non-rowers showed a brief facilitation of MEPs 2 min after light and intense exercise that was only present in the elite rowers after intense exercise. In the period 4 to 16 min after the light exercise the mean MEP amplitude was less depressed (relative to pre-exercise values) in elite rowers than in controls (mean 79.4 and 60.9% respectively). The authors propose that the differences are due to the energy requirements being closer to maximum capacity in non-rowers, therefore resulting in more fatigue. This notion was supported by the lack of any difference between the groups following intense exercise during which both groups worked at their own maximum.

To understand mechanisms responsible for neuromuscular fatigue, TMS should be further employed to applied sports research protocols. Different TMS techniques may be useful tools in training supervision as well as in the detection of overtraining situations. Although the above-mentioned studies suggest that aerobic exercises are not capable of causing MEP modulation, it should be pointed out that only low to moderate protocols were used. It would be interesting to investigate the effects of extreme situations, such as marathon or triathlon racing. Moreover, issues related to the arrangement of the amount and types of training during different training periods need to be examined. In an attempt to evoke the highest possible body adaptations, athletes and their trainers sometimes exceed the ability of the human body to regenerate. Accumulation of such catabolic loads can lead to the overtraining syndrome. Until

the present, biochemical (Maso, Lac, Filaire, Michaux, & Robert, 2004; Uusitalo et al., 2004) and psychological (Maso et al., 2004) methods have been mainly employed to better diagnose and understand overextending and pathological central fatigue (for reviews see Armstrong, & VanHeest, 2002; Pearce, 2002; Urhausen & Kindermann, 2002; Petibois, Cazorla, Poortmans, & Deleris, 2003). TMS could be tested for its potential use in the detection and prevention of overloading and the resulting overtraining. As the overtraining syndrome is postulated to be of CNS origin, correlates with MEP parameters could be expected.

A considerable amount of work has been done in the field of neuronal plasticity, with transcranial stimulation being used as a diagnostic tool (for review see Cohen et al., 1998; Siebner & Rothwell, 2003). As a still loosely defined term, neural plasticity describes the ability of the brain to change. Cortical plasticity encompasses a wide variety of phenomena and mechanisms, including modifications of cortical properties such as the strength of internal connections or representational patterns, or neuronal modifications, either morphological or functional (Donoghue et al., 1996). The mechanisms of such reorganization can be studied at a synaptic, cellular or regional level (Buonamano & Merzenich, 1998). The latter encompasses changes in the response of larger cell assemblies following prolonged input changes induced by different types of manipulations. In fact, all the measures of TMS can be used in the assessment of such modifications. By employing TMS, neuroplasticity has been documented as a result of (i) short-term deafferentation (Ridding & Rothwell, 1995; Brasil-Neto et al., 1993); (ii) long-term deafferentation (Hall, Flament, Fraser, & Lemon, 1990); (iii) implicit and explicit learning (Pascual-Leone, Grafman, & Hallett, 1994a); (iv) use of the dependent plasticity of motor cortical representations (Classen et al., 1998) and; (v) some other pathophysiological conditions (Hallett, 2001).

The acquisition of new motor skills is also associated with plastic changes in the controlling neural system. Learning to activate a synergistic combination of muscles in a new way will cause changes in cortical representations after a period of physical training (Cohen, Gerloff, Ikoma, & Hallett, 1995). Neural plasticity is thus an underlying mechanism for motor learning. An understanding of the patterns, mechanisms and functional relevance of cortical plasticity will hopefully lead to the design of effective strategies to enhance plasticity when beneficial, and to downregulate it when it is maladaptive (Pons, 1998).

Animal studies have suggested that the repetitive execution of simple or well-learned movements has little impact on the organisation of the motor cortex (Plautz, Milliken, & Nudo, 2000). Comparisons between pre-training and post-training maps of M1 movement representations revealed no task-related changes in the cortical area devoted to representation of individual distal forelimb movements. They concluded that repetitive motor activity alone does not produce functional reorganization of cortical maps. Instead, they propose that motor skill acquisition, or motor learning, is a prerequisite for driving representational plasticity in M1. Another study (Pearce, Thickbroom, Byrnes, & Mastaglia, 2000) investigated the characteristics of the corticospinal tract measured on the FDI in a group of elite racquet players. The major findings of the study were an increase in the corticomotor excitability of the playing hand and changes in the topography of the cortical motor map for the playing hand, which were not seen in a control group.

An even more specifically sports training oriented study (Carroll, Riek, & Carson, 2002) used TMS to test central vs. spinal neural adaptations to resistance training in humans. The results

of their experiment demonstrate that resistance training alters functional properties of the corticospinal pathway in humans, but failed to show substantial cortical effects. Additionally, their data suggest that the reorganisation of the corticospinal motor pathway that occurs in response to the repetitive execution of simple movements against a large resistance is independent of that which occurs during motor learning. This idea was further evidenced by Lundbye, Marstrand, and Nielsen (2003), who also demonstrated different neural adaptations as a response to strength and visual-motor skill task training respectively. TMS stimulus-response curves showed increased corticospinal excitability after 4 weeks of hand skill practice.

There are several other interesting research issues of physical long-term training in which TMS could be used for diagnostic purposes. Athletes from various sport disciplines could be compared for different neurocontrol parameters that would reveal mechanisms typical for specifically trained groups. It could be assumed that disciplines that are based on different motor abilities (strength, power, speed, precision, postural stability, etc.) require specific motor control that may be reflected in input-output properties of the central and peripheral nervous systems. Using the model of Pearce et al. (2000) it is possible to analyse other specific elite athletes in sports such as (i) soccer vs. basketball (upper and lower extremity skilled movements), (ii) ballet vs. sprint (posture maintenance and pliometric activity), (iii) dart throw vs. shot put (high precision at low force and high force with minor precision requirements).

Apart from plastic changes that take place during and after motor skill acquisition, many studies have been carried out concerning short-term modulations of corticospinal excitability during motor task preparation and execution (Johansson, Lemon, & Westling, 1994; Mills, & Kamiskidis, 1996). However, slow precision hand movements, such as reaching and grasping, have been studied in greatest depth (Gangitano, Mottaghy, & Pascual-Leone, 2001; Liepert, Dettmers, Terborg, & Weiller, 2001). During these manipulative and explorative motor acts corticospinal excitability continuously changes through different phases of the movement; thereby being additionally modulated by precision requirements, grip force, sensory feedback, etc. (Lemon, Johansson, & Westling, 1995). In general, it seems that many of these regulations of cortical excitability are derived from sensory information flow. The role of sensory input has been studied in great detail through voluntary motor control as well as at a more elementary level. The afferent flow has been demonstrated to play a major role in motor control (Wing, Haggard, & Flanagan, 1996), which represents a whole new sphere of scientific activity in which TMS has been widely applied.

In contrast to the on-line controlled prehension movements, TMS has also been used to unravel the neural control of pre-programmed fast ballistic movements (Mills & Kimiskidis, 1996). Previously, peripheral features of such rapid movements had been described as comprising: a three burst pattern, pre-movement depression, intramuscular synchronization of motor units and a consecutively high level of rate of force development, etc. (for review see Zehr & Sale, 1994). In addition to the output characteristics of the explosive movement, the central neural activity responsible for the preparation and execution of such motor tasks can now be measured (MacKinnon & Rothwell, 2000).

TMS has also been proved to be a useful method for the study of the involvement of the motor cortex during human locomotion and other cyclic movement activities. Petersen et al. (2001) demonstrated suppression of ongoing EMG activity during human walking that was provoked by subthreshold TMS. Christensen, Andersen, Sinkjer, and Nielsen (2001) showed

strong facilitation of the TMS-elicited MEPs in the inactive tibialis anterior muscle during the stance phase. Capaday et al. (1999) compared MEP input-output curves measured (i) during voluntary tonic activity of either the soleus or tibialis anterior muscle and (ii) during the early part of the swing phase and the stance phase of walking respectively. Their data suggest that during walking the corticospinal tract is more closely linked with the segmental motor circuits controlling the flexor (tibialis anterior) than with those controlling the extensor (soleus). Similar reports on the modulation of transmission in the corticospinal pathways to the soleus have also been proved during bicycling (Pyndt & Nielsen, 2003). Similarly, typical cyclic movement patterns found in sports could be analysed. Additionally, different techniques of running, cross country skiing, bicycling, etc. could be compared, which could reveal either a general modulation type or specificity for each individual movement activity.

It is clear that none of the described areas of TMS application could be excluded as irrelevant to sports science. It is believed that TMS could be further fruitfully implemented in kinesiology and its subdisciplines, helping to answer questions specific to sports. Basic knowledge of post-exercise corticospinal facilitation could be used to pose new questions and to explore the effects of different training methods thought to provoke neural adaptations. Research could be carried out to determine whether the proposed early central adaptations to activation training really occur. Furthermore, long-term neural adaptations to strength and power training could be assessed more analytically by the use of TMS and tools for peripheral neuromuscular excitability testing. Composing the input-output curve makes it possible to employ longitudinal studies that are needed to study specific adaptations over a longer time period. Manipulations of sensorimotor integration mechanisms seem very promising for optimising neural plasticity processes, with TMS being an indispensable tool for the evaluation of such manipulations. TMS and measures of cortical excitability might also be of assistance in the detection of other problems deriving from sports practice and theory. In short, there are many theoretical explanations of training states and effects that need to be tested. In our opinion, TMS could also be effectively employed in research into areas such as overtraining, endurance and fatigue, and the effects of sport psychological techniques.

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