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Invited editorial

Clinical applications of motor evoked potentials

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Abstract

Magnetic stimulation of brain and spinal roots provides a non-invasive evaluation of nervous propagation as well as of motor cortex excitability in healthy subjects and in patients affected by neurological diseases (i.e. multiple sclerosis, stroke, Parkinson's disease, myelopathies etc.). Motor areas can be reliably mapped and short- and long-term 'plastic' changes of neural connections can be studied and monitored over time. By evaluating excitatory and inhibitory phenomena following transcranial stimuli, the mechanisms of action of different drugs, including antiepileptics, can be studied. Moreover, transcranial stimulation of non-motor brain areas represents a probe for the evaluation of lateralized hemispheric properties connected with higher cortical functions. Recent studies suggest a therapeutic role of repetitive magnetic stimulation in psychiatric disorders. © 1998 Elsevier Science Ireland Ltd.

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1. Introduction

1.1. Historical background

Pioneering studies for non-invasive stimulation of the human brain can be dated to the early 1950s (Gualtierotti and Paterson, 1954); however, such techniques using repetitive electrical stimulation were poorly tolerated and often induced epileptic seizures and therefore were abandoned. At the beginning of the 1980s Merton and Morton (1980a,b) in Cambridge, England first developed and tried on themselves a dedicated electrical high-voltage, low-resistance stimulator able to elicit electromyographic (EMG) twitches when the scalp electrodes were overlying the appropriate area of the motor cortex. Such EMG responses, thereafter named motor evoked potentials (MEPs), had an extremely brief latency (about 20 ms to the hand muscles, and about to 30-40 ms to the leg or foot muscles) compatible with activation of a paucisynaptic, fast-propagating corticospinal tracts. The required intensity was very high (in the order of 1-1.5 kV) somewhat uncomfortable and poorly tolerated (Merton et al., 1982). However, it was soon shown that this technique could open new areas for research and clinical evaluation of motor pathways in intact, awake humans (Merton et al., 1982; Rossini et al., 1985a). A further refinement of the original technique was subsequently developed, employing a pericranial cathode and a stimulating anode on the motor cortex and, therefore, named 'unifocal'. This method allowed MEPs to be obtained with significantly lower electric currents (so commercially available stimulators could be used (Hassan et al., 1985; Rossini et al., 1985b). However, the major increase in transcranial stimulation (TCS) occurred with introduction in the mid-1980s of the first magnetic stimulator by Anthony Barker and colleagues from the University of Sheffield (Barker et al., 1985). This revolutionary technique used the brief and strong magnetic field provoked by the current discharged within a round coil by a bank of capacitors. Such magnetic field induced an electric current circulating up to few centimetres away from the coil's external edge with a direction opposite to the current flowing in the coil, and with an intensity proportional to the magnetic field. With the coil in direct contact with the subject's head, such induced electric currents crossed the extracerebral layers (scalp, skull and meninges) with minimal or no activation of the pain receptors and resulted in a well tolerated procedure. Since then,

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thousands of magnetic stimulators have been sold throughout the world, and hundreds of publications have been devoted to the research and clinical application of magnetic TCS in humans. Magnetic stimulation has been further refined by introducing double-coil or figure-of-eight or butterfly-coils which allowed a more focal type of stimulation, as well as double stimulators able to discharge paired stimuli or triplets within the same coil or within two independent coils applied on two separate scalp areas; this allows for the study of recovery curves as well as of the interactions between different brain areas (Rothwell et al., 1991; Kujirai et al., 1993). Exhaustive theoretical and technical discussion of magnetic stimulation can be found in the recent literature (Rösler et al., 1989; Cohen et al., 1990; Roth et al., 1991; Roth et al., 1994; Zimmermann and Simpson, 1996).

1.2. Neurophysiological background

Repetitive discharges along the corticospinal neurones can be triggered both in animals and humans by delivering single stimuli on the surface of the motor cortex. They are characterised by bursts of up to 8 descending waves separated by 1-1.5 ms intervals, the first wave being directly triggered in the pyramidal axon ('D' for Direct wave), the following ones being transynaptically elicited in the same neuron via one or more cortical interneurons ('I' for Indirect waves; Patton and Amassian, 1954; Day et al., 1987; Zarola et al., 1989; Berardelli et al., 1990; Rossini et al., 1991a). Their function is probably linked to a progressive depolarisation of spinal alpha-motoneurons until there are action potential discharges. According to the excitability status of the spinal motoneurons, either the initial part (D or I_1 waves) or the final part (I_2 in waves) of the descending burst will activate the motoneurons with the two conditions being separated by a few milliseconds.

Conduction in corticospinal tracts (central conduction time; CCT) can be measured directly and non-invasively using brain TCS combined with percutaneous stimulation of motor roots or using 'F-wave' recordings for the measurement of spine-to-muscle conduction time (Zarola et al., 1989; Rossini et al., 1987a). Magnetic stimulation on the posterior neck or the dorsal spine activates spinal roots at the level of the intervertebral foramen (Mills and Murray, 1986). Therefore, the cervical roots are excited about 3 cm away from the anterior horn cell; this distance is even longer for the lumbosacral cord and suggests that magnetic stimulation of roots is not accurate for CCT measurements and might miss a proximal partial or complete block of impulse propagation (Chokroverty et al., 1991). CCT measurements mature during childhood, reaching adult values around the age of 2 or 3 years (Koh and Eyre, 1988; Muller et al., 1991). CCT remains stable throughout adulthood; some authors (Eisen et al., 1991) report a significant prolongation in the elderly, not confirmed by others (Rossini et al., 1991a).

Since the pioneering studies of Merton and Morton (1980a,b) it has been observed that MEPs during contraction (contracted-MEPs) are shorter in latency and larger in amplitude than MEPs obtained during full muscular relaxation (relaxed-MEPs); maximal facilitation is exerted in the muscle(s) which act as prime mover(s) for the voluntary movement (Rossini et al., 1988; Tomberg and Caramia, 1991). Moreover, such facilitation is already evident well before the electromyographic burst appears in the target muscle as shown by delivering TCS during a reaction time paradigm for thumb or index finger lift or flexion (Starr et al., 1987; Rossini et al., 1988). The MEPs were selectively facilitated in a premovement period either in the extensor indicis proprius or in the first dorsal interosseus consistent with the 'prime mover' organisation. Moreover, the same low-threshold motor units first recruited by the voluntary contraction was also first recruited in the premovement epoch by TCS (Rossini et al., 1988, 1995).

For clinical setting purposes, a standardisation of the amount of muscular contraction required to record contracted MEPs has been proposed via the measurement of the root mean square value of the EMG which is partially related to the exerted muscular force. It has been established that at a level of 15% of RMSmax the latency of MEP reaches the minimal value (Ravnborg et al., 1991). Others (Lim and Yiannikas, 1992) have expressed the amount of EMG as a percentage of the 'averaged maximum muscle power' calculated from 24 sets of EMG during maximum voluntary efforts; this has confirmed previous observations that with a voluntary contraction value between 2 and 6% of maximum surface EMG activity, MEPs with shortest latency and largest amplitudes can be recruited.

In a clinical context there are patients in whom no EMG activity can be voluntarily activated in the target muscle (TM). In these cases, other types of facilitatory manoeuvres can be performed: these include vibration of the examined muscles (Rossini et al., 1987a; Rossini, 1990), prestimulation of the mixed nerve innervating the TM (Mariorenzi et al., 1991), and active contraction of the muscle(s) homologous to the paralysed one(s) on the opposite body side (Rossini et al., 1987a). Facilitatory effects of peripheral nerve stimulation on MEPs have been shown both in the arm (Mariorenzi et al., 1991) and leg (Kasai et al., 1992); latencies for maximal effects are respectively around 25 and 60 ms, and are compatible with fast peripheral inputs to the sensorimotor cortex. In normals, the cumulative effect of active contraction and vibration of the TM is less than the summation of the two facilitatory effects alone. When voluntary contraction and vibration are combined in a muscle affected by spasticity, however, a cumulative facilitation is obtained (Caramia et al., 1991). This phenomenon has been explained by the possibility that in 'spastic' spinal motoneurons the reafferent activity from the spastic muscles and the decreased reactivity to descending impulses would be altered by the enhanced pre-synaptic inhibition of Ia fibres with vibration.

In contrast to contracted-MEPs (which are utilised for

CCT measurements), relaxed-MEPs latencies reach the adult value during adolescence; therefore, the latency jump separating the two is significantly larger in children than in adults and represents, along with the progressive decrement of the excitability threshold and the consequent increase of amplitude, an index of brain maturation (Caramia et al., 1993). Recently, it has been demonstrated that the latency jump between relaxed- and contracted-MEPs is influenced by the amount of tonic cutaneous input from the skin overlying the target muscle. This is particularly true for the hand muscles; in fact, it has been shown that transient anaesthesia of the skin enveloping the first dorsal interosseous (FDI) muscle produces a significant decrease of the MEP latency jump, together with a reduced cortical representation of the FDI, while no significant changes were seen in another muscle (the ADM) with the same peripheral innervation and outside the anaesthetised area (Rossini et al., 1996a,b).

Besides provoking MEPs, single pulses of magnetic TCS of the motor cortex may also elicit tingling paraesthesias in the contralateral hand (Amassian et al., 1991). In this minority of subjects, paraesthesias were felt when TCS was delivered either at or anterior to the sites provoking MEPs implying a source in precentral rather than in parietal cortex. This is considered a 'central sense of movement' since it is maintained during anaesthesia and paralysis of the hand following ischaemic block.

As discussed above, magnetic fields pass unattenuated through high resistance body structures including skull and scalp; for this reason a stimulus threshold for eliciting MEPs in a given muscle during complete relaxation can be defined (Caramia et al., 1989, 1991; Rossini, 1990); the procedure for threshold measurement has recently been described by a panel of international experts as the intensity which elicits reproducible MEPs in about 50% of a cascade of 10-20 stimuli (Rossini et al., 1994). Interhemispheric threshold differences are not significant, provided a 'biphasic' stimulus and a lateralized coil positioning are employed (Rossini, 1990); this parameter is remarkably less variable than absolute threshold values (Cicinelli et al., 1997) and, therefore, can be reliably employed in testing patients with monohemispheric lesions of various aetiologies (Traversa et al., 1997). It is not clear whether excitability threshold can physiologically vary because of hemispheric dominance, but it is affected by ageing (McDonnell et al., 1991; Rossini et al., 1991a), and changes with the content of alpha activity in the background EEG (Fig. 1) (Rossini et al., 1991a). Mental simulation of movement can also significantly affect excitability threshold, and consequently, the amplitude of MEPs (Izumi et al., 1995; Abbruzzese et al., 1996). Such a procedure can also selectively enhance the MEP amplitude in the muscle(s) which are prime movers for the mentally simulated program without involving other muscles (Fig. 2); this is particularly evident for forearm muscle acting on the wrist joint (Rossini et al., 1996c).

Besides excitatory effects, TCS delivered on the scalp is also known to produce inhibitory effects (silent periods; SP), whose recurrence and duration are largely dependent upon the stimulus intensity (Uncini et al., 1993; Classen and Benecke, 1995; Rossini et al., 1995). Fuhr et al. (1991) have studied the excitability of the spinal motoneuronal pool during the SP by measuring the H-reflex amplitude at different intervals after TCS; the H-reflex was depressed at the beginning of the SP, while it regained normal amplitude in the later part, indicating that both a reduction of the spinal motoneuronal excitability (in the early SP) and a lack of cortical drive (in the late SP) explain the EMG silence. Both in normals and in patients (i.e. spastic muscles) it is possible to record a SP in the absence of a MEP. This demonstrates that excitatory and inhibitory messages either run through separate descending routes from the cortex or travel along the same tract but are discharged at different thresholds (Wassermann et al., 1993; Rossini et al., 1995). Double coil TCS has allowed testing the excitatory and inhibitory influences of transcallosal fibres connecting primary motor areas on the two hemispheres as well as the crossed effects of cerebellar conditioning TCS (Ferbert et al., 1992; Meyer et al., 1992; Salerno and Georgesco, 1996). Paired stimuli separated by brief (1-10 ms) and relatively long (50-100 ms) intervals have shown complex patterns of excitation inhibition recovery cycles which are significantly modulated by the intensity of the conditioning stimulus (Rossini et al., 1987b; Claus et al., 1992; Valls-Solè et al., 1992).

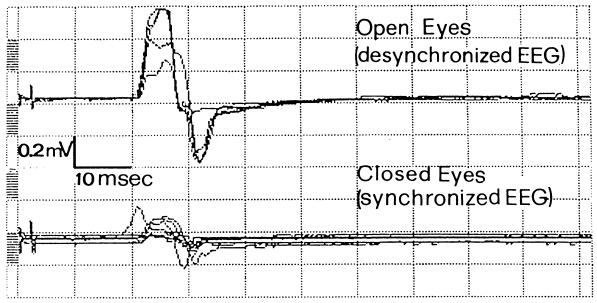

Fig. 1. The amplitude of relaxed-MEPs was evaluated during TCS with stable intensity; the subjects were randomly asked to close the eyes and maintain mental inactivity (lower traces) or to open the eyes and to perform mental calculations (upper traces). Spectral analysis of the on-going EEG demonstrated that the alpha band was much larger with eyes closed. This corresponded to small and unreproducible MEPs (partly modified from Rossini et al., 1991a).

2. Clinical studies

2.1. Stroke

The analysis of the relationship between clinical recovery of hand and arm function in stroke and the characteristics of MEPs to TCS have been evaluated in several studies (Berardelli et al., 1987, 1991; Caramia et al., 1988, 1991, 1996b;

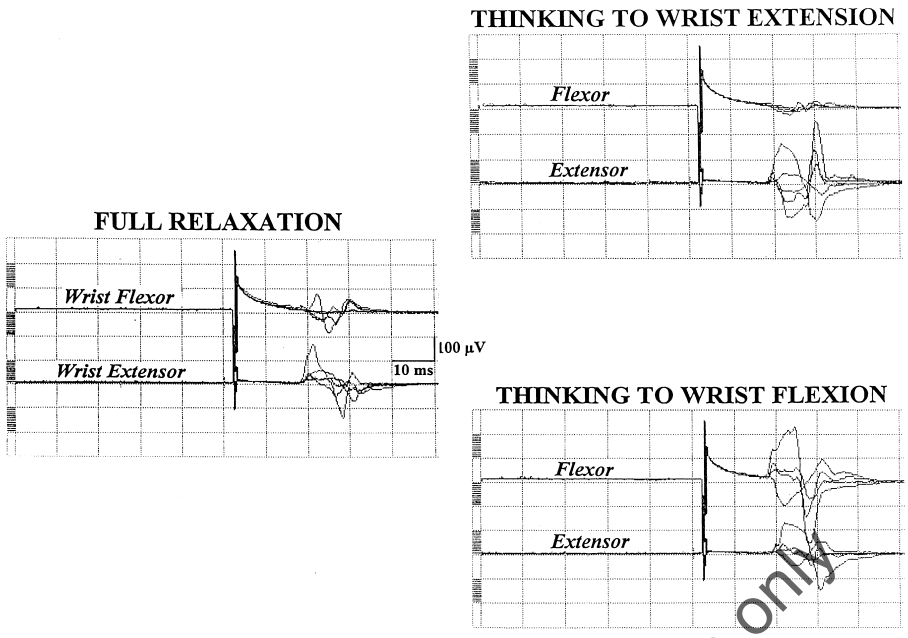

Fig. 2. Original tracings in a representative subject during near-threshold magnetic TCS of the left motor cortex in a task of 'thinking to move' the wrist joint. MEPs are recorded simultaneously from right flexor and extensor muscle at forearm. The first 50 ms are a pre-trigger analysis time; 4-5 MEPs are superimposed in each trace. Note that the motor program dispatched, but not executed, is exerting an amplitude facilitation (without latency changes) on the 'prime mover' muscle. When the flexor muscle is acting as antagonist (first trace on the right panel) an inhibitory effect is taking place.

Abbruzzese et al., 1991; Hömberg et al., 1991; Ferbert et al., 1992; Heald et al., 1993a,b; Catano et al., 1995, 1996; Turton et al., 1996; Traversa et al., 1997). MEPs are often absent in the most severely affected stroke patients. In less affected patients, MEPs are usually of longer latency, smaller amplitude and with a higher than normal excitability threshold. The presence of MEPs in the earliest stages of stroke have been found to correlate with a good functional recovery (Heald et al., 1993a,b; Catano et al., 1996). Most patients with a slow and incomplete recovery initially lack MEPs in all tested upper limb muscles; in those that later were able to activate hand muscles, MEPs returned at or just before recovery. The recovery of MEPs latency was highly correlated with return of muscle strength and hand function (Turton et al., 1996). Ipsilateral responses can be found (mainly from more proximal muscles) during stimulation of the unaffected hemisphere. Some authors consider these important for recovery (Caramia et al., 1993, 1996b), while others identified them mainly in patients who deal poorly (Turton et al., 1996).

Uozumi et al. (1991) examined the ratio between the background EMG area during maximal voluntary contraction and the area of MEP recorded in the same condition. Another clinically useful index is the amplitude ratio between the MEP and the M response to direct stimulation of the motor nerve trunk (MEP/M-wave ratio). Some authors (Thompson et al., 1987) considered abnormalities of this index as specific for pyramidal tract involvement, even superior to a prolongation of the CCT.

The presence and duration of the SP has also been employed as a clinical tool, mainly by considering the difference between an affected and a healthy limb (Uozumi et al., 1991). The shorter duration of the SP in patients with corticospinal tract involvement, reflects either a reduced central inhibitory effect or a hyperexcitability of spinal motoneurons. Hömberg et al. (1991) did not find significant asymmetries between right and left hemisphere threshold to TCS in controls subjects; this is in line with other data (Caramia et al., 1991) and represents a point of importance when evaluating right/left hemisphere threshold asymmetries in neurological patients. Abnormally reduced MEP/M-wave amplitude ratio have been found in nearly all patients suffering from cerebral infarction, presumably due to the small MEP elicitable in the paralysed hand muscles; in the affected limb, an asymmetrically shorter SP was also observed (Hömberg et al., 1991). CCTs were analysed to investigate the intactness of cortico-motoneuronal connections in 51 patients with variable degrees of chronic upper motor neurone syndromes (Hömberg et al., 1991). A gross correlation between clinical impairment and degree of MEPs abnormalities was found. Covariations of clinical data with TCS was better than covariation with the size of lesion on CT scan. Variability of CCT values on repeated measurements is reported in this study, possibly due to the fact that direct stimulation of cervical and lumbosacral roots has been employed for spine-to-muscle time evaluation. In this respect, combined measurements with 'F-wave' recordings and direct roots stimulation should help in reducing spontaneous variability of CCT measurements (Rossini, 1990).

Relaxed-MEPs are often missing in the affected limbs of stroke patients. In the study by Hömberg et al. (1991), MEPs

could only be obtained with a significantly prolonged latency when the stimulating coil was positioned either on the scalp vertex or on the hemisphere with the lesion; no 'ipsilateral' MEP was triggered from the non-affected hemisphere. Only in one case (6 months after a large hemispheric infarction) with a dense left hemiplegia, a clear, but delayed, left thenar MEP was elicited during stimulation of the intact hemisphere. The authors found a significant correlation between functional hand deficits on one side and the characteristics (latency, amplitude, threshold) of MEPs on the other; normal CCTs are compatible with tiny clinical deficits affecting fine finger and hand movements. A significant correlation was found between the site of brain lesions in CT images and the extent of MEP abnormalities. No attempts have been made to correct the coil positioning on the affected hemisphere for possible tissue retraction around the brain lesion with displacement of the motor cortex. However, corrections can be made by scanning the scalp with a focal stimulator in search of the 'hot spot' site, that is the point triggering MEPs with minimal latencies and largest amplitudes (Cicinelli et al., 1997; Traversa et al., 1997) (Fig. 3). Latency prolongation of MEPs has been ascribed in this and other papers (Berardelli et al., 1991) with increasingly less probability to: (1) reduced number of active pyramidal neurones (PN), (2) increased temporal dispersion of the descending volley, (3) activation of slower than normal PN populations from the lesioned motor cortex, (4) slow corticospinal tracts activation from hemispheric areas outside the precentral strip (pre-motor and supplementary motor areas etc.), (5) reinnervation of the affected muscles by slow efferents, (6) contribution of slower conducting fibres from the unaffected hemisphere.

Abbruzzese et al. (1991) analysed MEPs in proximal and distal muscles to electrical TCS in 32 patients suffering from lacunar infarcts. CCTs and threshold for eliciting MEPs were significantly increased on the affected side. These abnormalities were correlated with pyramidal signs. Abnormalities of CCT were observed in more than 50% of examined patients with minor cerebral ischaemia of lacunar type. Such abnormalities were more frequent when the interval separating the test from the stroke was briefer than 9 days, concurrent with a worse clinical status. While prolonged CCTs correlated with the level of weakness, the increase in threshold correlated with the presence of brisk tendon reflexes. This is in agreement with previous observation in corticospinal tract lesions of varying aetiologies in which a higher than normal threshold was frequently combined with signs of spasticity (Caramia et al., 1991). Fries et al. (1991) examined 5 patients with isolated lacunar infarcts of the posterior limb of the internal capsule, considering them a clinical model of unilateral pyramidotomy. MEPs were recorded from both hands during relaxation, but 'patients were asked to extend their feet to an angle of approximately 90 degrees at the ankle'. This kind of manoeuvre and the high intensity threshold for the damaged hemisphere might have contaminated the hand recordings with inadvertent bilateral contraction (i.e. mirror movements were present in all the examined patients). However, it is of interest that MEPs were bilaterally recorded only during TCS of the damaged hemisphere, with ipsilateral

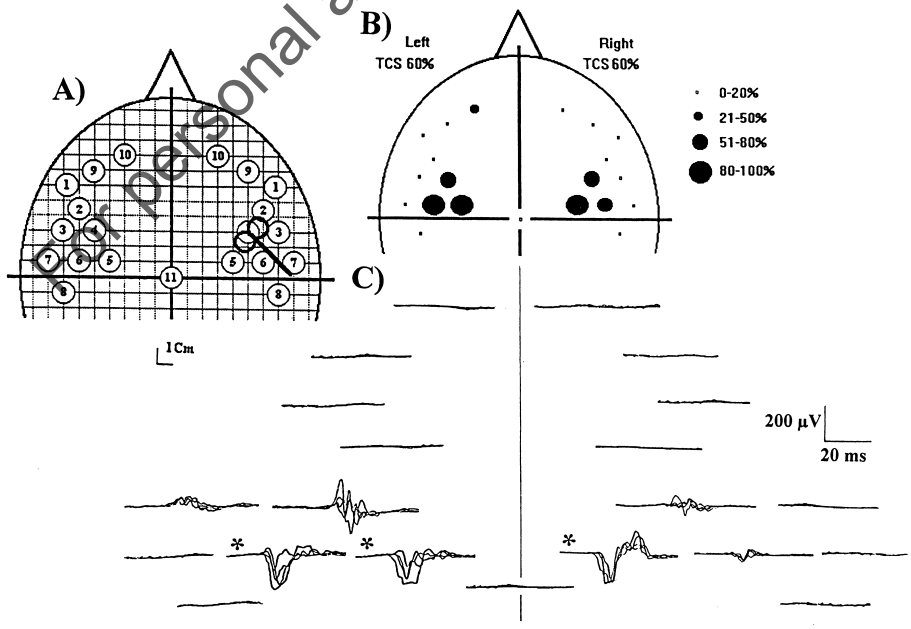

Fig. 3. (A) schematic representation showing the mapping procedure. Eleven scalp sites for each hemisphere were stimulated and MEPs recorded by the contralateral Abductor Digiti Minimi muscle: this allowed to cover a scalp area 0-8 cm lateral to the sagittal plane and from 1 cm posterior to 8 cm anterior to the coronal plane. A representation of the figure-of-eight coil is also shown. (B) Mapping of both hemispheres of a healthy subject: the size of the black circles indicates the percentage amplitude of the MEPs elicited from a given scalp position compared to that of the 'hot spot' (i.e. the scalp eliciting MEPs with the highest amplitude and shortest latency). (C) Original traces obtained from each of the stimulated scalp positions: asterisks indicate the hot spot sites.

MEPs having shorter latencies than the contralateral ones. The possibility of ipsilateral MEPs mediated by corticoreticulospinal tract activation has been considered. Carr et al. (1993) investigated the patterns of central motor reorganisation in 33 patients with hemiplegic cerebral palsy examining MEPs and reflex pathways. They found evidence of reorganisation in 64% of patients, with novel ipsilateral motor pathways from the undamaged motor cortex to the hemiplegic hand. In 11 subjects, strong mirror movements were present probably due to an abnormal branching of corticospinal axons projecting bilaterally to homologous motoneuronal pools on both sides of the spinal cord. However, when TCS is performed with a focal stimulator at threshold intensities, ipsilateral MEPs are rare and rarely related to clinical outcome (Turton et al., 1996; Traversa et al., 1997).

2.1.1. Mapping of corticospinal projections

Non-invasive mapping of the motor cortex has been carried out both with electrical and magnetic TCS (Rossini et al., 1987a; Cohen et al., 1991); the use of a figure-of-eight focal coil placed on different positions of the scalp provides the best results (Wassermann et al., 1992; Brasil-Neto et al., 1992a). The reliability of this method has been recently demonstrated by reproducing similarly shaped motor maps within the same individuals in different occasions (Mortifee et al., 1994). Mapping procedures well as MEPs to single stimuli have been successfully utilised to show the 'plastic' reorganisation of the corticospinal tracts occurring in patients following different types of chronic lesions such as limb amputation (Cohen et al., 1991; Benecke et al., 1991; Fuhr et al., 1992), spinal cord injury (Levy et al., 1990; Topka et al., 1991) or hemiplegic cerebral palsy (Farmer et al., 1991); in this work, the scalp representation areas of individual upper limb muscles were delineated via a figure-of-eight coil on the hemisphere opposite to a normal and amputated limb. In the amputated limb, the representation of the surviving muscles was larger and had a lower excitability threshold. Other evidence for corticospinal modulation has been described in humans at the end of a 1 week daily training period to acquire new fine motor skills (Pascual-Leone et al., 1995a) and in Braille readers (Pascual-Leone et al., 1995b); the same authors had previously shown that a transient deafferentation of the entire arm below the elbow is able to gradually induce a parallel and reversible enlargement of the cortical representation of the muscles immediately proximal to the anaesthetised forearm (Brasil-Neto et al., 1992b, 1993). If the area of sensory deprivation is restricted within the hand, it is still possible to observe short-term changes in the cortical representation of the muscle 'enveloped' by the anaesthetised skin (Rossini et al., 1996b). Functional changes in the motor cortex have been described in patients during unilateral immobilisation of the ankle joint without a peripheral nerve lesion; in this paper, Liepert et al. (1995) showed a reduction of the motor cortex area targeting MEPs to the immobilised tibial muscle which was quickly reversible following voluntary muscle contraction. Whether similar changes take place in immobilised hand muscles is still a matter of controversy (Zanette et al., 1997).

In stroke patients, it has been shown that cortical reorganisation of the motor output is still taking place between 2 and 4 months from the lesion; this is reflected in a progressive enlargement of the motor maps (more excitable sites) of the recovering paretic muscle (Traversa et al., 1997) (Fig. 4). Moreover, anomalous 'hot spot' sites (scalp positions where TCS elicits MEPs of maximal amplitude and minimal

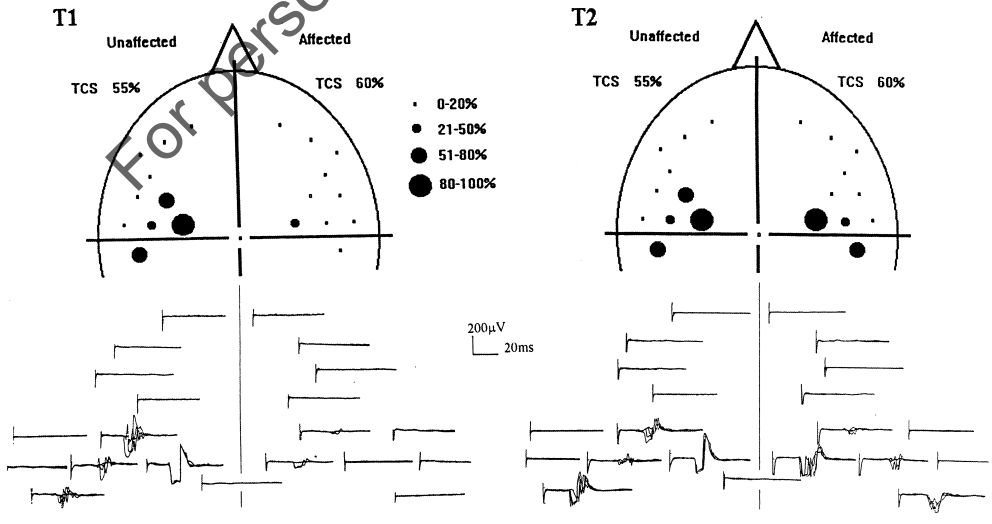

Fig. 4. Motor maps of a patient obtained with the methodology shown in Fig. 3 who suffered from a right haemorrhage hemispheric stroke with mainly cortical involvement. Note the striking amplitude asymmetry of maps in T1 (left panel; 2 months after the ictus), with a remarkable recovery at T2 (right panel; after 8 weeks of neurorehabilitation). In this particular patient, the good clinical recovery was combined with a symmetrical motor map distribution, without 'anomalous' hot spot sites (that is, cortical sites of stimulation usually not eliciting MEPs, according to the map of Fig. 3) (from Traversa et al., 1997 with permission).

latency) never seen in the healthy can be encountered both on the affected and the unaffected hemispheres (Traversa et al., 1997). In the meantime, the amplitude of contracted-MEPs can be larger than normal from the unaffected hemisphere (UH). This might reflect hyperexcitability of UH, since these abnormal amplitudes continue to increase whenever the contracted-MEPs from the affected hemisphere (AH) remain abnormally small while they decrease when the latter recovers to normal values. Clinical recovery parallels the recovery of a normal amplitude of contracted-MEPs from the AH probably because transcallosal modulatory influence of the AH on the UH (mainly inhibitory) is progressively restored (Cicinelli and Traversa, 1998).

2.2. Epilepsy and antiepileptic drugs

Hufnagel et al. (1990) reported a markedly increased excitability threshold in a group of epileptic patients with focal EEG interictal abnormalities and attributed this to the depressant action of antiepileptic drugs (AEDs). It was observed that the higher the amount of interictal activity, the lower the excitability threshold during TCS. Enhanced excitability threshold due to AEDs has also been described in generalised epilepsy (Reutens et al., 1993a). In another paper, Tassinari et al. (1990) confirmed the increased excitability threshold due to AEDs in 3 groups of patients suffering from different forms of epilepsy. This excitability decreased when the AEDs were stopped. However, a recent study (Ziemann et al., 1996a), suggests that AEDs with different modes of action produce different effects on motor system excitability, at least after a single oral dose in healthy volunteers: inhibitory AEDs (GABAergic, including Gabapentine) reduced intracortical excitability (studied with a double shock TCS paradigm according to Kujirai et al., 1993) but had no effect on motor threshold. By contrast, sodium and calcium channels blockers (carbamazepine, CBZ; Lamotrigine) elevated motor threshold but did not have effects on intracortical excitability. The suppressive effect on MEPs (lengthening of the SP) by GABAergic drugs was also reported in two recent studies on ethanol (Ziemann et al., 1995) and lorazepam (Ziemann et al., 1996b). In another study based on a paired-shocks paradigm in subjects taking a single dose of CBZ, Schulze-Bonhage et al. (1996) demonstrated that CBZ significantly reduced the facilitatory effect of conditioning stimuli at an interstimulus interval of 10 ms.

Gianelli et al. (1994) analysed brain TCS in 20 patients suffering from idiopathic generalised epilepsy with typical 3 Hz spike-and-wave EEG complexes: the excitability threshold was significantly higher for patients than in controls even if they were not taking AEDs. After having ruled out the possibility that the changes might be due to altered spinal excitability, the authors suggest that the brain hypoexcitability may be due to an excess of inhibitory, probably GABAergic, circuits acting on cortical presynaptic terminals. In the same paper, smaller MEPs than normal were recorded when the stimulus was time-locked to the wave component, while minor or no decrements were evident when the stimulus was time-locked with the spike (Gianelli et al., 1994).

Mariorenzi et al. (1991) showed in normal subjects that it is possible to modulate cortical excitability by combining pre-stimulation of a mixed or a sensory nerve with appropriately timed magnetic TCS. Reutens et al. (1993b) used this protocol in two groups of epileptic patients: those suffering from idiopathic generalised epilepsy and those with progressive myoclonic epilepsy. In both groups the excitability threshold was higher than normal probably due to the effects of AEDs, but, in the progressive myoclonic epilepsy group, there was an exaggeration of the peak of facilitation induced by the conditioning pre-stimulation of the median nerve.

Recently (Caramia et al., 1996a), threshold measurements using individual stimuli were combined with a protocol employing paired stimuli (conditioning subthreshold + test suprathreshold) in order to evaluate excitatory and inhibitory aspects of altered brain excitability in patients with juvenile myoclonic epilepsy (JME) and grand mal seizures (GM). In JME patients undergoing AEDs treatment, threshold values were higher (in one untreated patient it was lower). Unlike normal controls, MEP inhibition was greatly diminished during paired shocks stimulation, probably due the loss of intracortical inhibitory mechanisms. In the two cases with GM, the recovery cycle matched that of controls in the range of 1-4 ms. The authors (Caramia et al., 1996a) suggest that the pattern of cortical inhibition as investigated by paired shocks share some similarities with that due to GABA in animals (Kujirai et al., 1993). McDonnell and Donnan (1995) studied a series of paraplegic patients suffering from spinal cord traumatic lesions and started on Baclofen (a potent GABA agonist acting at spinal level by reducing anterior horn excitability). They confirmed that the evaluation of changes in motor excitability threshold to TCS should always take into account concomitant pharmacological therapy.

2.3. Multiple sclerosis

Both magnetic and electrical brain stimulation have been used in patients suffering from multiple sclerosis (MS) (Cowan et al., 1984; Thompson et al., 1987; Rossini et al., 1987b); typically, there is either a bilateral or unilateral prolongation of the CCT consistent with demyelinating lesions of the corticospinal tracts. A higher than normal amount of contraction as calculated from the RMSmax of the EMG activity is necessary in MS patients in order to record an optimal MEP (Britton et al., 1991). Similar to other evoked potential modalities, MEPs vary considerably in latency, amplitude and shape in MS patients when they are measured in consecutive trials (Britton et al., 1991). In fact, while the onset latency fluctuates between 0.27 and

0.86 ms in controls (mean 0.59 ms) during 10-50 consecutive trials, this index ranges between 0.5 and 5.9 ms (mean 1.49 ms) in MS patients. One drawback of this technique is the fact that the onset latency of contracted MEPs is sometimes hardly discernible from the background EMG. Increased onset latency variability correlated significantly with impairment of fine finger movements and pathological finger jerks; the latter finding correlated with abnormally prolonged CCTs. The authors consider slower conduction and increased refractoriness to repetitive trains the cause for late 'I' waves to be much smaller in amplitude than earlier ones with resultant insufficient excitation for a motoneuron EPSP. Recently, Nielsen (1996) suggested use of a logarithmic transformation of amplitude data and a standardised level of contraction in order to obtain more stable parameters in the clinical setting. Joseph et al. (1991) examined lower limb MEPs in 25 MS patients. MEP abnormalities were encountered in 84% of patients. Both MEPs and somatosensory evoked potentials (SEPs) were altered in 68% of legs. CCT prolongations correlated significantly with the presence of a Babinski sign. Boniface et al. (1991) have carefully tested the firing characteristics of single motor units action potentials (MUAPs) in intrinsic hand muscles in a small sample (9 subjects) of MS patients. Peri-stimulus time histograms (PSTH) of a motor unit in the first interosseus muscle triggered by TCS were constructed in normals and in 9 MS patients: in healthy controls, the PSTH were characterised by two periods of increasing firing probability at post-stimulus intervals ranging between 20 and 31 ms (primary peak, fractionated into subpeaks at 0.6-2.4 ms intervals) and 56-90 ms (secondary peak). In MS patients the primary peak was either absent or delayed in onset; moreover, increased internodal intervals separating subpeaks were observed. Frequency-dependent blocks of impulse propagation across demyelinated plaques and differential thresholds to successive 'I' waves have been postulated among the probable causes of descending impulses desynchronization leading to less effective temporal summation of EPSPs at the spinal motoneuron. The eventual role played by abnormal reafferent information along group-I fibres in peripheral nerves and the lemniscal system has not been considered. Caramia et al. (1991) have found a significantly increased excitability threshold for relaxed MEPs in MS patients in 76.4% of upper limbs and 67.6% of lower limbs. The excitability threshold values for relaxed MEPs and CCTs for upper and lower limbs have been measured in 49 patients affected by various neurological disorders. An increased threshold was found in 75.5% of these patients while a prolonged CCT was present in 60% of upper and 72% of lower limbs. In 28.5% of the cases, threshold abnormalities were present alone. In 20.6%, relaxed MEPs were absent despite maximal stimulation; in many of these cases, active contraction was unable to synchronise an excitatory response represented by a MEP, while a SP interrupting the EMG burst was clearly present. In 16 of 34 patients, MEPs were abnormally polyphasic.

2.4. Upper and lower motor neuron diseases

Even if the clinical picture of motor neuron disease (MND) including weakness, wasting, fasciculations and hyperreflexia generally presents little difficulty in making a diagnosis, there are selected patients in whom this is not straightforward and where it is clinically relevant to evaluate upper motor neurone involvement, especially early in the course of the disease. Loss of corticospinal cells would be expected to result in decrease of amplitude of MEPs to TCS and also to cause prolongation of CCT (Ingram and Swash, 1987; Eisen et al., 1990; Berardelli et al., 1991; Caramia et al., 1991), because of the dropout of larger, faster conducting axons and a reduction in the amount of descending impulses impinging upon anterior horn cells thus increasing the time necessary for excitation. Uozumi et al. (1991) have observed a selective alteration of the EMG/MEP area ratio in patients suffering from lower motoneuronal involvement. The MEP/M-wave amplitude ratio was normal in patients with MND without hyperreflexia, while it has been reported altered in those with brisk tendon reflexes. Significantly briefer than normal SPs have been found in MND, while this index was longer than normal when the MND was combined with dementia. Caramia et al. (1991) have examined patients with primary lateral sclerosis (PLS) and amyotrophic lateral sclerosis (ALS); PLS patients had significantly increased values of excitability threshold and CCT for both upper and lower limbs. On the contrary, threshold for relaxed-MEPs elicitation was often lower than normal in ALS; such an alteration was frequent in muscles with relatively preserved muscular bulk and rich in fasciculations. In this cases, MEPs with lower than normal thresholds were sometimes indistinguishable in shape from spontaneous fasciculations (see Rossini and Caramia, 1992). Spastic limbs, with an advanced muscular atrophy often showed higher than normal threshold for relaxed-MEPs. These results fit well with those of Eisen et al. (1993), who found a normal or lower than normal cortical excitability threshold in the early stage of the disease but which progressively increased as the disease progressed. Recently (Kohara et al., 1996), the PSTH technique was applied in order to evaluate the occurrence of motor unit discharges evoked by sub-threshold TCS in hand muscles during slight voluntary contraction in 12 patients with ALS, 12 with upper motor neuron lesions, 9 with pure lower motor neuron diseases and 14 normal controls. Normal units showed an increase in discharge probability at latencies of 20-30 ms due to monosynaptic activation (primary peak). The discharge probability of the primary peak was significantly higher in ALS patients with a shorter duration of the disease; moreover, a double primary peak was found in 4 ALS patients. The authors (Kohara et al., 1996) conclude that the excitability of the surviving corticospinal tract is abnormally increased in ALS, especially in the early stage of the disease confirming early reports with electrical stimulation (Rossini et al., 1987b).

2.5. Movement disorders

Reports on TCS in patients affected by Parkinson's disease (PD) do not provide homogeneous results. In comparison with controls, Eisen et al. (1991) have found both larger than age-matched MEPs in 7 of 18 PD and smaller than age-matched MEPs in two. Rossini et al. (1991b) reported a higher than normal threshold for relaxed MEPs elicited in the rigid arm of mainly unilateral PD. Cantello et al. (1991) reported a decrement of the excitability threshold. Others (Priori et al., 1994a; Ridding et al., 1995) failed to show any difference between PD patients and controls. Conditioning of the brain excitability threshold via prestimulation of peripheral nerve fibres is lost in PD patients who have depressed frontal somatosensory evoked potentials (Rossini et al., 1991b). In this paper, long latency reflexes, SEPs and MEPs were examined in 35 PD patients. Conditioning of TCS via prestimulation of the median nerve did not produce any variation of the MEPs' amplitude as noted in controls whenever the frontal N30 of the SEPs was absent or reduced in amplitude. This supports an abnormality of sensory-motor integration in PD.

Inhibitory phenomena (SP) have been studied as well in PD, but there is no general consensus about the results. Many studies report a shortening of the SP in PD (Cantello et al., 1991; Priori et al., 1994a; Valzania et al., 1996), where the length was increased by decreasing the intensity of stimulation (Valls-Solè et al., 1994) while others found no difference between SP duration in PD and healthy controls (Ridding et al., 1995). The duration of the SP can be shortened in normal subjects and in patients with PD by levodopa administration (Cantello et al., 1991; Priori et al., 1994a); the same effect can be induced by neuroleptics in drug-induced parkinsonisms (Priori et al., 1994a). These effects were thought mainly due to modulation of basal ganglia output via the ventrolateral thalamus on the excitability of inhibitory interneurones in the motor cortex. Abnormal excitability of motor brain circuitries in parkinsonism has also been found by using a double stimulus: this has shown a decrement of cortico-cortical inhibition at short (1-5 ms) interstimulus intervals (Ridding et al., 1995). Recently, Valzania et al. (1996) and Berardelli et al. (1996) have found a significant test MEP inhibition at longer interstimulus intervals of 75-250 ms. Both excitability threshold and SP duration are remarkably affected by therapeutic thalamic stimulation (Pascual-Leone et al., 1996c).

CCTs studies in patients affected by Huntington's disease (HD) did not show abnormalities (Caramia et al., 1988; Eisen et al., 1989; Hömberg and Lange, 1990). On the other hand, Meyer et al. (1992) found a diminished corticospinal excitability in 74% of HD patients. Tegenthoff et al. (1996) found a significant prolongation of the SP in a group of patients suffering from a classical form of HD, whilst patients suffering from a primary rigid HD variant had a shortening of the SP. The impaired excitability of the corticospinal system in HD, probably due to increased inhibition of the motor cortex via the basal ganglia, was previously postulated by Priori et al. (1994b).

Magnetic TCS has been used to assess motor system excitability in 11 patients with task-specific dystonia (Ikoma et al., 1996). MEPs were recorded bilaterally from flexor carpi radialis muscles during stimulation of different intensities and different levels of voluntary contraction of the target muscle. Excitability thresholds at rest did not differ from those of control subjects with increasing stimulus intensity, the MEP/M area ratio was significantly greater in patients than in controls; this ratio was similar in both groups with increase in the degree of voluntary contraction. SPs were similar in patients and controls. The authors (Ikoma et al., 1996) conclude that cortical motor excitability is increased in dystonia. Their findings did not confirm the results of Mavroudakis et al. (1995) who found longer than normal inhibitory effects on SPs in the target muscle(s) of dystonic patients.

2.6. Intraoperative monitoring

An important application of corticospinal tract TCS is by intraoperative monitoring of motor tract function during spinal or cerebral surgery to avoid the devastating neurological injury which may complicate these procedures. SEP recordings alone are not entirely satisfactory due to the possibility of 'false negative' results (i.e. post-operative motor deficit despite normal SEP monitoring). Motor tract potentials have been successfully recorded via epidural electrodes during TCS (Boyd et al., 1986; Pelosi et al., 1988; Berardelli et al., 1990; Thompson et al., 1992). The value of surface recordings after single shocks has been challenged because of possible contamination by muscle artifacts even under deep anaesthesia and neuromuscular block. Magnetic stimulation after general anaesthesia often fails to elicit any descending response; in the few cases when it does, controversy exists whether these are due only to 'late I-waves' or due to the entire sequence of 'D- and I-waves' (Berardelli et al., 1990; Thompson et al., 1992).

Due to the pain involved, TCS with electric pulses is now used in awake subjects only for research studies. However, in the anaesthetised subjects, it still represents an effective tool for monitoring the integrity of corticospinal pathways during spinal surgery (Boyd et al., 1986; Inghilleri et al., 1989; Burke et al., 1992). The limits of acceptable latency/amplitude changes however, have not been fully defined. Repetitive trains of electric shocks delivered on the motor cortex can enhance the probability of recording a stable MEP under general anaesthesia as has been previously demonstrated for spinal cord stimulation (Taylor et al., 1994). Multipulse transcranial magnetic 'bifocal' stimuli have been successfully employed for intraoperative monitoring of lower limb MEPs: by using trains of 3-6 pulses separated by 2 ms. Jones et al. (1996) obtained consistent

EMG responses of more than 100 μV in amplitude in 21 of 22 patients who underwent general anaesthesia for spinal surgery. Nitrous oxide is known to easily suppress the MEP (Zentner, 1991) but responses persisted with concentrations as high as 74% (Jones et al., 1996; Rodi et al., 1996). Transient loss of MEPs has been found during the excision of an intramedullary neoplasm with a post-operative deterioration of right leg strength.

2.7. Other applications

Brain stimulation has been used in order to show that the excitability threshold to magnetic TCS is increased in the motor cortex contralateral to a cerebellar lesion (Meyer et al., 1994; Di Lazzaro et al., 1994). These asymmetries are probably linked to modifications occurring in the excitatory rather than in the inhibitory cortical circuits; in fact, SPs induced by TCS of the same absolute intensity do not show interside differences (Di Lazzaro et al., 1995).

Schady et al. (1991) studied 25 patients affected by hereditary spastic paraplegia from 17 kinships including Type I, Type II and intermediate forms. The authors failed to record MEPs in 33% of patients; when present, MEPs were delayed in 75% of cases. No correlation was found with hyperreflexia or a Babinski sign; no attempts were made to define threshold or amplitude abnormalities. Hayes et al. (1992) examined 8 patients with traumatic spinal cord injury. In all but one, relaxed-MEPs were absent. Combined stimulation of peripheral afferents and of corticospinal fibres acting on the same spinal motoneurons elicited MEPs revealing preserved corticospinal innervation in some patients despite absent MEPs to TCS alone. A train of impulses to the medial sole was used to condition MEPs in the tibialis anterior muscle to TCS in 8 patients with traumatic myelopathy. No response to TCS alone was recordable. However, when TCS and conditioning stimuli were combined, MEPs were recorded in 3 cases, thereby demonstrating the presence of surviving corticospinal fibres to a lower limb. Schneider et al. (1991) examined two generations (19 members) of a family affected by hereditary motor and sensory neuropathy with pyramidal signs (HMSN type V). CCT to the hand muscles was normal, while that to biceps was slightly prolonged in 3 cases. CCT to the lower limbs was normal in all the non-affected members, while all the affected members showed both CCT prolongations and low amplitude MEPs.

Corticospinal tract abnormalities during magnetic TCS have been demonstrated by Cruz Martinez and Anciones (1991) in two siblings suffering from Cockayne's syndrome. Such an observation is consistent with signs of diffuse hypomyelination observed in MRI in this disease.

MEPs to magnetic TCS have been recorded from bulbocavernous and anal sphincter muscles (Opsomer et al., 1989). CCT have been calculated by direct stimulation of the sacral roots. Abnormally prolonged CCTs to pelvic muscles have been calculated in patients suffering from dorsal and lumbosacral myelopathies of various aetiologies (herpetic myelitis, MS etc.) The combined use of motor and somatosensory evoked potentials together with sacral reflex recordings has been advocated for the evaluation of patients with urinary and sexual dysfunctions (Ghezzi et al., 1991).

MEPs and SEPs have been analysed in patients submitted to radiotherapy of the spine for Hodgkin's disease (De Scisciolo et al., 1991). The authors describe diffuse abnormalities in both MEPs and SEPs which might have been caused by chemotherapy and disease relapse as well as chronic radiation damage. Despite such uncertainties, previous studies have suggested the usefulness of MEP recordings and follow-up in patients with therapeutic or accidental radiation to the spinal cord. Radiation therapy may induce a plexopathy which is often complicated by induration and oedema involving the supraclavicular region. This makes electrical stimulation at the Erb's point technically difficult. In these patients, magnetic cervical root stimulation may be useful to demonstrate brachial plexus continuity (Boyaciyan et al., 1996).

TCS has been applied between attacks in 12 patients suffering from unilateral classic migraine with sensorimotor auras and in 10 patients with common migraine and unilateral headache (Maertens de Noordhout et al., 1992). They found that in classic migraine the excitability threshold for relaxed-MEPs was increased on the side with auras compared with the unaffected side in parallel with reduction of MEP amplitudes. In patients with common migraine, MEPs were normal.

Samii et al. (1996) studied the postexercise facilitation of MEPs to magnetic TCS in 12 patients with chronic fatigue syndrome and 10 depressed patients. They suggested that the postexcercise cortical excitability was significantly reduced in both groups compared to that of a control population.

Recently, magnetic stimulation has been studied in a large series of patients affected by facial palsy of different aetiologies (Rösler et al., 1995). In addition to distinguishing between central and peripheral facial lesions, the authors state that the method was very sensitive to detect subclinical dysfunctions in meningo-radiculitis and
malignant meningeal diseases. Pre-symptomatic or subclinical central motor involvement can be shown by TCS in Behçet's disease (Parisi et al., 1996).

Ipsilateral motor evoked potentials were elicited in lower limb muscles and striated sphincters by a recently developed method using magnetic stimulation of both proximal and distal cauda equina sites. Based on F-response latencies and the lack of attenuation when target muscles were vibrated, the authors (Maccabee et al., 1996) postulate that the proximal response is a directly elicited 'M' response arising near or at the rootlet exit zone of the conus medullaris. These proximal responses were mainly elicited by a vertically oriented coil junction (and cranially directed induced current). Over the distal cauda equina, 'M'

responses from lumbar roots were optimally excited by a horizontally oriented coil junction.

2.8. MEPs and higher brain functions

After the first report about the possibility of transiently suppressing visual perception by stimulating the occipital cortex about 80-100 ms after the presentation of a visual stimulus (Amassian et al., 1989), other non-motor brain areas have been examined by magnetic TCS, this has provided interesting tools for the analysis of lateralized properties of the dominant and non-dominant hemispheres as by inducing counting errors or 'speech arrest' following stimulation of the left temporal lobe (Pascual-Leone et al., 1991; Jennum et al., 1994; Michelucci et al., 1994). However, since information of higher functions is processed along several parallel loops involving many cortical areas, a single shock is often inadequate to interfere with these functions; this is overcome by using special kind of stimulators which deliver repetitive shocks on a single scalp position or by stimulating multiple areas of the brain simultaneously. The heating effect is prevented by cooling systems. Exhaustive reviews on the use and safety of this new generation of magnetic stimulators can be found in Pascual-Leone et al. (1996a) and Wassermann et al. (1996). With repetitive stimulators, the risk of inducing an epileptic seizure both in normal and epileptic subjects (Dhuna et al., 1991; Pascual-Leone et al., 1993; Wassermann et al., 1996) needs to be considered. By using such a technique, a transient neglect (Pascual-Leone et al., 1994) or a recall deficit (Grafman et al., 1994) may follow repetitive right parietal lobe stimulation. More recently, Pascual-Leone et al. (1996a) confirmed the pivotal role played by the left prefrontal cortex in mood regulation. In this elegant experiment, rapid-rate TCS was randomly delivered on right, left and midfrontal/prefrontal sites. Subjects were asked to score their mood after each sequence of stimuli and results were compared to the same analogue scales rated before the stimulation. A significant decrease in sadness and increase in happiness was selectively found after the stimulation of the left prefrontal cortex. Magnetic TCS may become a useful tool for psychiatric therapy. This was postulated in animal experiments (Fleischmann et al., 1995) and tentatively applied in humans with minor benefits using TCS delivered on the vertex at a low stimulation rate (Höflich et al., 1993; Koblinger et al., 1995). In a recent pilot study, George et al. (1996) treated 6 patients with drug-resistant depression by daily sessions of repetitive TCS on the left prefrontal cortex. Two had a full remission, two were improved, and in the remaining two TCS was ineffective. Finally, in a randomised placebo-controlled trial on 17 patients suffering from drug-resistant depression of a psychotic subtype, Pascual-Leone et al. (1996b) found that repetitive magnetic transcranial stimulation of the left dorsolateral prefrontal cortex induced a transient improvement in 11 patients lasting for about 2 weeks after 5 days of daily stimulation sessions. These results that obviously need confirmation, are revealing new perspectives for brain TCS and are an impetus for new research.

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