Invited review

The clinical diagnostic utility of transcranial magnetic stimulation: Report of an IFCN committee

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Abstract

The review focuses on the clinical diagnostic utility of transcranial magnetic stimulation (TMS). The central motor conduction time (CMCT) is a sensitive method to detect myelopathy and abnormalities may be detected in the absence of radiological changes. CMCT may also detect upper motor neuron involvement in amyotrophic lateral sclerosis. The diagnostic sensitivity may be increased by using the triple stimulation technique (TST), by combining several parameters such as CMCT, motor threshold and silent period, or by studying multiple muscles. In peripheral facial nerve palsies, TMS may be used to localize the site of nerve dysfunction and clarify the etiology. TMS measures also have high sensitivity in detecting lesions in multiple sclerosis and abnormalities in CMCT or TST may correlate with motor impairment and disability. Cerebellar stimulation may detect lesions in the cerebellum or the cerebellar output pathway. TMS may detect upper motor neuron involvement in patients with atypical parkinsonism and equivocal signs. The ipsilateral silent period that measures transcallosal inhibition is a potential method to distinguish between different parkinsonian syndromes. Short latency afferent inhibition (SAI), which is related to central cholinergic transmission, is reduced in Alzheimer’s disease. Changes in SAI following administration of cholinesterase inhibitor may be related to the long-term efficacy of this treatment. The results of MEP measurement in the first week after stroke correlate with functional outcome. We conclude that TMS measures have demonstrated diagnostic utility in myelopathy, amyotrophic lateral sclerosis and multiple sclerosis. TMS measures have potential clinical utility in cerebellar disease, dementia, facial nerve disorders, movement disorders, stroke, epilepsy, migraine and chronic pain.

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1. Introduction

Transcranial magnetic stimulation (TMS) was first described by Barker et al. (1985) as a non-invasive, painless way to stimulate the human brain. TMS works by passing a large, brief current through a wire coil placed on the scalp. The transient current produces a large and changing magnetic field, which induces electric current in the underlying brain. The area activated is relatively focal with a “figure-of-eight” or “butterfly” coils and more diffuse with a circular coil. The effect of TMS also depends on pulse waveform (monophasic vs. biphasic) and on the direction of the induced current in the brain according to coil orientation (Kammer et al., 2001). This is likely due to activation of various groups of cortical fibers (Di Lazzaro et al., 2004b).

TMS has been applied to many neurological and psychiatric disorders to explore the pathophysiology of these conditions, to examine the clinical diagnostic utility of different TMS techniques and as a possible treatment (Rothwell, 1997; Mills, 1999; Hallett, 2000; Chen, 2000; Curra et al., 2002; Chen, 2004; Rossini and Rossi, 2007). TMS may be delivered as single or paired pulses, or as regularly repeating pulses (repetitive TMS) (Wassermann, 1998; Wassermann and Lisanby, 2001). This review will focus on the clinical diagnostic utility of single and paired TMS. Repetitive TMS and its potential therapeutic use will not be discussed. The first section will provide a brief discussion of the several TMS techniques, but it is not intended to provide a detailed description of how TMS should be performed. The second section will discuss the application of these techniques in several diseases, with emphasis on the clinical diagnostic utility and limitations.

2. Commonly used TMS techniques

2.1. Measures of corticospinal projection

2.1.1. Motor threshold (MT)

MT refers to the lowest TMS intensity capable of eliciting small motor-evoked potentials (MEPs), and is usually defined as more than 50 µV in amplitude in muscles at rest or 200 µV in active muscles in at least five out of 10 trials (Rossini et al., 1994; Rothwell et al., 1999). This method is rapid and reproducible (Tranulis et al., 2006), but alternative methods have been proposed, including the determination of a lower threshold (highest stimulus intensity evoking no responses) and an upper threshold (lowest stimulus intensity evoking responses at each trial) (Mills and Nithi, 1997b), the visualization of movement (Pridmore et al., 1998), an automated threshold-tracking technique (Awiszus, 2003) or an analytical method based on the sigmoid curve fitting the probability of response as a function of stimulus intensity (Tranulis et al., 2006). The MT provides information about a central core of neurons in the muscle representation in the motor cortex. MT is lower for intrinsic hand muscles compared to proximal arm, lower limb and truncal muscles (Chen et al., 1998). This is likely related to differences in the strength of corticospinal projection. MT likely reflects neuronal membrane excitability because it is increased by drugs that block voltage-gated sodium channels (Ziemann et al., 1996b; Chen et al., 1997a). MT is decreased by non-NMDA glutamatergic agent (Di Lazzaro et al., 2003) but is not affected by drugs that alter GABA (Ziemann et al., 1996b) or NMDA glutamate transmission (Liepert et al., 1997; Ziemann et al., 1998a).

2.1.2. Recruitment curve

Also known as input-output or stimulus–response curves, this refers to the increase in MEP amplitude with increasing TMS intensity. Compared to MT, this measure assesses neurons that are intrinsically less excitable or spatially further from the center of activation by TMS (Hallett et al., 1999). Recruitment curves are likely related to the strength of corticospinal projections, and are generally steeper in muscles with low MT, such as intrinsic hand muscles (Chen et al., 1998). The slope of recruitment curve is increased by drugs that increase adrenergic transmission (e.g. dextroamphetamine), and is decreased by sodium and calcium channel blockers (e.g. lamotrigine) and by drugs that enhance the effects of GABA (e.g. lorazepam) (Borojerdí et al., 2001).

2.1.3. Central motor conduction time (CMCT)

2.1.3.1. Methods for measuring CMCT.

CMCT is an estimate of the conduction time of corticospinal fibers between motor cortex and spinal (or bulbar) motor neurons. It includes the times for excitation of cortical cells, conduction via the corticospinal (or corticobulbar) tract and excitation of the motor neuron sufficient to exceed its firing threshold. The estimate is made by subtracting the spinal motor neuron to muscle latency from the cortex to muscle latency. The spinal motor neuron to muscle latency may be estimated by two methods. The first depends on stimulating the peripheral nerve and eliciting F-waves and is only applicable in relatively distal muscles. Peripheral conduction time is then calculated as \((F + M - 1)/2\), where \(F\) is the shortest F-latency and \(M\) is the M-wave latency (Mills, 1999). Recently, on the basis of experiments in macaques (Olivier et al., 2002), it has been suggested that this method significantly overestimates CMCT and that the longest F-wave latency should be used. While there are theoretical reasons why the longest F-latency should be used (Olivier et al., 2002), in practical clinical situations the shortest F-latency is much easier to measure and has been used to develop normal ranges in most studies. The second approach to estimate the peripheral conduction time is to stimulate either electrically or magnetically over the vertebral column, a procedure that excites motor roots at their exit foramina (Mills and Murray, 1986). This method is applicable to most muscles, but overestimates the true CMCT, particularly for the lower limbs, because the con-
duction time in proximal root segment between cord and exit foramen is included.

CMCT is usually measured with the target muscle active, thereby giving the shortest latency from cortex to muscle. In this situation, the spinal motor neuron pool is close to firing threshold and there is the greatest opportunity for the earliest descending corticospinal volley to cause a discharge. In disease states, this may not be the case and a prolonged CMCT may be due to impaired summation of descending volleys at the motor neuron. Since for CMCT measurement the MEP latency is the only consideration, the force of muscle contraction need not be strictly controlled. With a given stimulus intensity and contraction of 10–20% maximum background force, latency variation is much less than amplitude variation (Mills, 1999). It is acceptable to record five responses and then measure the shortest latency, best done by superimposing the responses. If the amplitude of response to root stimulation is of interest, for example, if conduction block in motor roots is suspected, then electrical stimulation is preferred because supramaximal root stimulation cannot be achieved using magnetic stimulation (Mills, 1999).

If both the F-wave method and stimulation over the cervical or lumbar regions are used, an estimate of the motor root conduction time (time from motor neuron cell body to root exit foramen) can be found by subtracting the peripheral conduction time estimated by the stimulation method from that estimated by the F-wave method (Banerjee et al., 1993).

2.1.3.2. Influence of age, height and side on CMCT. CMCT in neonates determined using electrical stimulation was found to be markedly longer than in adults (Duron and Khater-Boidin, 1988). The maturation of corticomotor threshold has been documented (Muller et al., 1991; Fietzek et al., 2000). In the resting state, responses are very difficult to obtain until the age of two and motor threshold remains above adult levels until about age 10. In adults, CMCT has no correlation or only a weak correlation with age (Claus, 1990; Eisen et al., 1990; Mano et al., 1992; Mills et al., 1997b).

Since CMCT depends on the length of the conduction pathway, a relationship between CMCT and height can be expected. However, the conduction distance from motor cortex to the cervical segments is much shorter than to the lumbar segments and any relationship with height may be lost. Therefore, CMCT to upper limb muscles has no correlation or only a weak correlation with height, whereas CMCT to lumbar segments is strongly correlated with height (Rossini et al., 1987; Chu, 1989; Claus, 1990; Ghezzi et al., 1991; Ravnborg et al., 1991; Toleikis et al., 1991; Furby et al., 1992; Wochnik-Dyjas et al., 1997). Formulae for calculating the upper limit of normal CMCT taking height into account have been proposed (Claus, 1990).

No differences in CMCT to upper limbs have been found between men and women (Claus, 1990; Toleikis et al., 1991; Furby et al., 1992; Mills and Nithi, 1997b). CMCT to the lower limbs is marginally shorter in women than men even allowing for differences in age and height (Tobimatsu et al., 1998). Most studies have reported no significant side-to-side differences in CMCT (Eisen et al., 1990; Mills and Nithi, 1997b).

2.1.4. The triple stimulation technique (TST)

The triple stimulation technique (TST) is a collision method. It was first designed to measure conduction blocks in peripheral nerves (Roth and Magistris, 1989) and was subsequently adapted to study corticospinal conduction (Magistris et al., 1998). The TST circumvents a number of problems encountered with transcranial electrical (TES) or magnetic stimulation. Transcranial stimulation yields MEPs that are smaller than compound muscle action potential (CMAP) evoked by peripheral nerve stimuli, even with voluntary contraction of the target muscle. The size of MEPs (amplitude, duration and area) also varies considerably from one stimulus to the next and among individuals (Magistris et al., 1998; Rosler et al., 2002). The MEP size is further influenced by spinal motor neurons discharging more than once in response to a single transcranial stimulus. The TST synchronizes the response of the motor neurons driven to discharge by the transcranial stimulus, thereby avoiding phase cancellation that accompanies the desynchronization of the biphasic motor unit potentials. In addition, the TST eliminates repetitive discharges from the measured response.

2.1.4.1. Method for TST. A comprehensive description of the TST and normal values has been provided in several publications (Magistris et al., 1998; Magistris et al., 1999; Rosler et al., 1999; Buhler et al., 2001; Magistris and Rosler, 2003) (Fig. 1). In brief, three stimuli are given in sequence with appropriate delays. The first stimulus is TMS. It is followed by two supramaximal stimuli given to the nerve supplying the target muscle, first distally (close to the muscle) and then proximally (as proximally as possible on the nerve). Two collisions of the evoked action potentials occur. If a spinal motor neuron was excited by TMS, its descending action potential collides with the antidromic potential evoked by the distal peripheral stimulus. If a spinal motor neuron was not excited by TMS, the antidromic potential evoked by the distal stimulus does not collide and ascends. After a second delay, the proximal stimulus evokes the response that will be studied. The action potentials evoked by the proximal nerve stimulus will only descend to the target muscle if no antidromic potential is ascending from the peripheral stimulus and they will collide if an action potential ascends. Therefore, only those action potentials will descend on the axons that were excited initially by TMS. In contrast to the original desynchronized action potentials evoked by TMS, the action potentials are now synchronized because they are elicited by a single proximal nerve stimulus. The response is compared to that of a control curve, obtained by a triple stimulation performed on the peripheral nerve (Fig. 1).
proportion of the spinal motor neuron pool of the target muscle discharged by TMS is given by the amplitude ratio of the TST test to the TST control curves. A TST amplitude ratio of nearly 100% can always be obtained in healthy subjects. This method has been adapted to allow assessment of muscles other than hand muscles (Buhler et al., 2001; Magistris and Rosler, 2003; Ziemann et al., 2004; Humm et al., 2004b). Dedicated commercial software packages for TST are available.

2.1.4.2. Clinical utility of TST. The TST showed that both TES and TMS are able to excite all motor units of the target muscle in healthy subjects, and that the small size of MEPs is caused by phase cancellation due to discharge desynchronization (Magistris et al., 1998; Buhler et al., 2001). The TST allows precise quantification of central conduction failures caused by reduced excitability or loss of cortical motor neurons, by conduction block or loss of corticospinal axons (Magistris et al., 1999; Buhler et al., 2001). It is two to three times more sensitive than standard TMS procedures to detect corticospinal conduction deficits in patients with central nervous system disorders and is specially suited for the detection and quantification of small changes of central motor conduction. For example, TST has been used to study ipsilateral corticospinal projection in mirror movements (Ueki et al., 2005). TST may be used as an objective method to follow the course and to assess the effects of treatments of disorders that affect corticospinal conduction.

2.1.5. Stimulation of the corticospinal tract at the level of the foramen magnum

The method has been described in detail in recent reviews (Ugawa, 2002; Terao and Ugawa, 2002; Taylor and Gandevia, 2004) (Fig. 2). It can be achieved in humans by transmastoid electrical stimulation (Ugawa et al., 1991b) or magnetic stimulation (Ugawa et al., 1994d). The center of a double cone coil is placed over or just below the inion to produce upward current in the brain (Taylor et al., 2004). The subject’s head is tilted backwards by 30°–45° to induce current at the bottom of the skull. TMS is usually given during voluntary contraction of the target muscle to facilitate the response. Foramen magnum stimulation likely activates the corticospinal tract at the pyramidal decussation near the cervicomedullary junction (Ugawa et al., 1992, 1996; Oliviero et al., 2000). It produces a single descending volley (Berardelli et al., 1991b; Ugawa et al., 1994d), in contrast to multiple volleys from TMS of the motor cortex. Studies of interactions between cortical and foramen magnum stimulation suggested that both stimulations activate the same population of axons in the corticospinal tract (Taylor et al., 2002).
Foramen magnum level stimulation can be used together with CMCT to calculate the cortical–foramen magnum conduction time and the foramen magnum–spinal cord conduction time (Ugawa et al., 1996). It can be used to localize a corticospinal tract lesion above or below the foramen magnum, therefore achieving more precise lesion localization than CMCT alone. Stimulation at the foreman magnum may also detect subclinical involvement and multiple lesions in the corticospinal tract (Ugawa et al., 1992, 1996). For example, combined with cortical stimulation, foramen magnum stimulation can be used to detect delayed cortical–foramen magnum conduction time in patients with concomitant peripheral neuropathy (Ugawa et al., 1996). Abnormalities of the corticospinal tract were demonstrated with this method in Pelizaeus–Merzbacher disease (Nezu et al., 1998). One pitfall of this method is that slowly conducting descending tracts may be activated in rare patients with severe damage to the corticospinal tract (Ugawa and Kanazawa, 1999). Moreover, the diagnostic sensitivity and specificity of foramen magnum level stimulation have not been established.

Stimulation at the foramen magnum may also be used in research studies to separate changes in cortical and spinal excitability. Changes in response to foramen magnum level stimulation likely reflect changes in spinal excitability. For example, Boroojerdi et al. (2003) used foramen magnum level stimulation to show that the effects of botulinum toxin on the motor system are mainly due to peripheral rather than central mechanisms.

2.2. Measures of cortical inhibition and facilitation

The cortical motor output is the net result of the interplay between multiple systems that exert excitatory and inhibitory influences on the corticospinal neurons. TMS may be used to investigate these facilitatory and inhibitory mechanisms. Some of these TMS techniques involve paired-stimuli based on a conditioning-test paradigm. Stimulation parameters such as the intensity of the conditioning stimulus (CS) and test stimulus (TS) together with the time between the two stimuli (interstimulus interval, ISI) determine interactions between stimuli.

2.2.1. Short-interval intracortical inhibition (SICI)

When the CS is below and the TS is above the motor threshold (MT), the CS inhibits the response to TS at ISIs of 1–6 ms. The inhibition is referred to as short-interval intracortical inhibition (SICI) and was first described by Kujirai et al. (1993). SICI is commonly expressed as the ratio of the MEP amplitude produced by CS – TS to that produced by TS alone. Ratios below one represent inhibition and ratios above one represent facilitation.

2.2.1.1. Physiology of SICI. SICI likely has an intracortical origin because the same CS that suppressed the test MEP produced by TMS had no influence on MEP produced by direct stimulation of corticospinal axons with TES (Kujirai et al., 1993). A single TMS pulse evokes multiple descending volleys in the spinal cord, termed indirect (I) waves, and they are numbered according to their latencies. Further evidence that SICI is of cortical origin comes from epidural recordings showing that the I3 wave and subsequent I-waves produced by the TS are suppressed (Nakamura et al., 1997; Di Lazzaro et al., 1998).

SICI involves at least two phases, with maximum inhibition at ISIs of about 1 and 2.5 ms (Fisher et al., 2002; Roshan et al., 2003). The first phase may in part reflect refractoriness or excitability changes in axons (Fisher et al., 2002; Chan et al., 2002) but there is also evidence for neuronal inhibition (Roshan et al., 2003). Second phase of SICI is likely related to synaptic inhibition (Strafella and Paus, 2001; Fisher et al., 2002; Roshan et al., 2003), and is sensitive to pharmacological manipulations (Ziemann et al., 1996b). SICI has a slightly lower threshold than neural circuits mediating facilitation (Awiszus et al., 1999; Ilic et al., 2002; Orth et al., 2003) and is the lowest threshold system activated by TMS in the hand area of human motor cortex (Davey et al., 1994; Ziemann et al., 1996d; Awiszus et al., 1999). Hence, SICI may be a useful measure for assessing even minor changes in cortical excitability.
SICI increases with higher test MEP amplitudes from approximately 0.2 to 1 mV (Roshan et al., 2003). SICI also increases when the intensity of CS. When CS at increasing intensity is applied to the hand area of the motor cortex, SICI increases but further increase in CS intensity leads to reduced inhibition and eventually facilitation (U-shaped curve) (Schafer et al., 1997; Chen et al., 1999; Buteifsch et al., 2003). SICI is also observed in other muscles such as facial muscles (Paradiso et al., 2005), proximal arm, truncal and lower limb muscles (Chen et al., 1998), diaphragm (Demoule et al., 2003) and anal sphincter (Lefaucheur, 2005).

SICI is modulated by “physiological” phenomena such as the menstrual cycle and voluntary movement. In women, SICI is more prominent during the luteal phase than during the follicular phases, likely due to increased progesterone levels (Smith et al., 1999). Even minimal levels of voluntary activation of the target muscle significantly decrease SICI (Ridding et al., 1995c; Hanajima et al., 1998). Moreover, SICI progressively decreases just before onset of movement (Ridding et al., 1995c; Reynolds and Ashby, 1999). This reduction may serve to “release” cortical representations from inhibition, and focus subsequent excitatory drive to produce the intended movement (Floeter and Rothwell, 1999). In contrast, volitional inhibition induces an increase in SICI (Sohn et al., 2002). This finding suggested that SICI may serve to prevent unwanted muscle activation (Stinear and Byblow, 2003) and assists the corticospinal system in producing fractionated activity of intrinsic hand muscles (Zoghi et al., 2003; Rosenkranz and Rothwell, 2004).

2.2.1.3. Summary of SICI. SICI is a complex phenomenon and yet gives abundant information on cortical excitability under normal and pathological conditions. Conventional experimental approaches result in wide intra-subject variability that detracts from the value of SICI in clinical applications. The variability can be somewhat reduced by expressing the intensity of the CS as a percentage of the individual threshold for SICI rather than as a percentage of the active or rest motor threshold. This approach may be more sensitive than the conventional approach in detecting neurophysiological abnormalities (Stinear and Byblow, 2004).

2.2.2. Long-interval intracortical inhibition (LICI)

At ISIs of about 50–200 ms, a suprathreshold CS decreases the test MEP amplitude (Valls-Sole et al., 1992; Wassermann et al., 1996) and is referred to as long-interval intracortical inhibition (LICI). LICI probably shares some mechanisms with the suppression of voluntary muscle contraction induced by single suprathreshold TMS pulse known as the silent period (Wassermann et al., 1996), but these two measures of cortical inhibition are not identical because they can be affected differently in diseases (Berardelli et al., 1996).

At ISIs longer than 50 ms, LICI is a cortical phenomenon as shown by the lack of changes in spinal excitability (Fuhr et al., 1991), no suppression of the response to paired TES (Inghilleri et al., 1993), and by the marked reduction in the corticospinal volley evoked by TMS (Nakamura et al., 1997; Chen et al., 1999b; Di Lazzaro et al., 2002a). LICI decreases with increasing TS intensities, indicating that low threshold corticospinal neurons are more sensitive to LICI than high threshold corticospinal neurons (Sanger et al., 2001).

LICI and SICI are likely mediated by different inhibitory neurons and it has been shown that LICI inhibits SICI (Sanger et al., 2001). Voluntary muscle activation has no significant effect on the extent of LICI (Wassermann et al., 1996; Chen et al., 1997b). Pharmacological studies suggest that LICI is mediated by GABA<sub>A</sub> receptors (Roick et al., 1993; Siebner et al., 1998; Werhahn et al., 1999; McDonnell et al., 2006).

2.2.3. Short-interval intracortical facilitation (SICF)

At discrete ISIs of about 1.1–1.5, 2.3–3.0 and 4.1–4.5 ms, with both the CS and TS close to the MT (Tokimura et al., 1996) or suprathreshold CS and subthreshold TS (Zieman et al., 1999b; Chen and Garg, 2000; Hanajima et al., 2002), a facilitatory interaction known as facilitatory I-wave interaction or short-interval intracortical facilitation (SICF) can be observed in both arm and leg representations. It is thought that the CS partially depolarizes the initial axonal segment of neurons involved in generating late I-waves and makes them hyperexcitable, and these neurons are excited by the subsequent TS (Hanajima et al., 2002; Illic et al., 2002). This mechanism explains why SICF increases at discrete intervals corresponding to...
latency between I-waves and paired-pulse TS activates hyperexcitable interneurons one I-wave latency ahead of the site excited by TS alone (Ilic et al., 2002). Voluntary contraction induces only minor changes in SICF. Drugs that enhance GABAergic functions (Zieman et al., 1998c) reduce SICF, but it is not affected by sodium channel blockers (Zieman et al., 1998c) and the muscarinic receptor blocker scopolamine (Di Lazzaro et al., 2000b).

2.2.4. Intracortical facilitation (ICF)
Paired TMS with the CS below and the TS above the MT at ISIs of 8–30 ms induce an increase in the test MEP amplitude compared to TS alone and is known as intracortical facilitation (ICF). ICF appears to take place in the cortex (Zieman et al., 1996c; Nakamura et al., 1997; Di Lazzaro et al., 2006b) and is mediated by a neuronal population distinct from those mediating SICI (Zieman et al., 1996c; Chen et al., 1998; Ashby et al., 1999; Strafella and Paus, 2001). However, epidural recordings showed that ICF was not associated with a significant increase in the amplitude or number of descending volleys (Di Lazzaro et al., 2006b). Therefore, ICF may be due to a so far undetected effect on spinal cord excitability, alteration of the composition (but not the amplitude) of the descending volleys set up by the test stimulus, or there may be additional descending activity that is more dispersed than the epidural volleys and was not evident in the recording of descending corticospinal activity.

The threshold for eliciting ICF is higher than that for SICI (Kujirai et al., 1993; Zieman et al., 1996d; Chen et al., 1998). The NMDA receptor antagonist dextromethorphan reduces ICF (Zieman et al., 1998a), suggesting that glutamate plays a role in mediating ICF. Chronic administration of the selective serotonin re-uptake inhibitor paroxetine was found to increase ICF but had no effect on SICI or the silent period (Gerdelat-Mas et al., 2005).

Like SICI, ICF shows wide variability between subjects, but may be of lower variability than SICI (Di Lazzaro et al., 2000b). The recording of ICF may be of lower variability than SICI (Orth et al., 2003).

2.2.5. Interhemispheric inhibition and facilitation
Interhemispheric callosal connections can be studied by paired-pulse paradigm, with CS over one hemisphere and TS over the opposite hemisphere (Ferbert et al., 1992). A mild interhemispheric facilitation is produced at short ISIs (4–6 ms) (Hanajima et al., 2001), whereas a potent interhemispheric inhibition (IHI) results from longer ISIs (8–50 ms) (Ferbert et al., 1992; Chen et al., 2003). Long latency interhemispheric inhibition (ISI ~ 20–50 ms) is likely mediated by GABA_B receptors (Irlbacher et al., 2007). Women showed a higher transcallosal inhibition than men (De Gennaro et al., 2004a).

2.2.6. Contralateral silent period (SP)
Besides evoking MEPs in the target muscles, single TMS pulses delivered during voluntary muscle contraction produce a period of EMG suppression known as the silent period (SP) (Cantello et al., 1992). The SP evoked in the muscles of the upper limb originates largely from activation of cortical inhibitory interneurons, although spinal mechanisms are involved in the early part (Fuhr et al., 1991; Inghilleri et al., 1993; Roick et al., 1993; Uncini et al., 1993; Chen et al., 1999b). The SP recorded from the facial muscles originates solely in the cortex (Leis et al., 1993; Crucu et al., 1997), probably because facial and limb motor neurons come under different mechanisms of cortical control (Crucu et al., 1997). The SP and MEP have different topographies (Wassermann et al., 1993). The strength of corticospinal projection may influence the SP, since SP is longest in hand muscles and is shorter in proximal arm, leg muscles (Zieman et al., 1993), facial muscles (Werhahn et al., 1995), diaphragm (Lefaucheur and Lofaso, 2002) and anal sphincter (Lefaucheur, 2005). In upper limb muscles, the SP can be evoked at lower stimulus intensities than the MEP (Triggs et al., 1992).

SP duration is related to the intensity of stimulation but is not strongly related to the size of the preceding MEP (Triggs et al., 1992; Inghilleri et al., 1993) nor to the levels of background EMG activity (Inghilleri et al., 1993).

While the SP originates primarily in the motor cortex, nonprimary motor areas also influence its duration as suggested by studies in patients with lesions in brain areas projecting to the motor cortex but sparing the primary motor cortex (von Giesen et al., 1994; Classen et al., 1997). When the excitability of spinal circuits is unchanged, prolonged SP suggests increased whereas shortened SP suggests decreased inhibitory activity in the motor cortex.

SP duration can be modulated by physiological phenomena that change cortical excitability, such as hyperventilation (Priori et al., 1995), sleep deprivation (Scalice et al., 2006), muscle fatigue (Taylor and Gandevia, 2001), or after high-frequency rTMS (Daskalakis et al., 2006; Khedr et al., 2007). Pharmacological studies using benzodiazepines (Inghilleri et al., 1996; Zieman et al., 1996c), selective agonists of the benzodiazepine receptor subtype BZ1 (Mohammadi et al., 2006), baclofen (Inghilleri et al., 1996; Zieman et al., 1996c; Siebner et al., 1998), tiagabine (Werhahn et al., 1999) provided evidence that the SP reflects a long-lasting cortical inhibition mediated by GABA_B receptors. Dopaminergic drugs lengthen the SP in normal subjects (Priori et al., 1994a).

2.2.7. Ipsilateral silent period (iSP)
Ipsilateral inhibitory effects induced by motor cortex stimulation may be measured by the interruption of ongoing voluntary EMG activity, known as the ipsilateral silent period (iSP) (Ferbert et al., 1992; Meyer et al., 1995). Since the iSP is absent or delayed in patients with congenital, acquired or surgical lesions of the corpus callosum (Meyer et al., 1995, 1998), it is likely due to transcallosal inhibition.

However, stimulation of the corticospinal tract caudal to the corpus callosum showed that non-callosal pathways are also capable of generating the iSP (Compta et al., 2006). The recording of iSP has been proposed as a simple
clinical diagnostic tool for callosal function (Meyer et al., 1999).

2.2.8. Short latency afferent inhibition (SAI)

Afferent input can modify the excitability of the motor cortex with a complex time course (Mariorenzi et al., 1991). Most studies used median nerve stimulation followed by TMS of the contralateral motor cortex. Delwaide and Olivier (1990) reported that median nerve stimulation at the wrist suppresses MEP evoked by TMS 18–21 ms later in relaxed hand muscles. Similar effects could be seen after stimulation of the cutaneous nerves of the index finger. Since H-reflexes in forearm muscles were unaffected, the effect likely occurred at the cortical level (Delwaide and Olivier, 1990). This inhibitory phenomenon is termed short latency afferent inhibition (SAI). SAI begins about 1 ms after latency of the N20 component of the somatosensory evoked potential obtained from median nerve stimulation, and lasts for about 7–8 ms (Tokimura et al., 2000). MEP facilitation may be observed at slightly longer intervals (Mariorenzi et al., 1991). The direct demonstration of the cortical origin of SAI was provided through the recordings of descending corticospinal volleys from conscious patients with high cervical epidural electrodes (Tokimura et al., 2000). Later I-waves were strongly suppressed by afferent inputs while earlier descending waves were unaffected.

Since SAI is reduced or abolished by intravenous injection of the muscarinic antagonist scopolamine, muscarinic cholinergic cerebral circuits are involved in regulating SAI. SAI is also reduced by benzodiazepine lorazepam (Di Lazzaro et al., 2005b).

2.2.9. Long latency afferent inhibition (LAI)

Median nerve stimulation can suppress motor cortex excitability also at longer ISIs (Chen et al., 1999a) and this form of inhibition is termed long latency afferent inhibition (LAI). LAI is most consistent at about 200 ms ISI (Chen et al., 1999a; Sailer et al., 2002). Since spinal cord excitability is unchanged at this interval (Chen et al., 1999a), it is likely that LAI is of cortical origin.

2.2.10. Interhemispheric differences for measures of cortical excitability, inhibition and facilitation

Interhemispheric differences may be useful in evaluating conditions in which only one side is affected. Several studies reported lower threshold or higher MEP amplitude for the dominant compared to the non-dominant hemisphere (Triggs et al., 1994; Illic et al., 2004; De Gennaro et al., 2004b), although some studies found no difference (Mills et al., 1997b; Civardi et al., 2000). For SICI and ICF, most studies reported no significant interhemispheric asymmetry (Cicinelli et al., 2000; Maeda et al., 2002; Cahn et al., 2003), but there may be subtle differences in SICI (Illic et al., 2004; Hammond et al., 2004) and greater ICF in the dominant compared to the non-dominant hemisphere in right handed subjects (Cicinelli et al., 2000; Hammond et al., 2004). SP duration was found to be shorter (Priori et al., 1999), but stimulus intensity needed to activate evoque SP was lower (Lo and Fook-Chong, 2005) and at low conditioning stimulus intensities, LICI was stronger (Hammond and Garvey, 2006) in the dominant compared to the non-dominant hemisphere. IHI at ISI of about 10 ms was found to be slightly more prominent from the dominant to the non-dominant hemisphere in right handed individuals (Netz et al., 1995) but another study found no difference (De Gennaro et al., 2004b). In general, the side-to-side difference in TMS measures is considerably less than the interindividual variability (Wassermann, 2002).

2.2.11. Effects of aging

Several studies have examined the effect of aging on motor cortex excitatory and inhibitory circuits. Rossini and co-workers (Rossini et al., 1992) reported a significant increase in motor threshold in healthy subjects with aging. Age-related MEP amplitude reduction has been reported (Pitcher et al., 2003; Oliviero et al., 2006) and greater stimulus intensities may also be required to reach the maximal motor output in older subjects (Rossini et al., 1992; Pitcher et al., 2003; Oliviero et al., 2006). Possible mechanisms for these changes include age-related loss of both cortical and spinal motor neurons, reduced synchronization of I-waves or reduced recruitment of late I-waves in the motor cortex and decline of the neuromuscular system due to aging (Eisen et al., 1996; Pitcher et al., 2003). Normal aging is also associated with a relative decrease in the excitability of some cortical inhibitory circuits (Peinemann et al., 2001; Oliviero et al., 2006). Peinemann et al. (2001) reported reduced SICI in healthy old compared to young subjects, but these findings were not confirmed in other studies (Wassermann, 2002; Oliviero et al., 2006). Oliviero et al. (2006) reported shortening of SP with aging although the SP duration/MEP size ratio did not differ between young and old subjects. One possible mechanism is that reduced corticospinal outflow activates less recurrent axon collaterals leading to reduced inhibitory effect on corticospinal neurons (Orth and Rothwell, 2004). No significant effect of aging was found for SAI (Oliviero et al., 2006).

2.3. Cerebellar stimulation

The effects of cerebellar stimulation can be evaluated by the modulatory effect on the contralateral motor cortex. For example, the frontal EEG responses to magnetic stimulation of the cerebellum can be recorded with latencies of 8–14 ms (Amassian et al., 1992). The modulatory effect on the motor cortex by cerebellar stimulation was first studied by transmastoid electrical stimulation in humans (Ugawa et al., 1991a) and later by magnetic stimulation (Ugawa et al., 1995b). With magnetic cerebellar stimulation, the center of a double cone coil is placed over the midpoint between the inion and mastoid process on the target side (Ugawa et al., 1995b). This is different from pyramidal tract stimulation with the coil placed in the midline over...
the inion. The cerebellar stimulus suppresses MEPs at ISIs of 5–8 ms. This latency is compatible with the latency of frontal EEG response to contralateral cerebellar stimulation in humans (Amassian et al., 1992). Several studies support that the suppression at these intervals is due to cerebellar activation and followed by inhibition at the spinal level beginning at ISIs of 7–8 ms (Ugawa et al., 1991a; Saito et al., 1995; Werhahn et al., 1996). Cerebellar stimulation with a figure-of-eight coil results in less consistent effects and also results in more prominent spinal inhibition (Werhahn et al., 1996). The suppressive effect of cerebellar stimulation was absent in patients with degeneration of the cerebellar cortex or lesions in the cerebellothalamic-cortical pathway, but was present in patients with lesions in the afferent pathway to the cerebellum (Ugawa et al., 1994a,b, 1995a, 1997). Therefore, cerebellar stimulation likely activates Purkinje cells in the cerebellar cortex, leading to inhibition of deep brain cerebellar nuclei such as the dentate nucleus which have a disynaptic excitatory pathway to the motor cortex through the ventral thalamus.

![Diagram of TMS of the facial nerve and facial representation of the motor cortex](image)

Fig. 3. TMS of the facial nerve and facial representation of the motor cortex. (A) Placement of the stimulating coil and recording electrodes. 1. Stimulation of the facial representation of the motor cortex is performed over the opposite hemisphere. 2. For canicular stimulation of the facial nerve, the magnetic coil is placed over the parieto-occipital region (bottom of the coil being over the mastoid). 3. Stylomastoideal electrical stimulation is performed in the region of the stylomastoid foramen. Recording may be from any facial muscle. Recording here is from the nasalis muscle, with the inactive electrode placed on the tip of the nose to reduce volume-conducted activity from other facial muscles. (B) Three segments of the pathway, as delineated by the stimulation sites. (C) Examples of normal responses to TMS in facial muscles. Superimposed recordings from the nasalis muscle. The first deflection is the response to stylomastoideal stimulation. The second deflection is the TMS response evoked by “canicular” stimulation. The response is of similar size and configuration as the response to stylomastoideal stimulation. The third response (superimposition of five successive trials) is the TMS response to cortical stimulation performed during slight voluntary contraction of the nasalis muscle. Latencies are measured to take-off of the negative deflection. Amplitudes are measured from baseline to the negative peak of the CMAP and MEP. Note that in this normal subject the responses are reproducible but rather small (their average amplitude being 17% of the response to stylomastoideal stimulation).
(Ugawa et al., 1991a; Pinto and Chen, 2001). Cerebellar stimulation also reduces SICI and increases ICF of the contralateral motor cortex (Daskalakis et al., 2004).

Electrical cerebellar stimulation causes facilitation of MEPs from the contralateral motor cortex at earlier ISIs of 3–5 ms (Iwata et al., 2004). This facilitation is likely due to activation of dentate nucleus or superior cerebellar peduncle.

2.4. TMS of facial nerve and facial representations of the motor cortex

Only the distal part of the facial nerve is accessible to conventional testing by electrical stimulation since a large part of the nerve is located within the cranium. The blink reflex is therefore often used to study the intracranial nerve segments. However, the study of this indirect trigemino-facial reflex response has limitations. TMS can excite the facial nerve and the facial representation in motor cortex painlessly (Murray et al., 1987; Schriefer et al., 1988; Rosler et al., 1989; Benecke and Meyer, 1991; Paradiso et al., 2005). TMS is performed over the contralateral facial area of the motor cortex (“cortical stimulation”) and over the ipsilateral parieto-occipital region, with the base of the coil over the mastoid (“canalicular stimulation”) (Fig. 3A). Cortical motor-evoked potentials (MEPs) often require facilitation through voluntary contraction of the target muscle (Rosler et al., 1989). The TMS responses are compared to that evoked by electrical stimulation in the region of the stylomastoid fossa (“stylomastoideal stimulation”), or further along facial nerve branches. The three stimulation sites allow assessment of three segments (cortico-proximal, transosseal, and distal; Fig. 3B) of the cortico-facial projection.

The MEP after cortical stimulation and the compound muscle action potentials (CMAPs) to canalicular and stylomastoideal stimulations may be recorded from a variety of facial muscles. The nasalis, mentalis, and buccinator muscles provide large and clearly defined negative deflections. Fig. 3C provides an example. Recordings are performed bilaterally to allow for side-to-side comparison. A detailed description of the method and normal values have been provided previously (Rosler et al., 1989, 1995; Rimpilainen et al., 1993; Wolf et al., 1995). MEPs in facial muscles are small compared to CMAPs to peripheral facial nerve stimulation. Only a limited area of the scalp yields a response to a given facial muscle, usually with a rather high threshold. The response may sometimes be difficult to interpret due to contamination by uncrossed ipsilateral MEPs, by blink and other facial reflexes, by peripheral stimulation of the ipsilateral facial nerve, and possibly by responses of other neural structures such as muscles innervated by the trigeminal nerve (Turk et al., 1994; Urban et al., 1997; Paradiso et al., 2005). Nevertheless, facial muscle MEPs may demonstrate abnormal central conduction in CNS disorders such as multiple sclerosis (Westerink et al., 1991) and amyotrophic lateral sclerosis (Desiato et al., 2002).

The exact location of the stimulation site for TMS of the facial nerve remains controversial, but it likely occurs within the internal acoustic meatus, and is therefore termed “canalicular stimulation” (Schriefer et al., 1988; Rosler et al., 1989, 1991, 1994; Schmid et al., 1991, 1992; Rimpilainen et al., 1993; Wolf et al., 1995). At this site where the facial nerve leaves the low-resistance cerebrospinal fluid and enters the high-resistance petrous bone (Schmid et al., 1992), the facial nerve is highly excitable to TMS, with CMAP size and latency that are neither modified by changes in stimulation intensity, nor by large displacement of the coil position (Schmid et al., 1992).

2.5. Safety and contraindications

The contraindications for single and paired TMS are similar to those of magnetic resonance imaging and mainly involves intracranial ferromagnetic material such as aneurysm clips or other implants (Wassermann, 1998). Cardiac pacemaker is usually considered a contraindication, although it is unlikely to be damaged by TMS. Epilepsy may be considered a relative contraindication as the risk of inducing seizure with single- or paired-pulse TMS is very low (Wassermann, 1998). A mild headache may be induced by TMS.

3. Use of TMS in diseases

3.1. Myelopathy

3.1.1. Diagnosis of cord compression

A large study (Lo et al., 2004) examined MRI and TMS findings in 141 patients with myelopathy. Upper and lower limb CMCT correlated with the severity of cord compression based on MRI. The sensitivity of TMS in differentiating the presence from the absence of MRI cord abnormality was 100% and the specificity was 84.8%.

Myelopathy and radiculopathy commonly co-exist. A study examined 30 clinically and radiologically characterized patients (Abbruzzese et al., 1988), of whom 12 had myelopathy alone, 6 had radiculopathy alone and 12 had evidence of both. In the patients with myelopathy alone, CMCT to thenar muscles, biceps or tibialis anterior was prolonged in 92% of patients whereas the latencies from cervical root stimulation were normal. In contrast, patients with a combination of myelopathy and radiculopathy had prolonged latencies from both cortical and root stimulation in the upper limb muscles. In both groups, abnormalities in motor conduction were more prevalent than abnormalities in somatosensory evoked potentials. Several groups have confirmed this finding (Chistyakov et al., 1995; Kameyama et al., 1995; Kaneko et al., 1997). The technique may also detect incipient cord compression prior to the development of clinical or radiological signs. A study of 23 patients with cervical spondylotic myelopathy showed CMCT to be abnormal in 65% (Travlos et al., 1992). In a group of 67 patients with cervical...
spondylosis (Maertens de Noordhout et al., 1991), 51% had clinical and 66% had radiological evidence of cord compression, determined by myelography. CMCT was abnormal in 84% of patients with, and in 22% of those without radiological signs of cervical cord compression.

3.1.2. Determination of the level of cord compression

Although imaging studies may define the level of anatomical compression of the cord, this is not necessarily the segment of maximal functional compression and may be incongruent with the clinical signs. Furthermore, imaging may indicate several segments over which the cord is compressed and TMS can be used to define the most important segment of compression, especially in cervical myelopathy (Chan et al., 1998). For instance, in C6 myelopathy, CMCT to first dorsal intersosseus (C8, T1) and extensor digitorum communis (C7) muscles would be prolonged, but that to the deltoid (C5) muscle would be normal. By measuring CMCT to marker muscles for C5 to T1 segments, it was shown that whilst MRI could show multiple levels of compression from C4 to T1, central motor conduction studies correlated better with the clinical findings and localized the affected segment more precisely (Chan et al., 1998). Localization within the thoracic segments has been attempted by recording from multiple levels of paravertebral muscles. However, the multiple segmental innervation and difficulties of volume conduction mitigate against accuracy. Other marker muscles include: trapezius (C2, C3), deltoid (C5), biceps brachii (C6), extensor carpi radialis (C7), abductor digitii minimi (C8), rectus abdominis (T6–T12), quadriceps femoris (L2–L4), tibialis anterior (L4, L5), soleus (S1), anal sphincter or bulbocavernous muscles (S2–S4).

In contrast to the question of the anatomical level of lesion, TMS cannot determine the nature or cause of the lesion. For instance, there was no difference in prolongation of CMCT in cervical cord compression due to extra- and intramedullary lesions (syringomyelia and tumours) (Brunholz and Claus, 1994). In addition, pre-operative CMCT findings have no predictive value for the clinical outcome (Jaskolski et al., 1990).

3.1.3. Differentiating compressive myelopathy from amyotrophic lateral sclerosis (ALS)

A frequent differential diagnosis of myelopathy, especially when accompanied by radiculopathy, is amyotrophic lateral sclerosis (ALS). Both may have a combination of upper and lower motor neuron signs. A strategy is to demonstrate abnormal central motor conduction to muscles innervated by nerves emerging above the foramen magnum, such as the trapezius (Truffert et al., 2000) or the tongue (Urban et al., 1998). If CMCT is abnormal, it cannot be attributed to myelopathy and ALS is much more likely. Further, the slowing in central motor conduction in myelopathy is in the range found in demyelinating disease, whereas delays found in ALS usually amount to no more than a few milliseconds.

In summary, CMCT studies are useful in compressive myelopathy. They can be used to define the segments of maximal functional deficit and may be more sensitive than clinical or radiological studies. TMS is also useful in differentiating compressive myelopathy from ALS.

3.2. Amyotrophic lateral sclerosis (ALS)

Sporadic forms of motor neuron disease (MND) include amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA). Variable in clinical presentation, the diagnosis of MND may be difficult in the early stages. The potential for clinical overlap between MND and treatable immune-mediated motor neuropathies is also integral to the need for accurate early diagnosis of MND. Diagnosis of ALS depends on evidence of upper and lower motor neuron dysfunction. Evidence of lower motor neuron degeneration is obtained readily with EMG (Lambert, 1969). In contrast, evidence of upper motor neuron impairment in MND may be elusive, presumably obscured by the effects of lower motor neuron loss (Triggs and Edgar, 1995). This explains the interest in TMS in MND, with the hope that subclinical upper motor neuron dysfunction could be reliably detected. A large number of papers have been published on the subject (Eisen, 2004).

3.2.1. CMCT and MEP studies in ALS

Determination of the CMCT was the focus of initial investigations of MND patients with TMS. Schrieffer et al. (1989) reported abnormal CMCT in 14 out of 22 ALS patients, occasionally identifying subclinical UMN involvement. Prolonged CMCT and MEPs were the abnormalities observed most frequently. Eisen et al. (1990) reported that responses to TMS were abnormal in nearly all 40 patients examined. The abnormalities were small or unobtainable MEPs and prolonged MEP latencies, but CMCT was normal. Bartousek et al. (1993) also described increased MEP latencies in ALS patients.

The sensitivity of TMS for demonstrating upper motor neuron dysfunction in MND may be improved by the choice of the target muscle. For example, Urban et al. (2001) observed that the sensitivity of TMS in MND patients was increased by adding measurement of conduction to orofacial muscles to more traditional limb muscle recordings. Specificity of TMS in MND may be improved by recording MEPs in the trapezius muscles, since this method allows distinction from the possible pathophysiologic effects of cervical spondylosis (Truffert et al., 2000). Loss of dexterity of finger movements is commonly observed in ALS, which seems attributable mainly to dysfunction of the thumb and index finger. Thus, Weber et al. (2000) demonstrated preferential involvement of the cortical control of the thenar eminence muscles compared to the hypothenar muscles in ALS patients.
Sensitivity of TMS for identifying upper motor neuron dysfunction in MND may also be improved by using the TST (Magistris et al., 1998). Several studies (Rosler et al., 2000; Buhler et al., 2001; Komissarov et al., 2004; Rosler and Magistris, 2004) have reported that TST improved the sensitivity of TMS for detection of UMN dysfunction in MND compared to more traditional TMS methods.

3.2.2. Cortical excitability studies in ALS

Most initial studies of MND patients with TMS described an increase in MT and in some patients MEPs could not be elicited (Schriefer et al., 1989; Eisen et al., 1990; Berardelli et al., 1991a; Triggs et al., 1992). This initial observation has been replicated (Miscio et al., 1999; Schulte-Mattler et al., 1999; Triggs et al., 1999; Urban et al., 2001; de Carvalho et al., 2003b; Attarian et al., 2005). In contrast, Caramia and colleagues first described lower than normal MT in some ALS patients (Caramia et al., 1991). This finding has also been replicated (Kohara et al., 1996; Mills and Nithi, 1997a; Zanette et al., 2002b). The reason for this discrepancy is not entirely clear. It has been suggested that a normal (or even reduced) MT early in the course of illness is consistent with an early phase of cortical hyperexcitability and glutamate-induced excitatory neurotoxicity in ALS (Eisen et al., 1993; Mills and Nithi, 1997a). Some investigators (Eisen et al., 1993), but not others (de Carvalho et al., 2002), have observed that MT correlates with disease duration and increases with disease progression (Triggs et al., 1999; Pouget et al., 2000; Mills, 2003; Attarian et al., 2005).

3.2.3. Cortical inhibition in ALS

Several groups (Uozumi et al., 1991; Prout and Eisen, 1994; Triggs et al., 1999; Zanette et al., 2002a; Mills, 2003; Attarian et al., 2005) have observed that the duration of the silent period elicited with TMS is reduced in ALS patients, particularly early in the course of the illness (Prout and Eisen, 1994; Mills, 2003). However, SP can be elicited in patients in whom MEPs could not be identified, even at maximal stimulator output (Triggs et al., 1992). This observation suggested that some of the inhibitory and excitatory effects of TMS on the motor system are mediated by distinct cortical elements, which may have different susceptibilities to pathophysiological processes in MND. Decreased SICI has also been demonstrated in ALS (Yokota et al., 1996; Enterzari-Taher et al., 1997; Ziemann et al., 1997b; Zanette et al., 2002a).

3.2.4. Combination of TMS parameters

The sensitivity of TMS appears to depend on the severity of upper motor neuron dysfunction in the patients under investigation and the TMS parameters used. For example, Eisen et al. (1990) reported that the sensitivity of TMS approached 100% in 40 patients with clinically definite ALS. In contrast, Claus and colleagues (Claus et al., 1995) reported that TMS measures were abnormal in only about 50% of MND patients. They only included patients without definite UMN signs and they limited their assessment of TMS to CMCT and MEP amplitude. Subsequent clinical studies including other TMS parameters such as MT and SP measurement have found a higher degree of sensitivity in MND patients with only probable UMN signs (ALS-PUMNS). Miscio et al. (1999) reported that TMS was abnormal in 95% of 22 patients with definite ALS and 72% of patients with ALS-PUMNS. Schulte-Mattler et al. (1999) reported that TMS was abnormal in all 19 patients with definite ALS and in 67% of 9 patients with ALS-PUMNS. In a larger clinical series, Triggs et al. (1999) found that TMS was abnormal in 83% of 41 patients with definite ALS, 78% of 18 patients with progressive bulbar palsy, and 75% of 40 patients with ALS-PUMNS. In addition, TMS identified UMN involvement in 27% of 22 patients with pure LMN syndromes. Attarian et al. (2005) also demonstrated the utility of TMS for identifying subclinical UMN involvement in MND patients. These studies illustrate the importance of including assessment of multiple TMS parameters (Triggs et al., 1999). In addition, an electrophysiological index, taking into account CMCT and rest RMT values, was shown to correlate with functional status and to be useful in the follow-up of ALS patients (de Carvalho et al., 2003a). Finally, other TMS methods, such as mapping studies (de Carvalho et al., 1999), may be used in conjunction with evolving imaging technologies to improve diagnosis and increase our understanding of the pathophysiology of this illness.

3.3. Cerebellar disease

3.3.1. Cerebellar stimulation

Inhibition of the motor cortex from cerebellar stimulation is reduced in patients with cerebellar ataxia due to involvement of the cerebellar cortex or the cerebellar efferent pathways to the motor cortex (Di Lazzaro et al., 1994a; Ugawa et al., 1994a,b, 1995a, 1997). Normal suppression of the motor cortex is elicited in patients with non-cerebellar ataxia such as sensory ataxia and lesions of the cerebellar afferent pathways. In two patients with acute cerebellar ataxia, cerebellar inhibition was absent in the acute stage and recovered in parallel with clinical improvement (Matsunaga et al., 2001).

3.3.2. Studies of cortical excitability and measures of CMCT in cerebellar diseases

In patients with cerebellar damage, MT of the contralateral motor cortex is increased (Di Lazzaro et al., 1994b; Cruz-Martinez and Arpa, 1997) and this is due to changes in cortical excitability (Di Lazzaro et al., 1995). Some studies reported normal (Ugawa et al., 1994c) or increased SICI, and reduced ICF (Liepert et al., 1998; Schwenkreis et al., 2002; Restivo et al., 2002; Tamburin et al., 2004) in cerebellar ataxia. Interestingly, different genetic defects may result in different patterns of TMS abnormalities. For example, in patients with inherited spinocerebellar ataxia (SCA), reduced ICF may be more specific for...
SCA2 and SCA3 (Schwenkreis et al., 2002). Similarly, CMCT was found to be prolonged in patients with Friedreich’s ataxia (Cruz-Martinez and Palau, 1997) and SCA types 1, 2 (Restivo et al., 2000) and 6 (Lee et al., 2003). Increase in SICI and reduction of ICF was also observed in patients with cerebellar stroke of the superior or the inferior cerebellar artery’s territories (Liepert et al., 2004). These results in patients with cerebellar lesions are consistent with the effects of cerebellar stimulation on SICI and LICI in normal subjects (Daskalakis et al., 2004). In addition, SP was found to be prolonged in patients with cerebellar disease (Wessel et al., 1996; Oechsner and Zangemeister, 1999; Restivo et al., 2004).

3.4. Dementia

Several groups have documented increased motor cortex excitability in patients with Alzheimer’s disease (AD) (de Carvalho et al., 1997; Pepin et al., 1999; Alagona et al., 2001a; Pennisi et al., 2002; Di Lazzaro et al., 2002b, 2004a; Ferreri et al., 2003). Since spinal excitability, tested with H-reflexes and F-waves, is normal in AD (de Carvalho et al., 1997), this effect is likely to be due to increased excitability of motor cortical circuits in AD. AD patients have decreased rest MT and this finding does not correlate with the degree of reduction in intracortical inhibitory activity such as SAI and SICI (Di Lazzaro et al., 2004a). Moreover, drugs that may enhance cholinergic neurotransmission, such as cholinesterase inhibitor rivastigmine, does not change rest MT (Di Lazzaro et al., 2004a). In AD patients a slight and variable reduction in SICI has been observed in some studies (Liepert et al., 2001; Di Lazzaro et al., 2002b, 2004a), but SICI was reported to be normal in another study (Pepin et al., 1999).

About 70% of patients with a clinical diagnosis of AD have abnormal SAI and this may be related to cholinergic deficit (Di Lazzaro et al., 2002b, 2004a, 2005a). Abnormal SAI has also been reported in dementia with Lewy bodies (Di Lazzaro et al., 2007), a form of dementia that responds to cholinergic medications (Emre et al., 2004). In contrast, SAI was found to be normal in frontotemporal dementia (Di Lazzaro et al., 2006a), non-cholinergic form of dementia.

SAI can be increased within hours of the administration of a single oral dose of rivastigmine (Di Lazzaro et al., 2002b, 2004a, 2005a). Interestingly, abnormal SAI in conjunction with a large increase in SAI after a single dose of rivastigmine is associated with favorable changes in cognitive functions assessed by neuropsychological tests after one year of treatment (Di Lazzaro et al., 2005a). Conversely, a normal SAI, or an abnormal SAI that is not greatly increased by a single oral dose of rivastigmine, is associated with a poor response to long-term treatment. The evaluation of SAI in baseline conditions and after a single dose of acetylcholinesterase inhibitors may help in diagnosing a dysfunction of central cholinergic circuits in demented patients and may be useful in identifying those patients who are likely to respond to long-term treatment with acetylcholinesterase inhibitors.

3.5. Facial nerve disorders

In all idiopathic Bell’s palsy, a greatly diminished (or absent) response to canicular stimulation was observed from the time of symptom onset and lasts for several months (Schriefer et al., 1988; Glockier et al., 1994; Schrader and Schrader, 1995). Surprisingly, this response reduction is present even when clinical function of the nerve and response to cortical stimulation are preserved or restored (Glockier et al., 1994; Schrader and Schrader, 1995). Thus, a focal hypexcitability of the facial nerve to TMS may exist independent of the clinical function of the nerve. Although this focal hypexcitability is not related to conduction block, and does not have a prognostic value in Bell’s palsy (Cocito and De Mattei, 1992; Glockier et al., 1994; Rimpilainen et al., 1997), it can yield helpful diagnostic information. An early examination performed before completion of Wallerian degeneration with an absent response to canicular stimulation is highly suggestive of Bell’s palsy. In contrast, a normal response to canicular stimulation makes the diagnosis of Bell’s palsy unlikely and locates the dysfunction proximal to internal acoustic meatus (Schriefer et al., 1988; Schorpfiehl and Braune, 1997; Straub et al., 2000). A bilateral abnormal response is strongly suggestive of certain etiologies, in particular polyradiculo-neuropathy in disorders such as Guillain–Barré syndrome, Lyme’s disease, HIV infection, or sarcoidosis (Rosler et al., 1995; Kohler et al., 1995). In Lyme’s disease, bilateral involvement was often detected only electrophysiologically, and the timing of occurrence and disappearance of canicular inexcitability differed from that observed in Bell’s palsy (Rosler et al., 1995). An increase of the transosseal conduction time, as well as a simultaneous slowing of conduction on the distal segment with desynchronization of the response, is characteristic of demyelinating neuropathies such as in Guillain–Barré syndrome, with or without accompanying facial weakness (Schriefer et al., 1988; Rosler et al., 1995). In trauma and perioperative lesions of the facial nerve, TMS may be of interest to demonstrate continuity of the nerve (Kotterba et al., 1993; Har-El and McPhee, 2000). Unilateral absence of responses from all three stimulation sites is commonly observed in facial palsies related to herpes zoster and trauma, rarely in severe Bell’s palsy.

The addition of TMS to conventional electrical stimulation of the facial nerve helps to localize the dysfunction of the nerve along its course and contributes to identifying the etiology of peripheral facial nerve palsies. TMS can be used immediately after the occurrence of a facial palsy, since it can disclose conduction deficits and changes in excitability that do not depend on Wallerian degeneration, an advantage over both nerve conduction studies and EMG.
3.6. Multiple sclerosis (MS)

3.6.1. Nosologic sensitivity

The probability that a patient with clinically definite MS (CDMS) has a prolonged CMCT (nosologic sensitivity) is moderately high but varies between studies (56–93%) (Hess et al., 1986, 1987; Barker et al., 1986; Ingram et al., 1988; Rossini et al., 1989; Eisen and Shtybel, 1990; Van Der Kamp et al., 1991; Jones et al., 1991; Mayr et al., 1991; Kandler et al., 1991b; Ravnborg et al., 1992; Michels et al., 1993; Beer et al., 1995). The large variability is explained by many factors but most importantly by the selection and number of target muscles. Sensitivity increases if lower limb muscles are included (Jones et al., 1991; Mayr et al., 1991; Kandler et al., 1991b). Sensitivity is also influenced by the type of MS. Prolongation of CMCT is more pronounced in progressive MS than in relapsing–remitting MS (Filippi et al., 1995; Facchetti et al., 1997; Kidd et al., 1998; Humm et al., 2003). Conventional measurements of MEP amplitude by single-pulse TMS add little to the sensitivity of CMCT measurements (Hess et al., 1987; Kandler et al., 1991b; Ravnborg et al., 1992). However, the TST revealed a frequent occurrence of central conduction failure due to focal central conduction block (Humm et al., 2003, 2004a) or loss of corticospinal axons in the presence of normal CMCT and MEP measures (Magistris et al., 1999). In addition, axial muscles such as the diaphragm, paraspinous muscles, pelvic floor muscles and external sphincter muscles are often affected in MS. The corticospinal projection to these muscles is more difficult to test than limb muscles but TMS measures may reveal abnormalities (Eardley et al., 1991; Urban and Vogt, 1994; Garland et al., 1996; Lagueny et al., 1998; Hashimoto et al., 2000; Miscio et al., 2003; Brostrom et al., 2003).

3.6.2. Reclassification sensitivity

This refers to the percentage of patients with suspected MS who are reclassified by detection of subclinical lesions by TMS measures. The reclassification sensitivity of bilateral CMCT measurements to two upper limb and one lower limb muscle according to the Poser Committee Criteria (Poser et al., 1983) was lower (20%) compared to MRI (60%) or VEPs (29%), but among patients who were not reclassified by MRI, 32% could be reclassified by one of the EP measures (Beer et al., 1995). These data suggest that the utility of EPs may be underestimated in the current recommended diagnostic criteria for MS (McDonald et al., 2001; Polman et al., 2005).

3.6.3. Surrogate marker of motor impairment or disability, and prediction of disease course and treatment monitoring

Most studies indicated a significant correlation between CMCT or TST abnormalities and clinical motor signs or motor disability (Ingram et al., 1988; Van Der Kamp et al., 1991; Britton et al., 1991; Jones et al., 1991; Facchetti et al., 1997; Kidd et al., 1998; Magistris et al., 1999). For example, prolonged CMCTs improve during a relapse treated by high-dose corticosteroids and this correlates with clinical improvement (Kandler et al., 1991a; Salle et al., 1992; La Mantia et al., 1994; Fierro et al., 2002). CMCT measures integrated into a multimodal evoked potential (EP) score revealed close correlations with the Expanded Disability Status Scale (EDSS) (Bednarik and Kadanka, 1992; O’Connor et al., 1998; Fuhr et al., 2001; Comi et al., 2001; Leocani et al., 2006). With longitudinal measurements, changes in EP score correlated with changes in EDSS (O’Connor et al., 1998; Fuhr et al., 2001).

Recent studies reported that a multimodal EP score including CMCT measurements predicted the EDSS of CDMS patients 6–24 months later (Fuhr et al., 2001; Leocani et al., 2006; Kallmann et al., 2006; Feuillette et al., 2007). If confirmed, this may be important information because it may influence therapeutic decisions. No data is available yet for the positive predictive value of TMS measures for conversion to CDMS in patients who do not fulfill the current diagnostic criteria for CDMS (McDonald et al., 2001; Polman et al., 2005).

3.6.4. Other TMS measures

A number of other TMS measures have also been applied in MS patients but their clinical utility requires further study. These include MEP onset latency variation (Britton et al., 1991; Fujihara and Miyoshi, 1998), CMCT prolongation and MEP attenuation depending on stimulus frequency (Claus et al., 1992; Nielsen, 1997) or after fatiguing exercise (Liepert et al., 1996; Schubert et al., 1998; Petajan and White, 2000; White and Petajan, 2004; Liepert et al., 2005a), reduced SICF (Ho et al., 1999), reduced SICI (Caramia et al., 2004), prolonged transcallosal conduction time (Boroojerdi et al., 1998) and iSP duration (Boroojerdi et al., 1998; Hoppner et al., 1999; Schmieler et al., 2000). In particular, a strong correlation was found between EDSS scores and a composite TMS index (based on CMCT and iSP duration) in a large series of more than 100 patients, at least with progressive forms of MS (Schmieler et al., 2002).

In summary, TMS measures (CMCT, TST) have moderately high nosologic sensitivity and correlate better than MRI with motor impairment and motor disability both cross-sectionally and longitudinally. Subclinical corticospinal tract lesions may be detected by TMS.

3.7. Movement disorders

TMS studies have provided valuable information of the pathophysiology of movement disorders (Hallett, 2003), but currently only has a limited role as a diagnostic test. Several TMS techniques and measures commonly used in research and clinical practice will be discussed.

3.7.1. MT and CMCT

In Parkinson’s disease (PD), most studies found no change in MT but rest MT may be decreased in very rigid
patients (Cantello et al., 1991) and active MT may be increased in very bradykinetic patients (Ellaway et al., 1995). MT was found to be reduced in patients with obsessive compulsive disorder and comorbid tics (Greenberg et al., 2000). In other movement disorders, such as dystonia, Huntington’s disease (HD), myoclonus, essential tremor (ET), MT is normal.

Central motor conduction time is normal in PD, dystonia, HD, corticobasal degeneration (CBD), ET, myoclonus, and Tourette syndrome (TS), but can be prolonged in patients with multisystem atrophy (MSA), progressive supranuclear palsy (PSP) (Abbruzzese et al., 1991, 1997b), or mutations of the Parkin gene (De Rosa et al., 2006). Therefore, TMS may have a role in demonstrating CMCT abnormalities in patients with parkinsonism plus syndromes in whom pyramidal signs are equivocal, although the sensitivity in this situation is not known.

3.7.2. Measures of cortical inhibition and facilitation

3.7.2.1. SICI and LICI. In PD patients, SICI is reduced at rest and improved with dopaminergic medications (Ridding et al., 1995a), deep brain stimulation (DBS) of the subthalamic nucleus (Cunic et al., 2002) or low-frequency motor cortex rTMS (Lefaucheur et al., 2004). However, reduced SICI may occur only at certain CS intensities and could be due to increased facilitation rather reduced inhibition (MacKinnon et al., 2005). Active SICI appears unchanged (Berardelli et al., 1996; Chen et al., 2001). Some studies found increased LICI and dopaminergic medications restored it to normal levels (Berardelli et al., 1996), although other studies found decreased LICI that was also normalized by dopaminergic medications (Pierantozzi et al., 2001). Reduced SICI and increased LICI may be related to the finding that LICI inhibits SICI (Sanger et al., 2001).

In patients with upper limb dystonia, both task-specific (Butefisch et al., 2003) and rest SICI are reduced (Ridding et al., 1995b; Filippovic et al., 1997). Reduced rest SICI is not site-specific and was observed on both the affected and unaffected sides in patients with focal arm dystonia (Ridding et al., 1995b), and in hand muscles in patients with cervical dystonia (Kanovsky et al., 2003) and blepharospasm (Sommer et al., 2002). Rest SICI is transiently restored by botulinum toxin injection in the dystonic muscles (Filippovic et al., 1997), but the finding was not confirmed in a subsequent study on pure writer’s cramp (Borojordi et al., 2003). SICI is also reduced in cervical dystonia (Kanovsky et al., 2003), blepharospasm (Sommer et al., 2002), DOPA responsive dystonia (Huang et al., 2006), and in asymptomatic carriers of the DYTI gene mutation (Edwards et al., 2003). One study found reduced active LICI in patients with writer’s cramp (Chen et al., 1997b). However, another study found increased LICI using a slightly different paradigm in patients with different types of dystonia (Rona et al., 1998).

In HD, some researchers reported abnormal SICI and LICI (Tegenthoff et al., 1996; Abbruzzese et al., 1997a), but others found normal motor cortical excitability (Priori et al., 1994b; Hanajima et al., 1996). SICI is also reduced in patients with TS and correlated with motor hyperactivity, whereas tic occurrence is related to SP shortening (Greenberg et al., 2000). In contrast, patients with ET (Romeo et al., 1998) and patients with primary writing tremor (Modugno et al., 2002) have normal SICI and LICI.

Several studies reported markedly reduced SICI or SICI turned into facilitation in CBD and suggested that SICI could be a diagnostic test (Okuma et al., 2000; Frasson et al., 2003). Another study also found reduced SICI in CBD but the degree of abnormalities is similar to other parkinsonian syndromes such as MSA, PSP and PD (Kuhn et al., 2004). Both SICI and LICI were found to be abnormal in psychogenic dystonia (Espay et al., 2006). Therefore, testing of cortical inhibition may not distinguish between organic and psychogenic disorders.

3.7.2.2. ICF. ICF has been less widely studied than SICI and LICI. In some studies, ICF was reduced in advanced PD patients (Dauper et al., 2002; Bares et al., 2003; Lefaucheur et al., 2004). ICF was found to be normal or slightly increased in patients with dystonia (Sommer et al., 2002, HD (Abbruzzese et al., 1997a) or ET (Romeo et al., 1998).

3.7.2.3. SP. The SP is shortened in patients with PD (Cantello et al., 1991), especially at high stimulation intensity (Valls-Sole et al., 1994; Siebner et al., 2000). SP can be prolonged by dopaminergic medications (Priori et al., 1994a), surgical lesions of the internal globus pallidus (Straffella et al., 1997; Young et al., 1997) and rTMS of motor cortex (Siebner et al., 2000; Lefaucheur et al., 2004). In PD patients on dopaminergic medications, SP may be longer than in controls (Ridding et al., 1995a; Chen et al., 2001). In these patients, DBS of the internal globus pallidus reduces the SP (Chen et al., 2001).

A shortened SP is also observed in patients with dystonia involving hand (Filippovic et al., 1997) or facial muscles (Curra et al., 2000), and was not normalized by botulinum toxin injection (Allam et al., 2005). The SP is even shorter when dystonia affects upper and lower facial muscles concurrently than when dystonia affects upper or lower facial muscles alone. In patients with HD, the SP may be slightly shortened (Eisen et al., 1989) or abnormally long and variable (Tegenthoff et al., 1996; Modugno et al., 2001). This difference may be partly explained by the clinical form of HD (Tegenthoff et al., 1996) and the technique used to collect SP traces (Modugno et al., 2001). SP shortens with functional decline in HD and could be a marker of disease progression (Lefaucheur et al., 2006).

The SP is normal in ET and task-specific tremor, but shortened in cortical myoclonus (Brown et al., 1996; Inghilleri et al., 1998) and in TS (Greenberg et al., 2000).

3.7.2.4. iSP and IHI. Clinicopathologic evidence suggests differential involvement of cortex and corpus callosum in
various disorders presenting with a parkinsonian syndrome. One study found three out of seven patients with CBD had increased iSP threshold and reduced iSP duration, and these findings correlate with atrophy of the corpus callosum on MRI (Trompetto et al., 2003). In a series of 25 patients with parkinsonism, the iSP was abnormal in all patients with CBD and PSP, whereas it was intact in all patients with PD and MSA. MRI morphometry revealed that patients with CBD and PSP exhibited significant atrophy of the middle part of the corpus callosum compared to controls (Wolters et al., 2004). iSP measurements may be a useful clinical test to differentiate patients with different parkinsonian syndromes. In patients with focal hand dystonia, iSP is prolonged indicating increased transcallosal inhibition (Niehaus et al., 2001).

In PD, IHI is reduced in patients without mirror movement, especially at long ISIs of 20–50 ms (Li et al., 2007). IHI is also reduced in patients with cortical myoclonus (Brown et al., 1996), which may play a role in the spread of myoclonic activities.

3.7.2.5. SAI and LAI. In PD, SAI was found to be normal in patients off medications but administration of dopaminergic medication led to reduced SAI (Sailer et al., 2003). In a study that included PD patients with dementia, SAI was found to be increased whereas PSP patients had normal SAI (Nardone et al., 2005). In contrast, patients with MSA with parkinsonian features showed reduced SAI with direct stimulation (Mascia et al., 2005). Therefore, there may be different changes in cholinergic circuit in different parkinsonian disorders. LAI is reduced in PD and is unaffected by dopaminergic medications (Sailer et al., 2003). Subthalamic nucleus deep brain stimulation normalized both SAI and LAI in PD patients (Sailer et al., 2007). Other studies also found altered sensorimotor integration in PD (Delwaide and Olivier, 1990; Rossini et al., 2006; Lewis and Byblow, 2002; Sailer et al., 2003; Tamburin et al., 2003). In patients with focal dystonia, LAI is diminished or absent whereas SAI is normal (Abbruzzese et al., 2001). Other studies also showed altered responses to sensory stimuli (Rosenkranz et al., 2000; Siggelkow et al., 2002) and surround inhibition (Tamburin et al., 2002; Sohn and Hallett, 2004) in dystonia. Sensorimotor integration is also altered in cortical reflex myoclonus (Cantello et al., 1997).

3.7.3. Cerebellar stimulation

In essential tremor, cerebellar efferent pathway was found to be normal, suggesting that tremor rhythm is likely transmitted by cerebellar afferent inputs (Pinto et al., 2003). Thalamic deep brain stimulation increases the transmission through the cerebellothalamocortical pathway, suggesting that deep brain stimulation may activate rather than inhibit the target area (Molnar et al., 2004). Orthostatic tremor was reset by cerebellar stimulation but not by cortical stimulation (Wu et al., 2001). The authors concluded that the oscillator for orthostatic tremor involved the cerebellum or brainstem.

3.7.4. Summary of TMS studies in movement disorders

TMS has been very useful in understanding the pathophysiology of many movement disorders. Testing excitatory and inhibitory circuits in the motor cortex proved highly sensitive for disclosing abnormalities in the early stages of various diseases. However, they are often not useful in clinical practice because there is considerable overlap between values obtained in controls and patients, and the findings are not specific to a disease. For example, reduction of SICI and SP observed in some movement disorders are also seen in other neurological and psychiatric disorders. In some conditions, reduction in cortical inhibition may represent a compensatory response rather than a direct effect of the disease, or may represent a predisposing factor for the disease. TMS may help to establish UMN involvement by demonstrating abnormal CMCT in patients with atypical parkinsonism and equivocal pyramidal signs. Testing of transcallosal inhibition with the iSP may be used to distinguish between different parkinsonian syndromes, particularly in patients with CBD. Absence of SICI or SICI turning into facilitation may also be suggestive of CBD, but these observations need confirmation.

3.8. Stroke

In the first week after stroke, the presence of MEPs in the paretic limb in response to the stimulation of the affected hemisphere predicts good recovery (Heald et al., 1993; Catano et al., 1995; D’Olhaberriague et al., 1997; Escudero et al., 1998; Delvaux et al., 2003; Hendricks et al., 2003). Conversely, absence of MEPs in the paretic limb with concomitantly increased MEP amplitude in the contralateral limb in response to the stimulation of the unaffected hemisphere may predict poor recovery (Trompetto et al., 2000). The imbalance of motor cortex excitability towards hyperexcitability of the unaffected hemisphere parallels the severity of the lesions and diminishes with post-stroke functional recovery (Cicinelli et al., 1997; Traversa et al., 1998; Trompetto et al., 2000; Delvaux et al., 2003). The presence of ipsilateral MEPs in the paretic limb from stimulation of the unaffected hemisphere is usually associated with poor recovery (Turton et al., 1996; Netz et al., 1997; Gerloff et al., 2006), with possible exception of ipsilateral MEPs elicited by premotor stimulation (Carmia et al., 2000). The occurrence of ipsilateral MEPs in the normal hand after premotor stimulation of the affected hemisphere may also be associated with good recovery (Alagona et al., 2001b). These results are consistent with other studies suggesting that the premotor cortex contributes to functional recovery after stroke (Delvaux et al., 2003; Fridman et al., 2004).

The pattern of changes in cortical excitability following stroke, including MT, stimulus–response recruitment curve, and measures of cortical inhibition, appears to correlate with lesion location and motor performance (Liepert et al., 2005b). Regarding measures of cortical inhibition, SP duration is increased after subcortical stroke (Ahonen et al., 2001).
et al., 1998; Liepert et al., 2005b), except in patients with post-stroke movement disorder or epilepsy (Kessler et al., 2002). In contrast, SICI is reduced in the affected hemisphere in the acute phase of a motor cortical stroke (Liepert et al., 2000b, 2005b; Manganotti et al., 2002; Niehaus et al., 2003) and remains decreased thereafter, regardless of functional recovery. SICI also tends to be initially reduced in the unaffected hemisphere, but subsequently returns to normal values (Shimizu et al., 2002; Butefisch et al., 2003) or may be greater than in the affected hemisphere in patients with good recovery (Manganotti et al., 2002; Cicinelli et al., 2003). It has been proposed that stronger intracortical inhibition leads to reduced activity in the unaffected hemisphere, resulting in increased activity of the affected hemisphere, thereby promoting recovery. The role of competitive inhibition between both hemispheres is also supported by the loss of IHI from the affected to the unaffected hemisphere that could increase the excitability of the unaffected hemisphere in acute cortical stroke (Boroojerdi et al., 1996; Shimizu et al., 2002; Niehaus et al., 2003). Furthermore, in chronic stroke, IHI from the unaffected to the affected hemisphere is increased just before movement onset in the paretic limb (Murase et al., 2004; Duque et al., 2005). Thus, bilateral alterations of cortical excitability parallel the degree of impairment and the course of post-stroke recovery.

Finally, TMS can be used to demonstrate spatial cortical reorganization after stroke. Both mediolateral and anteroposterior shifts in motor cortex representation of the affected limbs correlated with the motor outcome following neurorehabilitation (Thickbroom et al., 2004). The mechanisms underlying functional brain reorganization associated with constraint-induced movement therapy (CIMT) were characterized by investigations using TMS and functional imaging (PET/MRI) (Chouinard et al., 2006; Hamzei et al., 2006). In particular, improvement in motor performance after CIMT correlates with enlargement in TMS motor cortical map (Liepert et al., 2000a) and with changes in cortical excitability in the lesioned hemisphere (Liepert, 2006).

3.9. Epilepsy

Changes in cortical excitability in patients with epilepsy varied with the type of epilepsy, the time of testing (ictal vs. interictal), and with antiepileptic drug intake (Tassinari et al., 2003). A reduced MT indicating cortical hyperexcitability was observed only in subsets of untreated patients with idiopathic generalized epilepsy (IGE) (Reutens and Berkovic, 1992; Reutens et al., 1993). In contrast, MT is usually increased in treated patients with IGE or partial epilepsy, likely due to antiepileptic treatment. MT is also increased in the 48 h after a generalized seizure (Delvaux et al., 2001). Finally, interhemispheric difference in MT can be exaggerated in patients with asymmetric motor seizures (Agulha et al., 2000), supporting a role for interhemispheric imbalance of cortical excitability in mediating lateralized ictal events.

Prolonged SP was reported in patients with untreated IGE (Maedonell et al., 2001) and in patients with partial motor seizures, whether the lesion was located within or outside the primary motor cortex (Classen et al., 1995; Cincotta et al., 1998, 2000). These findings may be due to spread of epileptic hyperexcitability to corticospinal inhibitory networks, or alteration in motor control independent of epilepsy. However, since the SP duration increases with the risk of seizure, it probably represents a compensatory interictal phenomenon (Cincotta et al., 2002).

Within 48 h after a generalized tonic–clonic seizure, ICF is reduced whereas SICI is normal (Delvaux et al., 2001), which may represent a protective mechanism against spread or recurrence of seizures. In contrast, ICF is normal and SICI is reduced in patients with progressive or juvenile myoclonic epilepsy (Manganotti et al., 2000, 2001, 2004). SICI could be reduced in the unaffected more than the affected hemisphere in patients with partial motor epilepsy (Werhahn et al., 2000). LICI was also found to be reduced in patients with progressive myoclonic epilepsy (Valzania et al., 1999) and in patients with IGE (Brodtmann et al., 1999). In addition, transcallosal inhibition may also be reduced, contributing to the spreading of epileptic activities (Brown et al., 1996).

Sensorimotor integration is altered in cortical reflex myoclonus and progressive myoclonic epilepsy, indicating a possible spread of an abnormal hypersynchronous discharge from somatosensory to motor networks at the level of the primary cortices or at a subcortical site (Cantello et al., 1997; Manganotti et al., 2001). Conversely, sensorimotor integration remains normal in juvenile myoclonic epilepsy (Manganotti et al., 2004), probably related to the finding that sensory stimuli evoke myoclonus and “giant” somatosensory evoked potentials in progressive but not in juvenile myoclonic epilepsy (Manganotti et al., 2001, 2004). Finally, cortical excitability studies may be applied to assess the mechanisms of action of antiepileptic treatments, either with drugs (Ziemann et al., 2004) or with implanted brain stimulation (Molnar et al., 2006).

3.10. Migraine and neuropathic pain

In patients with migraine, TMS has been used to test visual and motor cortex excitability. Increased MT in migraineurs was reported in some studies (Afra et al., 1998) but not in other studies (Bohotin et al., 2003; Gunaydin et al., 2006). In patients with migraine with or without aura, one study reported a shortened SP in hand muscles (Afra et al., 1998; Werhahn et al., 2000; Ozturk et al., 2002; Gunaydin et al., 2006), but the SP in facial muscles was reduced (Curra et al., 2007). Conversely, in patients with chronic migraine prolonged SP was reported (Ozturk et al., 2002). In patients with migraine with or without aura, SICI tested between attacks was normal (Afra et al., 1998), whereas in another group of migraineurs with aura SICI was reduced with normal ICF (Brighina et al., 2005).
Table 1
Summary of clinical diagnostic utility of different TMS techniques

<table>
<thead>
<tr>
<th>Condition/disease</th>
<th>Demonstrated utility</th>
<th>Potential utility</th>
</tr>
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<tbody>
<tr>
<td>Myelopathy</td>
<td>CMCT/TST</td>
<td>Cerebellar stimulation, CMCT</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Combination of CMCT/TST, MT, SP, SICI</td>
<td>SAi</td>
</tr>
<tr>
<td>Cerebellar diseases</td>
<td></td>
<td>TMS of facial nerve and motor cortex</td>
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<tr>
<td>Dementia</td>
<td></td>
<td>IHI/SP</td>
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<tr>
<td>Facial nerve disorder</td>
<td></td>
<td>SICI, CMCT/IHI/SP (differential diagnosis of parkinsonian syndromes)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>CMCT/TST</td>
<td>Ipsilateral and contralateral MEP recordings, IHI, IHI</td>
</tr>
<tr>
<td>Movement disorders</td>
<td></td>
<td>Cortical excitability studies</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>Phosphene threshold, facial SP</td>
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<tr>
<td>Epilepsy</td>
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<td>Cortical excitability studies</td>
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<tr>
<td>Migraine</td>
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<td>Chronic pain</td>
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The visual cortex may be hyperexcitable, in particular in migraine with aura, as suggested by reduced threshold for occipital TMS to induce phosphenes in migraineurs (Aurora et al., 1998; Battelli et al., 2002; Young et al., 2004; Gerwig et al., 2005; Gunaydin et al., 2006) using single or paired pulses. However, other authors found that this threshold was increased in the interictal period (Bohotin et al., 2003) or had increased variability over time (Antal et al., 2006).

Reduction in SICI or LICI in the motor cortex corresponding to the painful side has been reported in patients with chronic pain due to fibromyalgia (Salerno et al., 2000), complex regional pain syndrome (Schwenkreis et al., 2003; Eisenberg et al., 2005) and neuropathic pain due to peripheral or central nervous system lesion (Lefaucheux et al., 2006).

4. Summary of the clinical diagnostic utility of TMS

Table 1 shows the conditions in which different TMS techniques have demonstrated or potential diagnostic utility. The designation of demonstrated utility is based on multiple studies involving a large number of patients. The designation of potential utility is based on promising results but usually from a small number of studies. Further studies with more patients are needed to confirm these observations and establish the sensitivity and specificity of these measures.

References


