ABSTRACT: Transcranial magnetic stimulation (TMS) is a safe, noninvasive, and painless way to stimulate the human motor cortex in behaving human subjects. When it is applied as a single-pulse, measurements such as central conduction time, motor threshold, silent-period duration, recruitment curve, and mapping of muscle representation can be determined. Paired-pulse TMS is a useful way to examine cortical excitability. Single and paired-pulse TMS have been applied to study plasticity following amputation and cortical excitability in patients with dystonia. Another form of TMS is repetitive TMS (rTMS), with stimuli delivered repeatedly to a single scalp site. High-frequency rTMS can be used to transiently inactivate different cortical areas to study their functions. rTMS can also modulate cortical excitability. At stimulus frequencies higher than 5 Hz, rTMS increases cortical excitability, and stimulation around 1 Hz reduces cortical excitability. Modulation of cortical excitability by rTMS has therapeutic potential in psychiatric and neurological disorders.
 Muscle Nerve **Supplement 9:**S26–S32, 2000

STUDIES OF HUMAN MOTOR PHYSIOLOGY WITH TRANSCRANIAL MAGNETIC STIMULATION

ROBERT CHEN, MB, BChir, MSc, FRCP(C)

Division of Neurology and Playfair Neuroscience Unit, Toronto Western Research Institute, University of Toronto, Toronto, Ontario, Canada

Since the 19th century, neurophysiologists and neurologists have used brain stimulation to study cortical function. The first brain stimulation studies performed by Fritsch and Hitzig and by Ferrier established the concept of functional localization and contralateral control of movements. In the early 20th century, Sherrington and Penfield performed detailed mapping studies, leading to the well-known homunculus representation of the motor cortex.

The first successful motor cortex stimulation in an unanesthetized human through the intact skull was reported in 1980 with transcranial electrical stimulation (TES).[38] However, TES is considered painful by most subjects and is, therefore, not widely utilized. Transcranial magnetic stimulation (TMS) was first described in 1985.[2] Because the magnetic fields pass through the scalp and skull virtually unattenuated, the procedure is painless and has gained widespread acceptance as the method for noninvasive brain stimulation.

Abbreviations: EEG, electroencephalography; GABA, γ-aminobutyric acid; I wave, indirect wave; ICF, intracortical facilitation; ISI, interstimulus interval; LICI, long interstimulus interval intracortical inhibition; MEG, magnetoencephalography; MEP, motor-evoked potential; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SICI, short interstimulus interval intracortical inhibition; SP, silent period; TES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation

Key words: excitability; human; magnetic stimulation; motor cortex; plasticity

Correspondence to: R. Chen, Toronto Western Hospital, EC8-025, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8; e-mail: robert.chen@uhn.on.ca

TRANSCRANIAL MAGNETIC STIMULATION

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. Relatively focal stimulation can be achieved by a figure-of-eight coil. Coregistration of scalp positions with magnetic resonance images showed that the coil position that produces the largest motor-evoked potential (MEP) overlies the primary motor cortex.[18]

STUDIES OF THE MOTOR SYSTEM WITH TMS

The different ways that TMS can be used to study the human motor system are reviewed. Some of the author's works are used as examples of the different applications of TMS. Because the principles and applications of single and paired-pulse TMS are quite

different from that of repetitive TMS (rTMS), these are described separately.

SINGLE-PULSE TMS

Single-pulse TMS can measure central conduction time and corticospinal excitability and map muscle representations in the motor cortex.

Central Conduction Time. Central conduction is calculated by the subtraction of the peripheral conduction time (obtained by spinal magnetic or electrical stimulation or by F-wave measurement) from the MEP latency in the target muscle. Central conduction time is often delayed in diseases such as multiple sclerosis, stroke, and amyotrophic lateral sclerosis.[48]

Motor Threshold (MT). MT refers to the lowest TMS intensity capable of eliciting a small MEP (usually 50 μV). It provides information about a central core region of neurons in the muscle representation.[30] MT is lower for the activation of intrinsic hand muscles compared with proximal arm, lower limb, and truncal muscles.[14] This is likely related to differences in the strength of corticospinal projection. In addition, MT is increased by drugs that block voltage-gated sodium channels,[13,63] but it is not affected by drugs that alter γ-aminobutyric acid (GABA)[63] or glutamate transmission.[36,61] Thus, MT likely reflects neuronal membrane excitability.

MEP Amplitude. The MEP amplitude or area can be used to examine corticospinal excitability. For example, TMS delivered before and after voluntary movements showed that corticospinal excitability started to increase about 100 ms before EMG onset and remained elevated for about 160 ms after EMG offset but was depressed from about 500 to 1,000 ms after the offset of voluntary EMG.[16] These changes correlate well with findings in electroencephalography (EEG)[44] and magnetoencephalography (MEG)[50] studies. However, MEP amplitude alone cannot distinguish among changes in cortical, subcortical, and spinal excitability.

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.[30] Recruitment curves are likely related to the strength of corticospinal projections and are generally steeper in muscles with a low MT, such as intrinsic hand muscles.[14] The slope of the 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).[5]

Silent-Period (SP) Duration. The SP refers to the duration of the interruption of voluntary motor activity after TMS. Inhibition in the first part of the SP is at least in part due to spinal mechanisms, whereas the late part of the SP is largely due to cortical mechanisms.[12,23] The SP was found to be abnormal in some diseases, such as Parkinson's disease,[45] stroke, and dystonia.[15]

Mapping of Muscle Representation. Mapping is performed by stimulation at a number of different scalp positions with a focal figure-of-eight coil. The number of excitable scalp positions, the location of the optimal position for stimulation, and the center of gravity (an amplitude-weighted representative position on the motor map) can be determined. Motor maps are affected by the location and excitability of the motor representation[46] and are altered after stroke[17] and hemispherectomy.[3]

PAIRED-PULSE TMS

Paired-pulse TMS techniques are useful ways to assess cortical excitability. Several different techniques have been described.

Short Interstimulus Interval Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF). This is the most widely used paired-pulse technique and involves a subthreshold conditioning stimulus followed by a suprathreshold test stimulus.[35] The test response is inhibited at interstimulus intervals (ISIs) of 1–5 ms and is facilitated at ISIs of 8–30 ms. The inhibition and facilitation occur in the motor cortex rather than in subcortical structures.[35,39] SICI can be enhanced and ICF can be suppressed by drugs that increase $GABA_A$ activity[63] and by antiglutaminergic drugs,[36,61] whereas ion-channel blocking drugs have no effect on these parameters.[13,63] Thus, SICI and ICF may provide information on $GABA_A$ and glutaminergic systems in the motor cortex.

Long Interstimulus Interval Intracortical Inhibition (LICI). The difference between this technique and the aforementioned technique is that the conditioning pulse is suprathreshold rather than subthreshold and longer ISIs are used. The test MEPs are facilitated at ISIs of 20–40 ms and inhibited at longer ISIs

(≤200 ms).[58] This form of inhibition is also associated with reduced motor cortex excitability[12] and may be mediated by $GABA_B$ mechanisms.[52,60]

Indirect-Wave (I-Wave) Facilitation. This third paired TMS technique involves a suprathreshold first stimulus and a subthreshold second stimulus[64] or two near-threshold stimuli[56] at very short ISIs. MEP facilitation was observed at ISIs of 1.1–1.5, 2.3–2.7, and 3.9–4.5 ms for both arm and leg representations.[9] The timing of facilitation corresponds to the interpeak intervals of the corticospinal waves induced by TMS. The facilitation likely reflects an interaction between circuits responsible for the production of the indirect (I) corticospinal waves. I-wave facilitation is reduced by drugs that enhance GABAergic function, whereas sodium channel blockers had no effect.[65] This method is a promising way for investigating the pathophysiology of neurological disorders.

EXAMPLES OF STUDIES OF CORTICAL EXCITABILITY WITH SINGLE AND PAIRED TMS

Two examples are described to illustrate the use of single and paired TMS.

Motor Reorganization Following Amputation. Animal and human studies have shown that the motor system undergoes reorganization after peripheral nerve lesions and amputation, but the site and mechanisms of these plastic changes, especially in humans, are not known. In lower limb amputees, we found that the MT for TMS was significantly lower for the quadriceps femoris muscle on the amputated side compared with the same muscle on the intact side, whereas the MT for TES was similar for the two sides.[8] At threshold intensities, TMS activates corticospinal neurons predominately transynaptically (via interneurons), whereas TES predominately activates the pyramidal axons directly.[49] Therefore, the differences in the MT for TMS and TES in lower limb amputees suggests that the motor reorganization mainly occurred in the motor cortex.[8] Similarly, the percentage of the motoneuron pool recruited by TMS at maximum stimulator output was greater on the amputated than on the intact side, whereas there was no significant difference between the two sides with maximum TES or spinal electrical stimulation. One possible explanation for these changes involves the sodium channel, which has been implicated in other forms of plasticity.[31] Other mechanisms, such as long-term potentiation or axonal sprouting, may also be involved.[21]

Paired TMS studies demonstrated that SICI was also reduced on the amputated side compared with the intact side and with normal subjects (Fig. 1).[8] The reduced SICI suggests that reduction in GABAergic inhibition may be one of the mechanisms involved in motor reorganization. This is consistent with animal studies that showed that the reduction of GABAergic inhibition can unmask latent synapses,[32] and a decrease in GABA-containing neurons or its synthetic enzyme glutamic acid decarboxylase occurs after deafferentation of the somatosensory[59] and visual cortices.

Insight into the time course of plastic changes in the motor cortex may be obtained by a comparison of the findings following amputation, a model of long-term plasticity, with the findings following ischemic nerve block, a model of short-term plasticity. Ischemic nerve block led to a reduction in SICI but no change in MT.[62] Thus, modulation of GABAergic inhibition may occur after both short-term and long-term deafferentation, whereas changes in MT may require longer lasting deafferentation. These findings are compatible with the hypothesis that reduction in GABAergic inhibition induces a permissive state that allows long-term changes to occur.[22]

Evaluation of Cortical Inhibition in Dystonia. Dystonia is characterized by sustained muscle contraction, causing prolonged movements and abnormal posture. Patients with focal or task-specific dystonia are

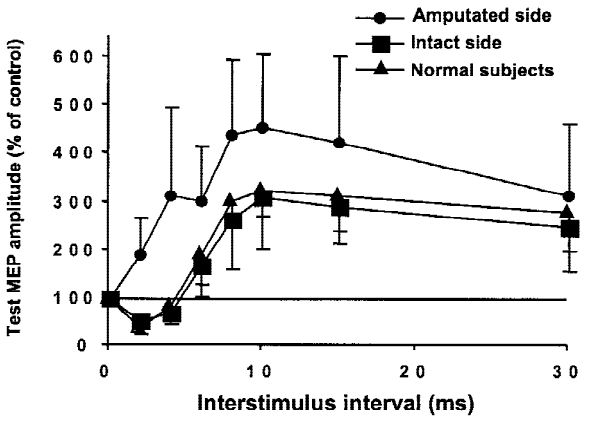

FIGURE 1. Paired TMS study in lower limb amputees. The first (conditioning) pulse was subthreshold, and the second (test) pulse was suprathreshold. An ISI of 0 represents the MEP amplitude of the test pulse alone, which is defined as 100%. Each point represents an average of 11 subjects for the amputated side, 7 subjects for the intact side, and 7 normal subjects. Each error bar represents one standard error of the mean. On the intact side and in normal subjects, there was inhibition at ISIs of 2 and 4 ms and facilitation at ISIs of 6 to 30 ms. On the amputated side, there was more facilitation than on the intact side at all ISIs. This figure was modified from Chen et al.[8]

usually symptomatic only when they perform certain skilled tasks, such as writing (writer's cramp). Previous studies showed reduced inhibition at the spinal cord[40] and brainstem[20] levels. SICI was found to be reduced in patients with focal dystonia tested at rest.[47]

To further explore the excitatory and inhibitory mechanisms in the motor cortex in writer's cramp patients, we tested LICI with paired suprathreshold conditioning and test pulses during rest and muscle activation.[15] In the symptomatic hemisphere, the first stimulus resulted in less inhibition of the response to the second stimulus in writer's cramp patients compared with age-matched controls at ISIs of 50–180 ms during voluntary muscle contraction (Fig. 2). There was no difference between patients and normal subjects in the asymptomatic hemisphere during both rest and active conditions and in the symptomatic hemisphere at rest. The SP was also reduced on the symptomatic side but not on the asymptomatic side. Thus, the inhibitory effects induced by magnetic stimulation in the motor cortex are reduced in writer's cramp patients but only on the symptomatic side during muscle activation. The reduced inhibition may relate to the overflow of muscle activity that characterizes this condition.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

rTMS can be used to transiently inactivate different cortical areas to investigate their functions and to change cortical excitability. These applications are discussed separately.

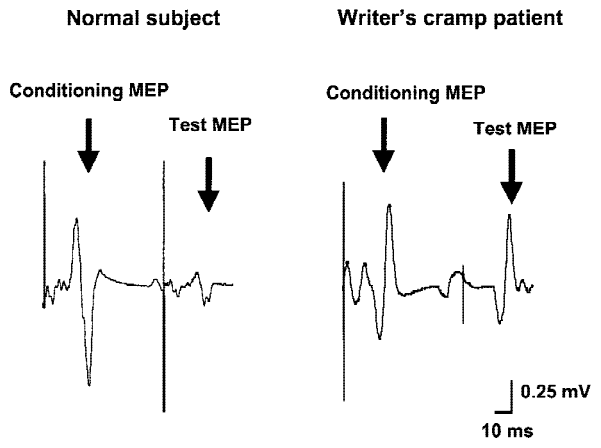

FIGURE 2. Paired TMS study in writer's cramp patient. Representative records of single trials at an ISI of 60 ms from a normal subject and a writer's cramp patient are shown. The first (conditioning) and second (test) pulses were identical and suprathreshold (110% of the MT). The test MEP is much less inhibited in the patient than in the normal subject. This figure was modified from Chen et al.[15]

DISRUPTION OF TASK PERFORMANCE BY rTMS

Appropriately timed single TMS pulses can disrupt cortical functions. For example, stimulation of the occipital cortex can suppress visual perception,[1] and stimulation of the sensory cortex stimulation can attenuate detection of sensory stimuli.[19] To disrupt more complex functions, a train of pulses at a high frequency (rTMS) is necessary. For example, rTMS of the speech area can cause speech arrest,[41] and when applied over the frontal cortex, it may lead to recall deficits.[28]

We performed a series of experiments to examine the role of the motor cortex and supplementary motor area in finger-movement sequences of different complexities.[7,11,26,27] Normal subjects were trained to play unimanual finger sequences on an electronic piano. Each sequence consisted of 16 notes, played to the 2-Hz beat of a metronome. After the first 4 notes, rTMS was applied to various scalp locations for approximately 2 s. With rTMS of the contralateral motor cortex, the stimulus intensities required to disrupt task performance were lower for the complex sequence than for the simple sequence. These findings suggest that the human motor cortex plays a greater role in the performance of complex finger movements compared with simple finger movements. Thus, the contralateral primary motor cortex not only acts as an executive area but also contributes to movement-sequence organization.[26] We also examined the role of the ipsilateral motor cortex.[11] rTMS of both the right and left motor cortices induced timing errors of the ipsilateral hand. There were more errors in the complex sequence than in the simple sequence and in the left hand than in the right hand. These results suggest that the ipsilateral motor cortex is involved in fine finger movements. The left hemisphere appears to play a greater role in the timing of ipsilateral complex sequences than the right hemisphere and may be more involved in the processing of complex motor programs. These findings are consistent with ipsilateral motor deficits in patients with hemispheric lesions[33] and the activation of the ipsilateral motor cortex with finger movements in functional imaging studies, particularly with more complex sequences.[34]

We also studied the effects of inactivation of the supplementary motor area.[27] rTMS of the supplementary motor area induced errors in the complex sequence but not in the simple sequence. More importantly, the errors occurred about 1 s later than stimulation over the primary motor cortex. There-

fore, the supplementary motor area appears to play a critical role in the organization of forthcoming movements in complex motor sequences that are rehearsed from memory and fit into a precise timing plan, in keeping with results from nonhuman primates.[54]

CHANGES IN CORTICAL EXCITABILITY INDUCED BY rTMS

rTMS can modulate cortical excitability, depending on the frequency of stimulation. At stimulus intensities greater than the MT, high-frequency rTMS (>5 Hz) increases cortical excitability,[43] whereas low-frequency (~ Hz) rTMS decreases cortical excitability.[6]

High-Frequency rTMS. High-frequency rTMS leads to an increasing MEP amplitude in the target muscle and may cause a spread of excitation to adjacent muscles.[4,43] The MEP amplitude induced by TMS was also increased for several minutes after stimulation,[43] but the MEP amplitude induced by TES was unchanged,[4] indicating that the increased excitability occurred at the cortical level.

High-frequency rTMS may have clinical applications. Several studies showed that daily rTMS to the left prefrontal cortex for 5 days to 2 weeks led to mood improvement in depressed patients,[25,42] although one study found no effect.[37] Stimulation of the right prefrontal cortex appears to improve mania.[29] The mechanism by which rTMS improves depression or mania may be related to an increase in cortical excitability in the areas stimulated or changes in other brain structures connected to the target area, such as the anterior cingulate cortex.[24]

Low-Frequency rTMS. We showed that suprathreshold, low-frequency rTMS at 0.9 Hz decreased the MEP amplitude, whereas stimulation at 0.1 Hz had no effect.[6] Other groups reported similar findings.[55] Interestingly, in patients with focal dystonia (writer's cramp), the same stimulation led to an increase rather than a decrease in MEP amplitude, further suggesting that motor cortical excitability is abnormal in these patients.[51] Low-frequency rTMS has potential therapeutic applications in diseases with increased cortical excitability, such as epilepsy, myoclonus, and dystonia. Recently, it was reported that subthreshold, low-frequency rTMS transiently reversed deficient intracortical inhibition, as tested by paired TMS, and transiently improved writing in writer's cramp patients.[53]

SAFETY OF TMS

The most serious adverse effect of TMS is the induction of seizures. Single-pulse TMS, with stimuli delivered no more than once every few seconds, does not appear to carry significant risk.[57] However, high-frequency rTMS, with a stimulus frequency higher than 1 Hz, has led to seizures in patients and in normal subjects.[57] Seizure induction is usually associated with rTMS of high frequency, high intensity, and short intertrain intervals. Safety guidelines for the selection of stimulus parameters have been revised on the basis of more recent experience.[10,57] To date, no further seizures have been reported under the new guidelines. Details of other safety concerns and suggested safety precautions for rTMS studies have recently been published.[57]

In conclusion, TMS is a useful method for studying cortical functions. Single-pulse and paired-pulse TMS can test cortical excitability. rTMS can transiently disrupt cortical functions and reveal the functional role of different areas, complementing other techniques such as functional imaging, EEG, and MEG. rTMS also has therapeutic potential in some neurological and psychiatric diseases.

The author's work was supported by the National Institute of Neurological Disorders and Stroke intramural program, Medical Research Council of Canada (grant no. MT 15128), the Canada Foundation for Innovation, and the University Health Network Krembril Family Chair in Neurology. The author is a Medical Research Council of Canada Scholar.

REFERENCES

1. Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell AP, Eberle LP. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroencephalogr Clin Neurophysiol 1989;74:458–462.
2. Barker AT, Jalinous R, Freeston IL. Non-invasive stimulation of the human motor cortex. Lancet 1985;II:1106–1107.
3. Benecke R, Meyer BU, Freund HJ. Reorganisation of descending motor pathways in patients after hemispherectomy and severe hemispheric lesions demonstrated by magnetic brain stimulation. Exp Brain Res 1991;83:419–426.
4. Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Curra A, Gilio F, Modugno N, Manfredi M. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res 1998;122:79–84.
5. Boroojerdi B, Battaglia F, Muellenbacher W, Cohen LG. Evaluation of the effects of CNS active drugs on cortical excitability in intact humans [abstract]. Neurology 1999; 52:Suppl 2:A457.
6. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1389–1403.
7. Chen R, Cohen LG, Hallet M. Role of the ipsilateral motor cortex in voluntary movement. Can J Neurol Sci 1997;24: 284–291.
8. Chen R, Corwell B, Yaseen Z, Hallett M, Cohen LG. Mechanisms of cortical reorganization in lower-limb amputees. J Neurosci 1998;18:3443–3450.
9. Chen R, Garg R. Facilitatory I wave interaction in proximal

arm and lower limb muscle representations of the human motor cortex. J Neurophysiol 2000;83:1426–1434.
10. Chen R, Gerloff C, Classen J, Wassermann EW, Hallett M, Cohen LG. Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. Electroencephalogr Clin Neurophysiol 1997;105:415–421.
11. Chen R, Gerloff C, Hallett M, Cohen LG. Involvement of the ipsilateral motor cortex in finger movements of different complexities. Ann Neurol 1997;41:247–254.
12. Chen R, Lozano AM, Ashby P. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. Exp Brain Res 1999;128:539–542.
13. Chen R, Samii A, Caños M, Wassermann E, Hallett M. Effects of phenytoin on cortical excitability in humans. Neurology 1997;49:881–883.
14. Chen R, Tam A, Bütefisch C, Corwell B, Ziemann U, Rothwell JC, Cohen LG. Intracortical inhibition and facilitation in different representations of the human motor cortex. J Neurophysiol 1998;80:2870–2881.
15. Chen R, Wassermann EM, Caños M, Hallett M. Impaired inhibition in writer's cramp during voluntary muscle activation. Neurology 1997;49:1054–1059.
16. Chen R, Yaseen Z, Cohen LG, Hallett M. The time course of corticospinal excitability in reaction time and self-paced movements. Ann Neurol 1998;44:317–325.
17. Cicinelli P, Traversa R, Rossini PM. Post-stroke reorganization of brain motor output to the hand: a 2–4 month follow-up with focal magnetic transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1997;105:438–450.
18. Classen J, Knorr U, Werhahn KJ, Schlaug G, Kunesch E, Cohen LG, Seitz RJ, Benecke R. Multimodal output mapping of human central motor representation on different spatial scales. J Physiol (Lond) 1998;512:163–169.
19. Cohen LG, Bandinelli S, Sato S, Kufta C, Hallett M. Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991;81:366–376.
20. Cohen LG, Ludlow CL, Warden M, Estegui M, Agostino R, Sedory SE, Holloway E, Dambrosia J, Hallett M. Blink reflex excitability recovery curves in patients with spasmodic dysphonia. Neurology 1989;39:572–577.
21. Darian-Smith C, Gilbert CD. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. Nature 1994;68:737–740.
22. Dykes RW. Mechanisms controlling neuronal plasticity in somatosensory cortex. Can J Physiol Pharmacol 1997;75: 535–545.
23. Fuhr P, Agostino R, Hallett M. Spinal motor neuron excitability during the silent period after cortical stimulation. Electroencephalogr Clin Neurophysiol 1991;81:257–262.
24. George MS, Stallings LE, Speer AM, Nahas Z, Spicer KM, Vincent DJ, Bohning DE, Cheng KT, Molloy M, Teneback C, Risch SC. Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely. Hum Psychopharmacol Clin Exp 1999;14:161–170.
25. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M, Post RM. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154: 1752–1756.
26. Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. The role of the human motor cortex in the control of complex and simple finger movement sequences. Brain 1998;121: 1659–1709.
27. Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 1997;120:1587–1602.
28. Grafman J, Pascual-Leone A, Alway D, Nichelli P, Gomez-Tortosa E, Hallett M. Induction of a recall deficit by rapid-rate transcranial magnetic stimulation. Neuroreport 1994;5: 1157–1160.
29. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Transcranial magnetic stimulation in mania: a controlled study. Am J Psychiatry 1998;155:1608–1610.
30. Hallett M, Chen R, Ziemann U, Cohen LG. Reorganization in motor cortex in amputees in normal volunteers after ischemic limb deafferentation. In: Paulus W, Hallett M, Rossini PM, Rothwell JC, editors. Transcranial magnetic stimulation. Amsterdam: Elsevier; 1999. p 183–187.
31. Halter JA, Carp JS, Wolpaw JR. Operantly conditioned motoneuron plasticity: possible role of sodium channels. J Neurophysiol 1995;73:867–871.
32. Jacobs K, Donoghue J. Reshaping the cortical map by unmasking latent intracortical connections. Science 1991;251: 944–947.
33. Jones RD, Donaldson IM, Parkin PJ. Impairment and recovery of ipsilateral sensory–motor function following unilateral cerebral infarction. Brain 1989;112:113–132.
34. Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science 1993;261:615–617.
35. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD. Corticocortical inhibition in human motor cortex. J Physiol (Lond) 1993;471: 501–519.
36. Liepert J, Schwenkreis P, Tegenthoff M, Malin JP. The glutamate antagonist riluzole suppresses intracortical facilitation. J Neural Transm 1997;104:1207–1214.
37. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. Am J Psychiatry 1999;156:946–948.
38. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. Nature 1980;285:227.
39. Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. J Physiol (Lond) 1997;498: 817–823.
40. Nakashima K, Rothwell JC, Day BL, Thompson PD, Shannon K, Marsden CD. Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. Brain 1989;112:681–697.
41. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 1991;41:697–702.
42. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348: 233–238.
43. Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847–858.
44. Pfurtscheller G, Stancák A Jr., Neuper C. Post-movement beta synchronization. A correlate of an idling motor area? Electroencephalogr Clin Neurophysiol 1996;98:281–293.
45. Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M. Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial magnetic brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. Brain 1994;117:317–323.
46. Ridding MC, Rothwell JC. Stimulus/response curves as a method of measuring motor cortical excitability in man. Electroencephalogr Clin Neurophysiol 1997;105:340–344.
47. Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and

inhibition in focal, task specific dystonia. J Neurol Neurosurg Psychiatry 1995;39:493–498.
48. Rossini PM, Rossi S. Clinical applications of motor evoked potentials. Electroencephalogr Clin Neurophysiol 1998;180–194.
49. Rothwell JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods 1997;74:113–122.
50. Salmelin R, Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 1994;60:537–550.
51. Siebner HR, Auer C, Conrad B. Abnormal increase in the corticomotor output to the affected hand during repetitive transcranial magnetic stimulation of the primary motor cortex in patients with writer's cramp. Neurosci Lett 1999;262: 133–136.
52. Siebner HR, Dressnandt J, Auer C, Conrad B. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 1998;21:1209–1212.
53. Siebner HR, Tormos JM, Ceballos-Baumann AO, Auer C, Catala MD, Conrad B, Pascual-Leone A. Low frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. Neurology 1999;52:529–537.
54. Tanji J, Shima K. Role for supplementary motor area cells in planning several movements ahead. Nature 1994;371: 413–416.
55. Tergau F, Tormos JM, Paulus W, Pascual-Leone A, Ziemann U. Effects of repetitive transcranial magnetic stimulation (rTMS) on cortico-spinal and cortico-cortical excitability [abstract]. Neurology 1997;48:A107.
56. Tokimura H, Ridding MC, Tokimura Y, Amassian VE, Rothwell JC. Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex. Electroencephalogr Clin Neurophysiol 1996;103:263–272.
57. Wassermann EM. Risk and safety in repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16.
58. Wassermann EM, Samii A, Mercuri B, Ikoma K, Oddo D, Grill SE, Hallett M. Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscle. Exp Brain Res 1996;109:158–163.
59. Welker E, Soriano E, Van der Loos H. Plasticity in the barrel cortex of the adult mouse: effects of peripheral deprivation on GAD-immunoreactivity. Exp Brain Res 1989;74:441–452.
60. Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol (Lond) 1999;517(pt. 2):591–597.
61. Ziemann U, Chen R, Cohen LG, Hallet M. Dextromethorphan decreases the excitability of the human motor cortex. Neurology 1998;51:1320–1324.
62. Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 1998;18:1115–1123.
63. Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 1996;40: 367–378.
64. Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W. Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol (Lond) 1998;511:181–190.
65. Ziemann U, Tergau F, Wischer S, Hildebrandt J, Paulus W. Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. Electroencephalogr Clin Neurophysiol 1998;109:321–330.