trained technicians. A neurologist or clinical neurophysiologist should supervise any investigation and provide a written medical report. The risk of adverse effects is very small.

(b) *Research studies (Class 3 studies and Class 2 studies) with single-pulse, paired-pulse TMS, rTMS at ⩽1 Hz* and other conventional or patterned rTMS which fall within known safety margins (see Tables 3–6) *on normal subjects and patients with stable medical conditions* can be carried out by trained professionals (MDs, Technicians, Psychologists, Physicists, Physiotherapists, Engineers), under the responsibility of the Principal Investigator, whose physical presence in the lab is not required, but who should be immediately available. He/she is also responsible of the training of TMS users. Medical assistance is strongly recommended for Class 2 studies on patients, for which personnel skilled in syncope and seizure management should be present in the lab. In these cases, a licensed physician should be identified as the medically responsible clinician and should oversee screening procedures, including assessment of risk factors, rTMS parameters and application protocol, and monitoring of subjects.

(c) *When rTMS is prescribed (by an MD) as treatment for any medical condition (Class 1 studies),* it is advisable that a licensed physician, serving as medically responsible clinician, closely supervises the rTMS application given the more likely medical instability of the patients. The rTMS application can be carried out by a properly trained medical assistant. All personnel have to be trained to recognize and to manage a seizure or a syncope, and there should be full access to emergency treatment and life-support equipment. The responsible clinician should also make sure that the medical assistant is properly trained in how to deal with potential acute complications.

Whenever monitoring is required by the type of study (see Section 7.2.4), the research team should always include a qualified clinical neurophysiologist to supervise the recording and interpretation of electrophysiological data. A physician, a nurse or other qualified personnel who has experience with rTMS and is skilled in the management of first aid for seizures should be present in the rTMS laboratory in these cases.

7.3.2. Training

To date, there is no official position about training requirements. It is however advisable that every TMS user, especially if he/she lacks medical training, has basic knowledge of brain physiology, of basic mechanisms of TMS, of the potential risks of the procedure, of the physiological changes induced, etc. The Principal Investigator of the study is responsible for guaranteeing the proper training of TMS operators working with him/her. Such training should also include the ability and certification to deal with potential acute complications of TMS. Training may vary according to the TMS use.

Teaching courses are not mandatory at the moment, but there are some offered in different countries and organized by public or private institutions, as well as by some national Societies of Clinical Neurophysiology. It is clear that training requirements will need to be consensual, and that different national guidelines may eventually need to be developed. The IFCN has commissioned a forthcoming paper on training requirements for TMS use.

7.4. Contraindications and precautions

The bulk of TMS studies over the last decade following the 1998 published guidelines suggest that the following considerations can be made, for which full consensus was reached:

1. The only absolute contraindication to TMS/rTMS is the presence of metallic hardware in close contact to the discharging coil (such as cochlear implants, or an Internal Pulse Generator or medication pumps). In such instances there is a risk of inducing malfunctioning of such implanted devices.
2. Conditions of increased or uncertain risk of inducing epileptic seizure are:
   a. Related to the *protocol of stimulation*:
      i. Any "novel paradigm" (i.e., that is not a classical method of high-/low-frequency rTMS, performed with a flat Figure 8 coil and biphasic pulse waveform). Pre-conditioning (i.e., priming), TMS applied on more than a single scalp region, and prolonged PAS protocols are included in this category.
      ii. Conventional high-frequency rTMS protocol with parameters of stimulation (intensity, frequency, train length or intertrain duration) exceeding the known safety limits reported in the Tables 4–6 of Section 7.2.

   b. Related to the *disease or patient's condition*:
      i. Personal history of epilepsy (untreated patients with one or a few past episodes), or treated patients.
      ii. Vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain, even without history of seizure, and without anticonvulsant medication
      iii. Administration of drugs that potentially lower seizure threshold (see Section 5.3 for a full list), without concomitant administration of anticonvulsant drugs which potentially protect against seizures occurrence
      iv. Sleep deprivation, alcoholism

3. Conditions of increased or uncertain risk of other events are:
   c. Related to patient's condition:
      i. Implanted brain electrodes (cortical or deep-brain electrodes) (see Section 3.4)
      ii. Pregnancy
      iii. Severe or recent heart disease

4. No risk: none of the previous conditions and single- or paired-pulse TMS or conventional low- or high-frequency rTMS protocol with parameters of stimulation (intensity, frequency, train length or intertrain duration) within the "safety limits" reported in the Tables 4–6 of Section 7.2.

7.5. A screening standard questionnaire for rTMS candidates

Investigators should consider using a standard questionnaire to screen rTMS candidates. The following questions represent the basic information required. Additional information may change according to particular demands. Consensus has been reached for this questionnaire.

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe in which occasion(s)
3. Have you ever had severe (i.e., followed by loss of consciousness) head trauma?
4. Do you have any hearing problems or ringing in your ears?
5. Are you pregnant or is there any chance that you might be?
6. Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.)
7. Do you have cochlear implants?
8. Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)

9. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
10. Do you have a medication infusion device?
11. Are you taking any medications? (Please list)
12. Did you ever have a surgical procedures to your spinal cord?
13. Do you have spinal or ventricular derivations?
14. Did you ever undergo TMS in the past?
15. Did you ever undergo MRI in the past?

Affirmative answers to one or more of questions 1–13 do not represent absolute contraindications to TMS, but the risk/benefit ratio should be carefully balanced by the Principal Investigator of the research project or by the responsible (treating) physician.

Acknowledgements

The workshop was supported by the International Federation of Clinical Neurophysiology (IFCN), the European Chapter of the IFCN, the National Institute of Neurological Disorders and Stroke, the University of Siena, as well as unrestricted gifts from Magstim, Nexstim, and Neuronetics. APL was also supported by the Berenson-Allen Family Foundation.

Authors thank Matteo Feurra, Psy. D. for providing Fig. 2.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2009.08.016.

References

Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci 1996;19:126–30.

Adams RD, Victor M. Faintness and Syncope. In: Principles of Neurology. 2nd ed. New York: McGraw Hill; 1977. p. 248–57 [Chapter 17].

Ajmone-Marsan C. Focal electrical stimulation. In: Purpura DP, Penry JK, Tower DB, Woodbury DM, Walter RD, editors. Experimental Models of Epilepsy. New York: Raven Press; 1972. p. 147–72.

Alagona G, Coco M, Rapisarda G, Costanzo E, Maci T, Restivo D, et al. Changes of blood lactate levels after repetitive transcranial magnetic stimulation. Neurosci Lett 2009;450:111–3.

Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. J Clin Psychiat 2007;68:416–21.

Amassian VE, Eberle L, Maccabee PJ, Cracco RQ. Modelling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: the significance of fiber bending in excitation. Electroencephalogr Clin Neurophysiol 1992;85:291–301.

Anderson B, Mishory A, Nahas Z, Borckardt JJ, Yamanaka K, Rastogi K, et al. Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. J ECT 2006;22:49–53.

Anderson BS, Kavanagh K, Borckardt JJ, Nahas ZH, Kose S, Lisanby SH, et al. Decreasing procedural pain over time of left prefrontal rTMS for depression: initial results from the open-label phase of a multi-site trial (OPT-TMS). Brain Stimul 2009;2:88–92.

Arai N, Okabe S, Furubayashi T, Terao Y, Yuasa K, Ugawa Y. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. Clin Neurophysiol 2005;116:605–13.

Arai N, Okabe S, Furubayashi T, Mochizuki H, Iwata NK, Hanajima R, et al. Differences in after-effect between monophasic and biphasic high-frequency rTMS of the human motor cortex. Clin Neurophysiol 2007;118:2227–33.

Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, et al. Focal electrical stimulation as a Sham control for rTMS: does it truly mimic the cutaneous sensation and pain of active prefrontal rTMS? Brain Stimul 2008;1:44–51.

Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello Jr JJ, Pascual-Leone A, et al. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav 2007;10:521–8.

Barker AT. An introduction to the basic principles of magnetic nerve stimulation. J Clin Neurophysiol 1991;8:26–37.

Basser PJ, Roth BJ. Stimulation of a myelinated nerve axon by electromagnetic induction. Med Biol Eng Comput 1991;29:261–8.

Bear MF. Bidirectional synaptic plasticity: from theory to reality. Philos Trans R Soc Lond B Biol Sci 2003;358:649–55.

Bernabeu M, Orient F, Tormos JM, Pascual-Leone A. Seizure induced by fast repetitive transcranial magnetic stimulation. Clin Neurophysiol 2004;115:1714–5.

Bestmann S, Ruff CC, Blankenburg F, Weiskopf N, Driver J, Rothwell JC. Mapping causal interregional influences with concurrent TMS-fMRI. Exp Brain Res 2008;191:383–402.

Bockart JJ, Smith AR, Hutcheson K, Johnson K, Nahas Z, Andrson B, et al. Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. J ECT 2008;22:259–64.

Bonato C, Miniussi C, Rossini PM. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. Clin Neurophysiol 2006;117:1699–707.

Boroojerdi B, Bushara KO, Corwell B, Immisch I, Battaglia F, Muellbacher W, et al. Enhanced excitability of the human visual cortex induced by short-term light deprivation. Cer Cortex 2000;10:529–34.

Boutros NN, Berman RM, Hoffman R, Miano AP, Campbell D, Ilmoniemi R. Electroencephalogram and repetitive transcranial magnetic stimulation. Depress Anxiety 2000;12:166–9.

Boutros NN, Miano AP, Hoffman RE, Berman RM. EEG monitoring in depressed patients undergoing repetitive transcranial magnetic stimulation. J Neuropsychiat Clin Neurosci 2001;13:197–205.

Bradley JK, Nyekiova M, Price DL, Lopez LD, Crawley T. Occupational exposure to static and time-varying gradient magnetic fields in MR units. J Magn Reson Imag 2007;26:1204–9.

Branston NM, Tofts PS. Analysis of the distribution of currents induced by a changing magnetic field in a volume conductor. Phys Med Biol 1991;36:161–8.

Bridgers SL, Delaney RC. Transcranial magnetic stimulation: an assessment of cognitive and other cerebral effects. Neurology 1989;39:417–9.

Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, et al. RTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci 2004;227:67–71.

Brix G, Seebass M, Hellwig G, Griebel J. Estimation of heat transfer and temperature rise in partial-body regions during MR procedures: an analytical approach with respect to safety considerations. Magn Reson Imag 2002;20:65–76.

Cantello R, Rossi S, Varrasi C, Ulivelli M, Civardi C, Bartalini S, et al. Slow repetitive TMS for drug-resistant epilepsy: clinical and EEG findings of a placebo-controlled trial. Epilepsia 2007;48:366–74.

Cappa SF, Sandrini M, Rossini PM, Sosta K, Miniussi C. The role of the left frontal lobe in action naming: rTMS evidence. Neurology 2002;59:720–3.

Chen R, Gerloff C, Classen J, Wassermannn EM, 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;105:415–21.

Chen R, Yung D, Li JY. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. J Neurophysiol 2003;89:1256–64.

Clow A, Lambert S, Evans P, Hucklebridge F, Higuchi K. An investigation into asymmetrical cortical regulation of salivary S-IgA in conscious man using transcranial magnetic stimulation. Int J Psychophysiol 2003;47:57–64.

Collado-Corona MA, Mora-Magaña I, Cordero GL, Toral-Martiñón R, Shkurovich-Zaslavsky M, Ruiz-Garcia M, et al. Transcranial magnetic stimulation and acoustic trauma or hearing loss in children. Neurol Res 2001;23:343–6.

Conca A, Konig P, Hausmann A. Transcranial magnetic stimulation induces 'pseudoabsence seizure'. Acta Psychiat Scand 2000;101:246–8.

Conte A, Gilio F, Iacovelli E, Bettolo CM, Di Bonaventura C, Frasca V, et al. Effects of repetitive transcranial magnetic stimulation on spike-and-wave discharges. Neurosci Res 2007;57:140–2.

Corthout E, Barker AT, Cowey A. Transcranial magnetic stimulation. Which part of the current waveform causes the stimulation? Exp Brain Res 2001;141:128–32.

Counter SA. Neurobiological effects of extensive transcranial electromagnetic stimulation in an animal model. Electroencephalogr Clin Neurophysiol 1993;89:341–8.

Counter SA, Borg E. Analysis of the coil generated impulse noise in extracranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1992;85:280–8.

Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. J Psychiat Neurosci 2005;30:83–90.

Davey KR, Epstein CM. Magnetic stimulation coil and circuit design. IEEE Trans Biomed Eng 2000;47:1493–9.

Davey KR, Riehl ME. Suppressing the surface field during transcranial magnetic stimulation. IEEE Trans Biomed Eng 2006;53:190–4.

De Lucia M, Parker GJM, Embleton K, Newton JM, Walsh V. Diffusion tensor MRI-based estimation of the influence of brain tissue anisotropy on the effects of transcranial magnetic stimulation. NeuroImage 2007;36:1159–70.

Deblieck C, Thompson B, Iacoboni M, Wu AD. Correlation between motor and phosphene thresholds: a transcranial magnetic stimulation study. Hum Brain Mapp 2008;6:662–70.

Deng ZD, Peterchev A, Lisanby SH. Coil design considerations for deep-brain transcranial magnetic stimulation (dTMS). Proc IEEE Eng Med Biol Soc 2008:5675–9.

Devlin JT, Watkins KE. Stimulating language: insights from TMS. Brain 2007;130:610–22.

Dhuna A, Gates J, Pascual-Leone A. Transcranial magnetic stimulation in patients with epilepsy. Neurology 1991;41:1067–71.

Di Lazzaro V, Thickbroom GW, Pilato F, Profice P, Dileone M, Mazzone P, et al. Direct demonstration of the effects of repetitive paired-pulse transcranial magnetic stimulation at I-wave periodicity. Clin Neurophysiol 2007;118:1193–7.

Di Lazzaro V, Pilato F, Dileone M, Profice P, Oliviero A, Mazzone P, et al. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J Physiol 2008;586:4481–7.
Di Lazzaro V, Dileone M, Pilato F, Profice P, Cioni B, Meglio M et al. Long-term motor cortex stimulation for amyotrophic lateral sclerosis. Brain Stimulation, 2009 [epub ahead of print].
Dräger B, Breitenstein C, Helmke U, Kamping S, Knecht S. Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification. Eur J Neurosci 2004;20:1681–7.
Duning T, Rogalewski A, Steinstraeter O, Kugel H, Jansen A, Breitenstein C, et al. Repetitive TMS temporarily alters brain diffusion. Neurology 2004;62:2144.
Dwork AJ, Arango V, Underwood M, Ilievski B, Rosoklija G, Sackeim HA, et al. Absence of histological lesions in primate models of ECT and magnetic seizure therapy. Am J Psychiat 2004;161:576–8.
Eaton H. Electric field induced in a spherical volume conductor from arbitrary coils: application to magnetic stimulation and MEG. Med Biol Eng Comput 1992;30:433–40.
Elwassif MM, Kong Q, Vazquez M, Bikson M. Bio-heat transfer model of deep brain stimulation-induced temperature changes. J Neural Eng 2006;3:306–15.
Enomoto H, Ugawa Y, Hanajima R, Yuasa K, Mochizuki H, Terao Y, et al. Decreased sensory cortical excitability after 1 Hz rTMS over the ipsilateral primary motor cortex. Clin Neurophysiol 2001;112:2154–8.
Epstein CM. Seizure or convulsive syncope during 1-Hz rTMS? Clin Neurophysiol 2006;117:2566–8.
Epstein CM, Davey KR. Iron-core coils for transcranial magnetic stimulation. J Clin Neurophysiol 2002;19:376–81.
Evers S, Böckermann I, Nyhuis PW. The impact of transcranial magnetic stimulation on cognitive processing: an event-related potential study. Neuroreport 2001a;12:2915.
Evers S, Hengst K, Pecuch PW. The impact of repetitive transcranial magnetic stimulation on pituitary hormone levels and cortisol in healthy subjects. J Affect Disord 2001b;66:83–8.
Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiat Clin Neurosci 1998;10:20–5.
Filippi MM, Oliveri M, Vernieri F, Pasqualetti P, Rossini PM. Are autonomic signals influencing cortico-spinal motor excitability? A study with transcranial magnetic stimulation. Brain Res 2000;881:159–64.
Fitzgerald PB, Brown TL, Marston NA, Oxley T, De Castella A, Daskalakis ZJ, et al. Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. Shizophrenia Res 2004;71:17–26.
Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiat 2006;163:88–94.
Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 2009;34:1255–62.
Flitman SS, Grafman J, Wassermannn EM, Cooper V, O'Grady J, Pascual-Leone A, et al. Linguistic processing during repetitive transcranial magnetic stimulation. Neurology 1998;50:175–81.
Foerster A, Schmitz JM, Nouri S, Claus D. Safety of rapid-rate transcranial magnetic stimulation: heart rate and blood pressure changes. Electroencephalogr Clin Neurophysiol 1997;104:207–12.
Folmer RL, Carroll JR, Rahim A, Shi Y, Hal Martin W. Effects of repetitive transcranial magnetic stimulation (rTMS) on chronic tinnitus. Acta Otolaryngol 2006;556(Suppl.):96–101.
Fregni F, Pascual-Leone AP. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 2007;3:383–93.
Fregni F, Simon DK, Wu A, Pascual-Leone A. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. J Neurol Neurosurg Psychiat 2005a;76:1614–23.
Fregni F, Thome-Souza S, Bermpohl F, Marcolin MA, Herzog A, Pascual-Leone A, et al. Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study. Stereotact Funct Neurosurg 2005b;83:57–62.
Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, et al. A Sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke 2006a;37:2115–22.
Fregni F, Otachi PT, Do Valle A, Boggio PS, Thut G, Rigonatti SP, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. Ann Neurol 2006b;60:447–55.
Frye RE, Rotenberg A, Ousley M, Pascual-Leone A. Transcranial magnetic stimulation in child neurology: current and future directions. J Child Neurol 2008;23:79–96.
Fuggetta G, Fiaschi A, Manganotti P. Modulation of cortical oscillatory activities induced by varying single-pulse transcranial magnetic stimulation intensity over the left primary motor area: a combined EEG and TMS study. Neuroimage 2005;27:896–908.
Fuggetta G, Pavone EF, Walsh V, Kiss M, Eimer M. Cortico–cortical interactions in spatial attention: a combined ERP/TMS study. J Neurophysiol 2006;95:3277–80.
Gandhi OP. Electromagnetic fields: human safety issues. Annu Rev Biomed Eng 2002;4:211–34.
Gates JR, Dhuna A, Pascual-Leone A. Lack of pathologic changes in human temporal lobes after transcranial magnetic stimulation. Epilepsia 1992;33:504–8.
Gentner R, Wankerl K, Reinsberger C, Zeller D, Classen J. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cer Cortex 2008;19:2053–6.
George MS, Wassermannn EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J Neuropsychiat Clin Neurosci 1996;8:172–80.
George MS, Nahas Z, Borckardt JJ, Anderson B, Foust MJ, Burns C, et al. Brain stimulation for the treatment of psychiatric disorders. Curr Opin Psychiat 2007;20:250–4.
Gerschlager W, Siebner HR, Rothwell JC. Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 2001;57:449–55.
Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. Am J Psychiat 2003;160:835–45.
Gilbert DL, Garvey MA, Bansal AS, Lipps T, Zhang J, Wassermannn EM. Should transcranial magnetic stimulation research in children be considered minimal risk? Clin Neurophysiol 2004;115:1730–9.
Green RM, Pascual-Leone A, Wassermann EM. Ethical guidelines for rTMS research. IRB 1997;2:1–7.
Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, Dieler A, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. Biol Psychiat 2009;65:778–84.
Gugino LD, Romero JR, Aglio L, Titone D, Ramirez M, Pascual-Leone A, et al. Transcranial magnetic stimulation coregistered with MRI: a comparison of a guided vs. blind stimulation technique and its effect on evoked compound muscle action potentials. Clin Neurophysiol 2001;112:1781–92.
Hallett M. Transcranial Magnetic Stimulation: A Primer. Neuron 2007;55:187–99.
Hallett M, Wassermann EM, Pascual-Leone A, Valls-Solé J. Repetitive transcranial magnetic stimulation. Recommendations for the practice of clinical neurophysiology: guidelines of the international federation of clinical neurophysiology. In: Deuschl G, Eisen A, editors. Electroencephalography and clinical neurophysiology, 2nd ed. (Suppl. 52); 1999. p. 105–113.
Hamada M, Hanajima R, Terao Y, Arai N, Furubayashi T, Inomata-Terada S, et al. Origin of facilitation in repetitive, 1.5 ms interval, paired pulse transcranial magnetic stimulation (rPPS) of the human motor cortex. Clin Neurophysiol 2007;118:1596–601.
Hamada M, Terao Y, Hanajima R, Shirota Y, Nakatani-Enomoto S, Furubayashi T, Matsumoto H, Ugawa Y. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. J Physiol 2008;586:3927–47.
Hansenne M, Laloyaux O, Mardaga S, Ansseau M. Impact of low frequency transcranial magnetic stimulation on event-related brain potentials. Biol Psychol 2004;67:331–41.
Harris J, Clifford C, Miniussi C. The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation? J Cogn Sci 2008;20:734–40.
Haupts MR, Daum S, Ahle G, Holinka B, Gehlen W. Transcranial magnetic stimulation as a provocation for epileptic seizures in multiple sclerosis. Mult Scler 2004;10:475–6.
Hausmann A, Marksteiner J, Hinterhuber H, Humpel C. Magnetic stimulation induces neuronal c-fos via tetrodotoxin-sensitive sodium channels in organotypic cortex brain slices of the rat. Neurosci Lett 2001;310:105–8.
Herwig U, Fallgatter AJ, Höppner J, Eschweiler GW, Kron M, Hajak G, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiat 2007;191:441–8.
Hidding U, Bäumer T, Siebner HR, Demiralay C, Buhmann C, Weyh T, et al. MEP latency shift after implantation of deep brain stimulation systems in the subthalamic nucleus in patients with advanced Parkinson's disease. Mov Disord 2006;21:1471–6.
Hill DL, McLeish K, Keevil SF. Impact of electromagnetic field exposure limits in Europe: is the future of interventional MRI safe? Acad Radiol 2005;12:1135–42.
Hoffman RE, Gueorguieva R, Hawkins KA, Varanko M, Boutros NN, Wu YT, et al. Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. Biol Psychiat 2005;58:97–104.
Hoffman RE, Hampson M, Wu K, Anderson AW, Gore JC, Buchanan RJ, et al. Probing the pathophysiology of auditory/verbal hallucinations by combining functional magnetic resonance imaging and transcranial magnetic stimulation. Cereb Cortex 2007;17:2733–43.
Holler I, Siebner HR, Cunnington R, Gerschlager W. 5 Hz repetitive TMS increases anticipatory motor activity in the human cortex. Neurosci Lett 2006;392:221–5.
Hsu KH, Nagarajan SS, Durand DM. Analysis of efficiency of magnetic stimulation. IEEE Trans Biomed Eng 2003;50:1276–85.
Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.
Huber R, Esser SK, Ferrarelli F, Massimini M, Peterson MJ, Tononi G. TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. PLoS ONE 2007;2:e276.
Hufnagel A, Elger CE. Responses of the epileptic focus to transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991;43(Suppl.):86–99.
International Commission on Non-ionizing Radiation Protection. Guidance on determining compliance of exposure to pulsed and complex non-sinusoidal

waveforms below 100 kHz with ICNIRP guidelines. Health Phys 2003;84:383–87.
Iezzi E, Conte A, Suppa A, Agostino R, Dinapoli L, Scontrini A, et al. Phasic voluntary movements reverse the aftereffects of subsequent theta-burst stimulation in humans. J Neurophysiol 2008;100:2070–6.
Illes J, Gallo M, Kirschen MP. An ethics perspective on transcranial magnetic stimulation (TMS) and human neuromodulation. Behav Neurol 2006;7:149–57.
Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 1997;8:3537–40.
Inghilleri M, Conte A, Currà A, Frasca V, Lorenzano C, Berardelli A. Ovarian hormones and cortical excitability. An rTMS study in humans. Clin Neurophysiol 2005;115:1063–8.
Ishikawa S, Matsunaga K, Nakanishi R, Kawahira K, Murayama N, Tsuji S, et al. Effect of theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials. Clin Neurophysiol 2007;118:1033–43.
Ives JR, Rotenberg A, Poma R, Thut G, Pascual-Leone A. Electroencephalographic recording during transcranial magnetic stimulation in humans and animals. Clin Neurophysiol 2006;117:1870–5.
Iyer MB, Schleper N, Wassermannn EM. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 2003;23:10867–72.
Jahanshahi M, Ridding MC, Limousin P, Profice P, Fogel W, Dressler D, et al. Rapid rate transcranial magnetic stimulation – a safety study. Electroencephalogr Clin Neurophysiol 1997;105:422–9.
Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiat 2008;69:222–32.
Jennum P, Winkel H, Fuglsang-Frederiksen A, Dam M. EEG changes following repetitive transcranial magnetic stimulation in patients with temporal lobe epilepsy. Epilepsy Res 1994;18:167–73.
Jing H, Takigawa M, Okamura H, Doi W, Fukuzako H. Comparisons of event-related potentials after repetitive transcranial magnetic stimulation. J Neurol 2001;248:184–92.
Joo EY, Han SJ, Chung SH, Cho JW, Seo DW, Hong SB. Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. Clin Neurophysiol 2007;118:702–8.
Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiat 2004;55:398–405.
Julkunen P, Pääkkönen A, Hukkanen T, Könönen M, Tiihonen P, Vanhatalo S, et al. Efficient reduction of stimulus artefact in TMS-EEG by epithelial short-circuiting by mini-punctures. Clin Neurophysiol 2008;119:475–81.
Kähkönen S, Kesäniemi M, Nikouline VV, Karhu J, Ollikainen M, Holi M, et al. Ethanol modulates cortical activity: direct evidence with combined TMS and EEG. Neuroimage 2001;14:322–8.
Kähkönen S, Wilenius J, Komssi S, Ilmoniemi RJ. Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation. Clin Neurophysiol 2004;115:583–8.
Kähkönen S, Komssi S, Wilenius J, Ilmoniemi RJ. Prefrontal transcranial magnetic stimulation produces intensity-dependent EEG responses in humans. Neuroimage 2005;24:955–60.
Kammer T, Beck S, Thielscher A, Laubis-Herrmann U, Topka H. Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. Clin Neurophysiol 2001;112:250–8.
Kanno M, Chuma T, Mano Y. Monitoring an electroencephalogram for the safe application of therapeutic repetitive transcranial magnetic stimulation. J Neurol Neurosurg Psychiat 2001;71:559–60.
Karlström EF, Lundström R, Stensson O, Mild KH. Therapeutic staff exposure to magnetic field pulses during TMS/rTMS treatments. Bioelectromagnetics 2006;27:156–8.
Katayama T, Rothwell JC. Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation. Clin Neurophysiol 2007;118:2506–11.
Keck ME, Sillaber I, Ebner K, Welt T, Toschi N, Kaehler ST, et al. Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. Eur J Neurosci 2000;12:3713–20.
Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiat 1999;46:1603–13.
Klirova M, Novak T, Kopecek M, Mohr P, Strunzova V. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode during pregnancy. Neuro Endocrinol Lett 2008;29:69–70.
Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–56.
Kofler M, Leis AA, Sherwood AM, Delapasse JS, Halter JA. Safety of transcranial magnetic stimulation in patients with abdominally implanted electronic devices. Lancet 1991;338:1275–6.
Komssi S, Aronen HJ, Huttunen J, Kesäniemi M, Soinne L, Nikouline VV, et al. Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin Neurophysiol 2002;113:175–84.
Komssi S, Kähkönen S, Ilmoniemi RJ. The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum Brain Mapp 2004;21:154–64.
Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiat Clin Neurosci 2000;12:376–84.
Kruger B. An update on the external ear resonance in infants and young children. Ear Hear 1987;8:333–6.
Kübler A, Schmidt K, Cohen LG, Lotze M, Winter S, Hinterberger T, et al. Modulation of slow cortical potentials by transcranial magnetic stimulation in humans. Neurosci Lett 2002;324:205–8.
Kühn AA, Trottenberg T, Kupsch A, Meyer BU. Pseudo-bilateral hand motor responses evoked by transcranial magnetic stimulation in patients with deep brain stimulators. Clin Neurophysiol 2002;113:341–5.
Kühn AA, Brandt SA, Kupsch A, Trottenberg T, Brocke J, Irlbacher K, et al. Comparison of motor effects following subcortical electrical stimulation through electrodes in the globus pallidus internus and cortical transcranial magnetic stimulation. Exp Brain Res 2004;155:48–55.
Kujirai T, Sato M, Rothwell JC, Cohen LG. The effect of transcranial magnetic stimulation on median nerve somatosensory evoked potentials. Electroencephalogr Clin Neurophysiol 1993;89:227–34.
Kumar R, Chen R, Ashby P. Safety of transcranial magnetic stimulation in patients with implanted deep brain stimulators. Mov Disord 1999;14:157–8.
Lang N, Siebner H, Ernst D, Nitsche MA, Paulus W, Lemon RJ, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. Biol Psychiat 2004;56:634–9.
Leafaucheur JP. Transcranial magnetic stimulation in the management of pain. Suppl Clin Neurophysiol 2004;57:737–48.
Lefaucheur JP, Drouot X, Von Raison F, Ménard-Lefaucheur I, Cesaro P, Nguyen JP. Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. Clin Neurophysiol 2004;115:2530–41.
Lempert T. Recognizing syncope: pitfalls and surprises. J R Soc Med 1996;89:372–5.
Levkovitz Y, Roth Y, Harel EV, Braw Y, Sheer A, Zangen A. A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. Clin Neurophysiol 2007;118:2730–44.
Li X, Nahas Z, Lomarev M, Denslow S, Shastri A, Bohning DE, et al. Prefrontal cortex transcranial magnetic stimulation does not change local diffusion: a magnetic resonance imaging study in patients with depression. Cogn Behav Neurol 2003;16:128–35.
Liebetanz D, Fauser S, Michaelis T, Czéh B, Watanabe T, Paulus W, et al. Safety aspects of chronic low-frequency transcranial magnetic stimulation based on localized proton magnetic resonance spectroscopy and histology of the rat brain. J Psychiat Res 2003;37:277–86.
Lin JT, Ziegler DK, Lai CW, Bayer W. Convulsive syncope in blood donors. Ann Neurol 1982;11:525–8.
Lisanby SH. Update on magnetic seizure therapy: a novel form of convulsive therapy. J ECT 2002;18:182–8.
Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA, Sham TMS. Intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiat 2001;49:460–3.
Litvak V, Komssi S, Scherg M, Hoechstetter K, Classen J, Zaaroor M, et al. Artifact correction and source analysis of early electroencephalographic responses evoked by transcranial magnetic stimulation over primary motor cortex. Neuroimage 2007;37:56–70.
Lomarev MP, Kanchana S, Bara-Jimenez W, Iyer M, Wassermannn EM, Hallett M. Placebo-controlled study of rTMS for the treatment of Parkinson's disease. Mov Dis 2006;21:325–31.
Lomarev MP, Kim DY, Richardson SP, Voller B, Hallett M. Safety study of high-frequency transcranial magnetic stimulation in patients with chronic stroke. Clin Neurophysiol 2007;118:2072–5.
Lontis ER, Voigt M, Struijk JJ. Focality assessment in transcranial magnetic stimulation with double and cone coils. J Clin Neurophysiol 2006;23:462–71.
Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. Biol Psychiat 2001;49:615–23.
Loo CK, Mitchell PB, Croker VM, Malhi GS, Wen W, Gandevia SC, et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression [see comment]. Psychol Med 2003;33:33–40.
Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol 2008;11:131–47.
Lorenzano C, Gilio F, Inghilleri M, Conte A, Fofi L, Manfredi M, et al. Spread of electrical activity at cortical level after repetitive magnetic stimulation in normal subjects. Exp Brain Res 2002;147:186–92.
Lu M-K, Bliem B, Jung P, Arai N, Tsai C-H, Ziemann U. Modulation of preparatory volitional motor cortical activity by paired associative transcranial magnetic stimulation. Hum Brain Map 2009 [Epub ahead of print].
Luft AR, Kaelin-Lang A, Hauser TK, Cohen LG, Thakor NV, Hanley DF. Transcranial magnetic stimulation in the rat. Exp Brain Res 2001;140:112–21.

Maccabee PJ, Amassian VE, Eberle LP, Cracco RQ. Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: locus of excitation. J Physiol 1993;460:201–19.
Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients. Clin Neurophysiol 2006;117:455–71.
Magistris MR, Rösler KM, Truffert A, Myers JP. Transcranial stimulation excites virtually all motor neurons supplying the target muscle. A demonstration and a method improving the study of motor evoked potentials. Brain 1998;121:437–50.
Magistris MR, Rösler KM, Truffert A, Landis T, Hess CW. A clinical study of motor evoked potentials using a triple stimulation technique. Brain 1999;122:265–79.
Málly J, Stone TW. New advances in the rehabilitation of CNS diseases applying rTMS. Expert Rev Neurother 2007;7:165–77.
Marg E, Rudiak D. Phosphenes induced by magnetic stimulation over the occipital brain: description and probable site of stimulation. Optom Vis Sci 1994;71:301–11.
Mariorenzi R, Zarola F, Caramia MD, Paradiso C, Rossini PM. Non-invasive evaluation of central motor tract excitability changes following peripheral nerve stimulaiton in healthy humans. Electroenceph Clin Neurophysiol 1991;81:243–50.
Martens L. Different basic dosimetric quantities for the characterization of exposure to low-frequency electric and magnetic fields and the implication for practical exposure conditions and guidelines. Health Phys 2007;92:515–20.
Mashour GA, Walker EE, Martuza RL. Psychosurgery: past, present, and future. Brain Res Brain Res Rev 2005;48:409–19.
Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. Science 2005;309:2228–32.
Massimini M, Ferrarelli F, Esser SK, Riedner BA, Huber R, Murphy M, et al. Triggering sleep slow waves by transcranial magnetic stimulation. Proc Natl Acad Sci 2007;104:8496–501.
Matsumi N, Matsumoto K, Mishima N, Moriyama E, Furuta T, Nishimoto A, et al. Thermal damage threshold of brain tissue: histological study of heated normal monkey brains. Neurologia Medico-Chirurgica 1994;34:209–15.
Matsumiya Y, Yamamoto T, Yarita M, Miyauchi S, Kling JW. Physical and physiological specification of magnetic pulse stimuli that produce cortical damage in rats. J Clin Neurophysiol 1992;9:278–87.
May A, Hajak G, Gänssbauer S, Steffens T, Langguth B, Kleinjung T, et al. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. Cereb Cortex 2007;17:205–10.
Menkes DL, Gruenthal M. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. Epilepsia 2000;41: 240–2.
Michael N, Gösling M, Reutemann M, Kersting A, Heindel W, Arolt V, et al. Metabolic changes after repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex: a Sham-controlled proton magnetic resonance spectroscopy (1H MRS) study of healthy brain. Eur J Neurosci 2003;17:2462–8.
Miranda PC, Hallett M, Basser PJ. The electric field induced in the brain by magnetic stimulation: a 3D finite-element analysis of the effect of tissue heterogeneity and anisotropy. IEEE Trans Biomed Eng 2003;50:1074–85.
Misawa S, Kuwabara S, Shibuya K, Mamada K, Hattori T. Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia. J Neurol Sci 2005;234:37–9.
Mistry S, Verin E, Singh S, Jefferson S, Rothwell JC, Thompson DG, et al. Unilateral suppression of pharyngeal motor cortex to repetitive transcranial magnetic stimulation reveals functional asymmetry in the hemispheric projections to human swallowing. J Physiol 2007;585:525–38.
Morbidi F, Garulli A, Prattichizzo D, Rizzo C, Manganotti P, Rossi S. Off-line removal of TMS-induced artifacts on human electroencephalography by Kalman filter. J Neurosci Methods 2007;162:293–302.
Mottaghy FM, Gangitano M, Horkan C, Chen Y, Pascual-Leone A, Schlaug G. Repetitive TMS temporarily alters brain diffusion. Neurology 2003;60:1539–41.
Muellbacher W, Ziemann U, Boroojerdi B, Hallett M. Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. Clin Neurophysiol 2000;111:1002–7.
Münchau A, Bloem BR, Irlbacher K, Trimble MR, Rothwell JC. Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. J Neurosci 2002;22:554–61.
Nadeem M, Thorlin T, Gandhi O, Persson M. Computation of electric and magnetic stimulation in human head using the 3D impedance method. IEEE Trans Biomed Eng 2003;50:900–7.
Nagarajan SS, Durand DM, Warman EN. Effects of induced electric fields on finite neuronal structures: a simulation study. IEEE Trans Biomed Eng 1993;40:1175–88.
Nahas Z, Bohning D, Molloy M, Oustz J, Risch C, George M. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxiousdepression in pregnancy: a case report. J Clin Psychiat 1999;60:50–2.
Nahas Z, DeBrux C, Chandler V, Lorberbaum JP, Speer AM, Molloy MA, et al. Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. J ECT 2000;16:380–90.
Neveu PJ, Barnéoud P, Vitiello S, Kelley KW, Le Moal MA. Brain neocortex modulation of mitogen-induced interleukin 2, but not interleukin production. Immunol Lett 1989;21:307–10.
Nikouline V, Ruohonen J, Ilmoniemi RJ. The role of the coil click in TMS assessed with simultaneous EEG. Clin Neurophysiol 1999;110:1325–8.
Nowak DA, Hoffmann U, Connemann BJ, Schonfeldt-Lecuona C. Epileptic seizure following 1 Hz repetitive transcranial magnetic stimulation. Clin Neurophysiol 2006;117:1631–3.
Nyffeler T, Wurtz P, Lüscher HR, Hess CW, Senn W, Pflugshaupt T, et al. Extending lifetime of plastic changes in the human brain. Eur J Neurosci 2006;24:2961–6.
Obermann LM, Pascual-Leone A. Report of seizure induced by continuous theta burst stimulation. Brain Stim 2009, in press.
O'Reardon J, Solvason B, Janicak P, Sampson S, Isenberg K, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multi-site randomized controlled trial. Biol Psychiat 2007;62:1208–16.
O'Shea J, Johansen-Berg H, Trief D, Göbel S, Rushworth MF. Functionally specific reorganization in human premotor cortex. Neuron 2007;54:479–90.
Padberg F, di Michele F, Zwanzger P, Romeo E, Bernardi G, Schüle C, et al. Plasma concentrations of neuroactive steroids before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. Neuropsychopharmacology 2002;27:874–8.
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.
Pascual-Leone A, Cohen LG, Shotland LI, Dang N, Pikus A, Wassermannn EM, et al. No evidence of hearing loss in humans due to transcranial magnetic stimulation. Neurlology 1992;42:647–51.
Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Sol_ J, Brasil-Neto JP, Wassermannn EM, Cohen LG. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol 1993;89:120–30.
Paus T, Sipila PK, Strafella AP. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. J Neurophysiol 2001;86:1983–90.
Peinemann A, Reimer B, Löer C, Quartarone A, Münchau A, Conrad B, Siebner HR. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. Clin Neurophysiol 2004;115:1519–26.
Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston, MA: Little, Brown; 1954.
Peterchev AV, Jalinous R, Lisanby SH. A transcranial magnetic stimulator inducing near-rectangular pulses with controllable pulse width (cTMS). IEEE Trans Biomed Eng 2008;55:257–66.
Post A, Keck ME. Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms? J. Psychiatr. Res. 2001;35:193–215.
Price GW. EEG-dependent ERP recording: using TMS to increase the incidence of a selected pre-stimulus pattern. Brain Res. Brain Res. Protoc. 2004;12:144–51.
Prikryl R, Kucerova H. Occurrence of epileptic paroxysm during repetitive transcranial magnetic stimulation treatment. J. Psychopharmacol. 2005;19:313.
Quartarone A, Rizzo V, Bagnato S, Morgante F, Sant'Angelo A, Girlanda P, Siebner HR. Rapid-rate paired associative stimulation of the median nerve and motor cortex can produce long-lasting changes in motor cortical excitability in humans. J Physiol. 2006;575:657–70.
Ray PG, Meador KJ, Epstein CM, Loring DW, Day LJ. Magnetic stimulation of visual cortex: factors influencing the perception of phosphenes. J Clin Neurophysiol 1998;15:351–7.
Restuccia D, Ulivelli M, De Capua A, Bartalini S, Rossi S. Modulation of high-frequency (600 Hz) somatosensory-evoked potentials after rTMS of the primary sensory cortex. Eur J Neurosci 2007;26:2349–58.
Riches SF, Collins DJ, Scuffham JW, Leach MO. EU Directive 2004/40: field measurements of a 1.5 T clinical MR scanner. Br J Radiol 2007a;80:483–7.
Riches SF, Collins DJ, Charles-Edwards GD, Shafford JC, Cole J, Keevil SF, et al. Measurements of occupational exposure to switched gradient and spatially-varying magnetic fields in areas adjacent to 1.5 T clinical MRI systems. J Magn Reson Imag 2007b;26:1346–52.
Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? Nat Rev Neurosci 2007;8:559–67.
Robertson EM, Théoret H, Pascual-Leone A. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. J Cogn Neurosci 2003;15:948–60.
Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G. Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. Cereb Cortex 2008a;18:2010–8.
Romei V, Rihs T, Brodbeck V, Thut G. Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. Neuroreport 2008b;19:203–8.
Rosa MA, Odebrecht M, Rigonatti SP, Marcolin MA. Transcranial magnetic stimulation: review of accidental seizures. Rev Bras Psiquiatr 2004;26:131–4.
Rossi S, Rossini PM. TMS in cognitive plasticity and the potential for rehabilitation. Trends Cogn Sci 2004;8:273–9.
Rossi S, Pasqualetti P, Rossini PM, Feige B, Ulivelli M, Glocker FX, et al. Effects of repetitive transcranial magnetic stimulation on movement-related cortical activity in humans. Cereb Cortex 2000;10:802–8.
Rossi S, Cappa SF, Babiloni C, Pasqualetti P, Miniussi C, Carducci F, et al. Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci 2001;4:948–52.
Rossi S, Ulivelli M, Bartalini S, Galli R, Passero S, Battistini N, et al. Reduction of cortical myoclonus-related epileptic activity following slow-frequency rTMS. Neuroreport 2004a;15:293–6.

Rossi S, Miniussi C, Pasqualetti P, Babiloni C, Rossini PM, Cappa SF. Age-related functional changes of prefrontal cortex in long-term memory: a repetitive transcranial magnetic stimulation study. J Neurosci 2004b;24:7939–44.
Rossi S, Pasqualetti P, Zito G, Vecchio F, Cappa SF, Miniussi C, et al. Prefrontal and parietal cortex in human episodic memory: an interference study by repetitive transcranial magnetic stimulation. Eur J Neurosci 2006;23:793–800.
Rossi S, De Capua A, Ulivelli M, Bartalini S, Falzarano V, Filippone G, et al. Effects of repetitive transcranial magnetic stimulation on chronic tinnitus. A randomized, cross-over, double-blind, placebo-controlled study. J Neurol Neurosurg Psychiat 2007a;78:857–63.
Rossi S, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, et al. A real electromagnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). Clin Neurophysiol 2007b;118:709–16.
Rossi S, Cappa SF, Rossini PM. Higher cognitive functions: memory and reasoning. In: Epstein C, Ziemann U, Wassermannn EM, Walsh V, Paus T, Lisanby SH, editors. Oxford handbook of transcranial stimulation. London: Oxford University Press; 2007c. p. 501–16.
Rossini PM, Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic and research potential. Neurology 2007;68:484–8.
Rossini PM, Desiato MT, Caramia MD. Age-related changes of motor evoked potentials in healthy humans: non-invasive evaluation of central and peripheral motor tracts conductivity and excitability. Brain Res 1992;593:14–9.
Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994;91:79–92.
Rossini PM, Rossi S, Babiloni C, Polich J. Clinica neurophysiology of ging brain: from normal aging to neurodegeneration. Prog Neurobiol 2007;83:375–400.
Rotenberg A, Harrington MG, Birnbaum DS, Madsen JR, Glass LES, Jensen FE, et al. Minimal heating of titanium skull plates during 1 Hz repetitive transcranial magnetic stimulation. Clin Neurophysiol 2007;118:2536–8.
Rotenberg A, Hjunji Bae E, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone AP. Repetitive transcranial magnetic stimulation in the treatment of epilepsia partialis continua. Epilepsy Behav 2009;14:253–7.
Roth BJ, Basser PJ. A model of the stimulation of a nerve fiber by electromagnetic induction. IEEE Trans Biomed Eng 1990;37:588–97.
Roth BJ, Pascual Leone A, Cohen LG, Hallett M. The heating of metal-electrodes during rapid-rate magnetic stimulation – a possible safety hazard. Electroenceph Clin Neurophysiol 1992;85:116–23.
Roth Y, Zangen A, Hallett M. A coil design for transcranial magnetic stimulation of deep brain regions. J Clin Neurophysiol 2002;19:361–70.
Roth Y, Amir A, Levkovitz Y, Zangen A. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure 8 and deep h-coils. J Clin Neurophysiol 2007;24:31–8.
Ruohonen J, Ollikainen M, Nikouline V, Virtanen J, Ilmoniemi RJ. Coil design for real and sham transcranial magnetic stimulation. IEEE Trans Biomed Eng 2000;47:145–8.
Ruohonen J, Ilmoniemi RJ. Physical principles for transcranial magnetic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell J, Wassermann EM, Puri BK, editors. Handbook of transcranial magnetic stimulation. New York: Oxford University Press; 2002.
Sack AT, Cohen Kadosh R, Schuhmann T, Moerel M, Walsh V, Goebel R. Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. J Cogn Neurosci 2009;21:207–21.
Santiago-Rodríguez E, Cárdenas-Morales L, Harmony T, Fernández-Bouzas A, Porras-Kattz E, Hernández A. Repetitive transcranial magnetic stimulation decreases the number of seizures in patients with focal neocortical epilepsy. Seizure 2008;17:677–83.
Satow T, Mima T, Hara H, Oga T, Ikeda A, Hashimoto N, et al. Nausea as a complication of low-frequency repetitive transcranial magnetic stimulation of the posterior fossa. Clin Neurophysiol 2002;113:1441–3.
Satow T, Mima T, Yamamoto J, Oga T, Begum T, Aso T, et al. Short-lasting impairment of tactile perception by 0.9Hz-rTMS of the sensorimotor cortex. Neurology 2003;60:1045–7.
Schrader LM, Stern JM, Koski L, Nuwer MR, Engel Jr J. Seizure incidence during single- and paired-pulse transcranial magnetic stimulation (TMS) in individuals with epilepsy. Clin Neurophysiol 2004;115:2728–37.
Schrader LM, Stern JM, Fields TA, Nuwer MR, Wilson CL. A lack of effect from transcranial magnetic stimulation (TMS) on the vagus nerve stimulator (VNS). Clin Neurophysiol 2005;116:2501–4.
Schulze-Bonhage A, Scheufler K, Zentner J, Elger CE. Safety of single and repetitive focal transcranial magnetic stimuli as assessed by intracranial EEG recordings in patients with partial epilepsy. J Neurol 1999;246:914–9.
Schürmann M, Nikouline VV, Soljanlahti S, Ollikainen M, Basar E, Ilmoniemi RJ. EEG responses to combined somatosensory and transcranial magnetic stimulation. Clin Neurophysiol 2001;112:19–24.
Schutter DJ, van Honk J, d'Alfonso AA, Peper JS, Panksepp J. High frequency repetitive transcranial magnetic over the medial cerebellum induces a shift in the prefrontal electroencephalography gamma spectrum: a pilot study in humans. Neurosci Lett 2003;336:73–6.
Sgro J, Stanton P, Emerson R. Theoretical and practical performance of magnetic stimulators and coils. Electroencephalogr Clin Neurophysiol 1991;43(Suppl.):279–83.
Sibon I, Strafella AP, Gravel P, Ko JH, Booij L, Soucy JP, et al. Acute prefrontal cortex TMS in healthy volunteers: effects on brain 11C-alphaMtrp trapping. Neuroimage 2007;34:1658–64.
Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. J Neurosci 2004;24:3379–85.
Siebner HR, Peller M, Lee L. TMS and positron emission tomography: methods and current advances. In: Wassermann EM, Epstein CM, Ziemann U, Walsh V, Paus T, Lisanby SH, editors. The Oxford handbook of transcranial magnetic stimulation. Oxford: Oxford University Press; 2008. p. 549–67.
Siebner HR, Bergmann TO, Bestmann S, Massimini M, Johansen-Berg H, Mochizuki H, et al. Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul 2009;2:58–80.
Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. Brain Topogr 2008;21:1–10.
Silvanto J, Muggleton NG, Cowey A, Walsh V. Neural activation state determines behavioral susceptibility to modified theta burst transcranial magnetic stimulation. Eur J Neurosci 2007;26:523–8.
Silverstein FS, Jensen FE. Neonatal seizures. Ann Neurol 2007;62:112–20.
Smith MJ, Keel JC, Greenberg BD, Adams LF, Schmidt PJ, Rubinow DA, et al. Menstrual cycle effects on cortical excitability. Neurology 1999;53:2069–72.
Sommer M, Tergau F, Wischer S, Paulus W. Paired-pulse repetitive transcranial magnetic stimulation of the human motor cortex. Exp Brain Res 2001;139:465–72.
Sommer J, Jansen A, Drager BOS, Breitenstein C, Deppe M, Knecht S. Transcranial magnetic stimulation – a sandwich coil desing for a better Sham. Clin Neurophysiol 2006a;117:440–6.
Sommer M, Alfaro A, Rummel M, Speck S, Lang N, Tings T, et al. Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex [see comment]. Clin Neurophysiol 2006b;117:838–44.
Steinhoff BJ, Stodieck SR, Zivcec Z, Schreiner R, von Maffei C, Plendl H, et al. Transcranial magnetic stimulation (TMS) of the brain in patients with mesiotemporal epileptic foci. Clin Electroencephalogr 1993;24:1–5.
Steven MS, Pascual-Leone A. Transcranial magnetic stimulation and the human brain: an ethical evaluation. In: Illes J, editor. 21st Century neuroethics: defining the issues in research, practice and policy. Oxford, UK: Oxford University Press; 2006. p. 201–11.
Stewart LM, Walsh V, Rothwell JC. Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. Neuropsychologia 2001;39:415–9.
Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001;21:RC157.
Strens LH, Oliviero A, Bloem BR, Gerschlager W, Rothwell JC, Brown P. The effects of subthreshold 1 Hz repetitive TMS on cortico–cortical and interhemispheric coherence. Clin Neurophysiol 2002;113:1279–85.
Szuba MP, O'Reardon JP, Rai AS, Snyder-Kastenberg J, Amsterdam JD, Gettes DR, et al. Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. Biol Psychiat 2001;50:22–7.
Tassinari CA, Cincotta M, Zaccara G, Michelucci R. Transcranial magnetic stimulation and epilepsy. Clin Neurophysiol 2003;114:777–98.
Tergau F, Neumann D, Rosenow F, Nitsche MA, Paulus W, Steinhoff B. Can epilepsies be improved by repetitive transcranial magnetic stimulation? Interim analysis of a controlled study. Clin Neurophysiol 2003(Suppl. 56):400–5.
Tharayil BS, Gangadhar BN, Thirthalli J, Anand L. Seizure with single-pulse transcranial magnetic stimulation in a 35-year-old otherwise-healthy patient with bipolar disorder. J ECT 2005;21:188–9.
Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, et al. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. Neurology 2002;59:560–2.
Theoret H, Kobayashi M, Valero-Cabre A, Pascual-Leone A. Exploring paradoxical functional facilitation with TMS. Clin Neurophysiol 2003;56(Suppl.):211–9.
Thickbroom GW, Byrnes ML, Edwards DJ, Mastaglia FL. Repetitive paired-pulse TMS at I-wave periodicity markedly increases corticospinal excitability: a new technique for modulating synaptic plasticity. Clin Neurophysiol 2006;117:61–6.
Thielscher A, Kammer T. Linking physics with physiology in TMS: a sphere field model to determine the cortical stimulation site in TMS. Neuroimage 2002;17:1117–30.
Thielscher A, Kammer T. Electric field properties of two commercial figure-8 coils in TMS: calculation of focality and efficiency. Clin Neurophysiol 2004;115:1697–708.
Thut G, Northoff G, Ives JR, Kamitani Y, Pfennig A, Kampmann F, et al. Effects of single-pulse transcranial magnetic stimulation (TMS) on functional brain activity: a combined event-related TMS and evoked potential study. Clin Neurophysiol 2003a;114:2071–80.
Thut G, Théoret H, Pfennig A, Ives J, Kampmann F, Northoff G, et al. Differential effects of low-frequency rTMS at the occipital pole on visual-induced alpha desynchronization and visual-evoked potentials. Neuroimage 2003b;18:334–47.
Thut G, Ives JR, Kampmann F, Pastor MA, Pascual-Leone A. A new device and protocol for combining TMS and online recordings of EEG and evoked potentials. J Neurosci Methods 2005;141:207–17.
Tiitinen H, Virtanen J, Ilmoniemi RJ, Kamppuri J, Ollikainen M, Ruohonen J, et al. Separation of contamination caused by coil clicks from responses elicited by transcranial magnetic stimulation. Clin Neurophysiol 1999;110:982–5.
Tofts PS. The distribution of induced currents in magnetic stimulation of the brain. Phys Med Biol 1990;35:1119–28.

Tsuji T, Rothwell JC. Long lasting effects of rTMS and associated peripheral sensory input on MEPs, SEPs and transcortical reflex excitability in humans. J Physiol 2002;540:367–76.

Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Raju TR, Gangadhar BN. Modulation of cardiac autonomic functions in patients with major depression treated with repetitive transcranial magnetic stimulation. J Affect Disord 2007;104:231–6.

Valero-Cabré A, Pascual-Leone A, Rushmore RJ. Cumulative sessions of repetitive transcranial magnetic stimulation (rTMS) build up facilitation to subsequent TMS-mediated behavioural disruptions. Eur J Neurosci 2008;27:765–74.

Van Der Werf YD, Paus T. The neural response to transcranial magnetic stimulation of the human motor cortex. I. Intracortical and cortico–cortical contributions. Exp Brain Res 2006;175:231–45.

Van Der Werf YD, Sadikot AF, Strafella AP, Paus T. The neural response to transcranial magnetic stimulation of the human motor cortex. II. Thalamocortical contributions. Exp Brain Res 2006;175:246–55.

Vernieri F, Maggio P, Tibuzzi F, Filippi MM, Pasqualetti P, Melgari JM et al. High frequency repetitive transcranial magnetic stimulation decreases cerebralvasomotor reactivity. Clin Neurophysiol 2009 [Epub ahead of print].

Wagner TA, Zahn M, Grodzinsky AJ, Pascual-Leone A. Three-dimensional head model simulation of transcranial magnetic stimulation. IEEE Trans Biomed Eng 2004;51:1586–98.

Wagner T, Fregni F, Eden U, Ramos-Estebanez C, Grodzinsky A, Zahn M, et al. Transcranial magnetic stimulation and stroke: a computer-based human model study. Neuroimage 2006;30:857–70.

Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. Annu Rev Biomed Eng 2007;9:527–65.

Wagner T, Eden U, Fregni F, Valero-Cabre A, Ramos-Estebanez C, Pronio-Stelluto V, et al. Transcranial magnetic stimulation and brain atrophy: a computer-based human brain model study. Exp Brain Res 2008;186:539–50.

Wassermannn EM. Risk and safety of 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.

Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, et al. Use and safety of a new repetitive transcranial magnetic stimulator. Electroencephalogr Clin Neurophysiol 1996;101:412–7.

Wassermannn EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 2001;112:1367–77.

Weissman JD, Epstein CM, Davey KR. Magnetic brain stimulation and brain size: relevance to animal studies. Electroencephalogr Clin Neurophysiol 1992;85:215–9.

Weyh T, Wendicke K, Mentschel C, Zantow H, Siebner HR. Marked differences in the thermal characteristics of figure-of-eight shaped coils used for repetitive transcranial magnetic stimulation. Clin Neurophysiol 2005;116:1477–86.

Wolpe PR. Treatment, enhancement, and the ethics of neurotherapeutics. Brain Cogn 2002;50:387–95.

Wolters A, Schmidt A, Schramm A, Zeller D, Naumann M, Kunesch E, et al. Timing-dependent plasticity in human primary somatosensory cortex. J Physiol 2005;565:1039–52.

Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ, et al. Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int J Neuropsychopharmacol 2008;11:119–30.

Yoshida T, Yoshino A, Kobayashi Y, Inoue M, Kamakura K, Nomura S. Effects of slow repetitive transcranial magnetic stimulation on heart rate variability according to power spectrum analysis. J Neurol Sci 2001;184:77–80.

Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. Clin Neurophysiol 2005;116:775–9.

Zwanzger P, Ella R, Keck ME, Rupprecht R, Padberg F. Occurrence of delusions during repetitive transcranial magnetic stimulation (rTMS) in major depression. Biol Psychiat 2002;51:602–3.

Clinical Neurophysiology 121 (2010) 1930–1933

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Cortico-conus motor conduction time (CCCT) for leg muscles

Hideyuki Matsumoto [a,*], Ritsuko Hanajima [a], Yuichiro Shirota [a], Masashi Hamada [a], Yasuo Terao [a], Shinya Ohminami [a], Toshiaki Furubayashi [a], Setsu Nakatani-Enomoto [b], Yoshikazu Ugawa [b]

[a] Department of Neurology, Division of Neuroscience, Graduate School of Medicine, The University of Tokyo, Japan
[b] Department of Neurology, School of Medicine, Fukushima Medical University, Japan

ARTICLE INFO

Article history:
Accepted 19 April 2010
Available online 14 May 2010

Keywords:
Magnetic stimulation
Motor evoked potential
Cortico-conus motor conduction time (CCCT)
Central motor conduction time (CMCT)
Pyramidal tract

ABSTRACT

Objective: To measure the conduction time from the motor cortex to the conus medullaris (cortico-conus motor conduction time, CCCT) for leg muscles using magnetic stimulation.
Methods: Motor evoked potentials (MEPs) were recorded from tibialis anterior muscles in 51 healthy volunteers. To activate spinal nerves at the most proximal cauda equina level or at the conus medullaris level, magnetic stimulation was performed using a MATS coil. Transcranial magnetic stimulation of the motor cortex was also conducted to measure the cortical latency for the target muscle. To obtain the CCCT, the latency of MEPs to conus stimulation (conus latency) was subtracted from the cortical latency.
Results: MATS coil stimulation evoked reproducible MEPs in all subjects, yielding CCCT data for all studied tibialis anterior muscles.
Conclusions: MATS coil stimulation provides CCCT data for healthy subjects.
Significance: This novel method is useful for evaluation of corticospinal tract function for leg muscles because no peripheral component affects the CCCT.
© 2010 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Magnetic stimulation enables us to evaluate the corticospinal tract function non-invasively by measuring the central motor conduction time (CMCT) (Rossini et al., 1994; Chen et al., 2008). The CMCT is usually obtained by subtracting the motor evoked potential (MEP) latency to magnetic stimulation over the spinal enlargement (spinal latency) from that to magnetic stimulation over the primary motor cortex (cortical latency). Magnetic stimulation over the spinal enlargement activates the spinal nerve at the neuro-foramina level (Ugawa et al., 1989b). Therefore, the CMCT described above includes the conduction time through the spinal nerves running in the spinal canal (Rossini et al., 1994; Chen et al., 2008).

Maccabee et al. reported that an 8-shaped coil can activate the most proximal cauda equina at around the conus medullaris (Maccabee et al., 1996). They proposed the possibility that this stimulation method might enable us to measure the conduction time from the motor cortex to the conus medullaris [cortico-conus motor conduction time (CCCT)]. The CCCT necessarily reflects the corticospinal tract function more correctly than the conventional CMCT because peripheral components (some conduction time within the cauda equina) do not contribute to CCCT, especially in patients with peripheral neuropathy. The CCCT, however, has not been widely used yet.

A few alternative methods can be used to measure the proximal spinal nerve conduction time, such as F-wave measurement and high-voltage electrical stimulation (Ugawa et al., 1988a,b, 1989a, 1995; Claus, 1990; Eisen and Shtybel, 1990). However, F-wave measurement provides no information about the lesion sites, and high-voltage electrical stimulation is often associated with severe pain. Especially, high-voltage electrical stimulation is not tolerated by patients with skin problems (Matsumoto et al., 2005, in press).

We have developed a new method to activate the most proximal cauda equina at around the conus medullaris level using a specially devised coil [magnetic augmented translumbosacral stimulation (MATS) coil] (Matsumoto et al., 2009a,b).

The aim of this paper is to apply the MATS coil to CCCT measurement. The relation between MEP latency and body height was also studied.

2. Materials and methods

2.1. Subjects

Subjects were 51 healthy volunteers (25 men and 26 women). Their mean age and body height were 42.1 ± 15.5 (mean ± standard deviation (SD); range 24–78) years and 163.9 ± 9.3 (144–185) cm.

* Corresponding author. Address: Department of Neurology, Division of Neuroscience, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: +81 3 5800 8672; fax: +81 3 5800 6548.
E-mail address: hideyukimatsumoto@mail.goo.ne.jp (H. Matsumoto).

1388-2457/$36.00 © 2010 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.clinph.2010.04.014

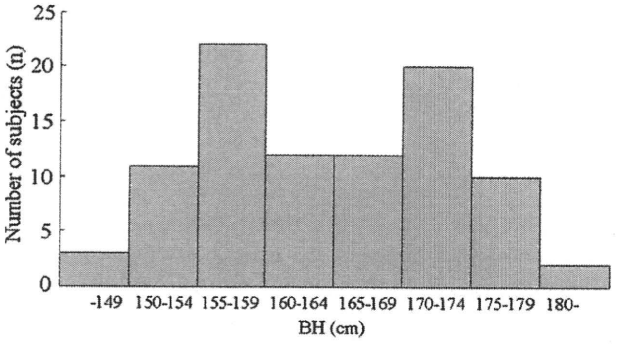

Fig. 1. Histogram of body height. There is no extremely skewed distribution of body height in our study.

The histogram of body height is shown in Fig. 1. No extremely skewed distribution of body height was observed.

Informed consent to participate in this study was obtained from all subjects. The protocol was approved by the Ethics Committee of the University of Tokyo. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

2.2. Stimulation, recording and analysis

During the examination, MEPs were recorded from the tibialis anterior muscle (TA) as subjects sat comfortably on a bed. The TA muscle was selected because this muscle could be easily contracted and recorded compared to other leg muscles. Disposable silver–silver chloride disc electrodes of 9 mm diameter were placed in a belly tendon montage over TA. Signals were amplified with filters set at 20 Hz and 3 kHz and recorded using a computer (Neuropack MEB-9100; Nihon Kohden Corp., Japan).

Magnetic stimulation was conducted using a monophasic stimulator (Magstim 200; The Magstim Co. Ltd., UK). For cortical magnetic stimulation, a double-cone coil (The Magstim Co. Ltd., UK) was placed over the Cz (international 10–20 system), with induced currents flowing mediolaterally over the contralateral leg motor area (Terao et al., 1994, 2000). The MEP onset latency was measured in the active condition (cortical latency).

Fig. 2 portrays the placement of MATS coil (diameter 20 cm, 0.98 T; The Magstim Co. Ltd., UK) when recording MEPs from the right TA. The MATS coil was always placed from the midline to the contralateral side of the body (the opposite side from the recorded muscle) to prevent some non-target parts of the coil from activating distal peripheral nerves for the target TA. The most proximal cauda equina at around the conus medullaris was activated using the MATS coil, whose edge was positioned over the first lumbar (L1) spinous process for inducing currents to flow upward in the body (Matsumoto et al., 2009b). For the neuro-foramina level stimulation, the edge of MATS coil was positioned over the fifth lumbar (L5) spinous process for inducing currents to flow 45° downward from horizontal direction (Matsumoto et al., 2009a). This direction of induced currents (45°) was optimal to elicit MEPs because the induced currents should flow along the anatomical course of spinal nerves (Ugawa et al., 1989b; Epstein et al., 1991; Mills et al., 1993; Maccabee et al., 1996; Ruohonen et al., 1996; Matsumoto et al., 2009a). In L1 and L5 level stimulation, the onset latencies of MEPs were measured in the relaxed condition (L1 and L5 level latencies).

To obtain the minimal and reproducible MEP latency, the stimulus intensity was increased gradually and several MEPs evoked by stimulation at several different intensities were superimposed. The CCCT, conventional CMCT, and cauda equina conduction time (CECT) were obtained (92 sides). The CCCT was obtained by subtracting the L1 level latency from the cortical latency, the conventional CMCT by subtracting the L5 level latency from the cortical latency, and the CECT by subtracting L5 level latency from L1 level latency. Linear regression analysis was conducted to investigate the relation between each conduction time and body height.

The MEP sizes were compared between the simulation positions (60 sides). The base-to-peak amplitude of MEP was mea-

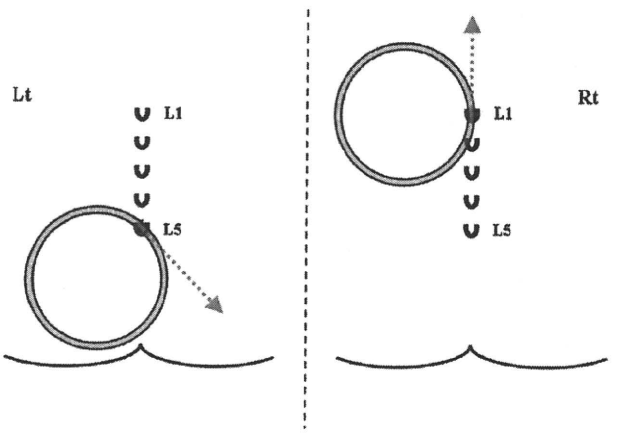

Fig. 2. MATS coil stimulation method. This figure shows positions of MATS coil when MEPs are recorded from right TA. For the most proximal cauda equina stimulation, the edge of MATS coil is positioned over the first lumbar spinous process for inducing currents to flow upward. For neuro-foramina level stimulation, the edge of the MATS coil is positioned over the fifth lumbar spinous process for inducing currents to flow 45° downward from a horizontal direction.

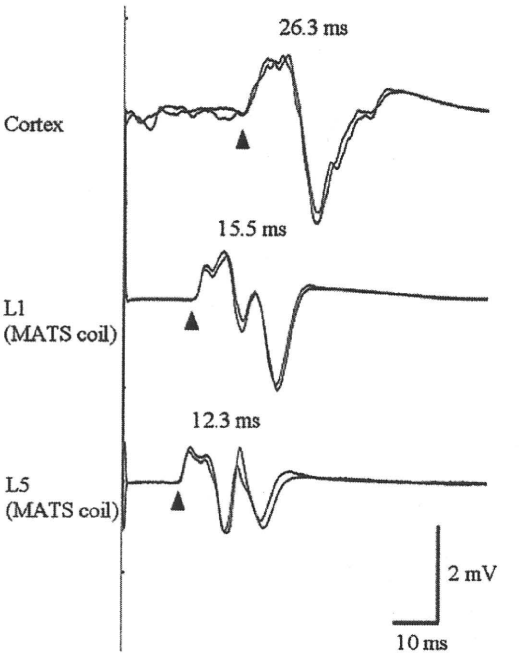

Fig. 3. Representative MEPs in a normal subject. The conventional CMCT is obtained by calculating the latency difference between MEPs to cortical and L5 level stimulation. Similarly, the CCCT is obtained by calculating the latency difference between MEPs to cortical and L1 level stimulation.

sured. At L1 and L5 levels, the intensity was increased gradually to the maximal stimulator output (100%). The amplitudes of maximal MEPs were compared between two level stimulation positions (maximal MEP means an MEP to supramaximal stimulation or MEP to submaximal stimulation with maximal stimulator output). The MEP amplitudes of the two level stimulation positions were compared using Wilcoxon's signed rank test; p values less than 0.05 were considered statistically significant.

3. Results

No subjects experienced any intolerable discomfort during MATS coil stimulation. No side effect was noted. Fig. 3 shows representative MEPs in a normal subject. The conventional CMCT was obtained using the MEPs to cortical and L5 level stimulation (14.0 ms). Moreover, L1 level stimulation evoked discernible MEPs. The CCCT was 10.8 ms, and the CECT 3.2 ms.

In all subjects, L1 level MATS coil stimulation evoked reproducible MEPs. The L1 level latency was longer than L5 level latency. The mean latencies and conduction times are presented in Table 1.

The correlations between each conduction time and body height are depicted in Fig. 4. Significant and positive linear relations were found between the conventional CMCT and body height ($p < 0.001$; conventional CMCT = 0.045 × body height + 7.166, $R = 0.366$), and between CECT and body height ($p = 0.001$; latency = 0.032 × body height − 2.602, $R = 0.331$). No significant correlation was found between CCCT and body height ($p = 0.298$).

The MEPs to L1 level stimulation (median: 1.0 mV, 25–75 percentiles: 0.5–1.8 mV) were significantly smaller than MEPs to L5 level stimulation were (1.3 mV, 1.0–3.5) ($p < 0.001$).

Table 1
Normal values of latencies (51 subjects, 92 sides).

	Mean ± SD (ms)
Cortical latency	26.1 ± 1.6
L1 level latency	14.0 ± 1.4
L5 level latency	11.5 ± 0.9
CCCT	12.3 ± 1.2
Conventional CMCT	14.6 ± 1.2
CECT	2.6 ± 0.9

CCCT, cortico-conus motor conduction time; CMCT, central motor conduction time; CECT, cauda equina conduction time; SD, standard deviation.

4. Discussion

In all subjects, L1 level MATS coil stimulation elicited discernible MEPs to measure onset latency. It enabled us to obtain CCCTs. The CCCT is more suitable for evaluating the corticospinal function for leg muscles than the conventional CMCT because no cauda equina conduction component contributes to CCCT. Another superior point of this stimulation method is the evaluation of conduction through the cauda equina using CECT. The authors have earlier reported some utility of this stimulation method for evaluating cauda equina conduction in patients with peripheral neuropathy (Matsumoto et al., 2010).

In this study, the CECT was found to be 2.6 ± 0.9 ms, which is similar to previously reported values obtained using an 8-shaped coil (2.3 or 2.6 ms) (Maccabee et al., 1996; Maegaki et al., 1997). Therefore, L1 level MATS coil stimulation does activate the cauda equina at the root exit site from the conus medullaris, as described in previous reports (Maccabee et al., 1996; Maegaki et al., 1997; Matsumoto et al., 2009b), namely at the conus medullaris level. Therefore, the latency difference between cortical and L1 level stimulation was designated as the cortico-conus motor conduction time (CCCT).

Regarding the relation between each conduction time and body height, the conventional CMCT and CECT had significant correlation with body height, but the CCCT did not. These results are not completely consistent with those of previous reports (Chu, 1989; Ugawa et al., 1989a; Claus, 1990; Furby et al., 1992). Previous reports have described that the conventional CMCT for lower extremities is significantly affected by the body height (Chu, 1989; Furby et al., 1992), according with our results. On the other hand, the correlation between the CCCT and body height is contro-

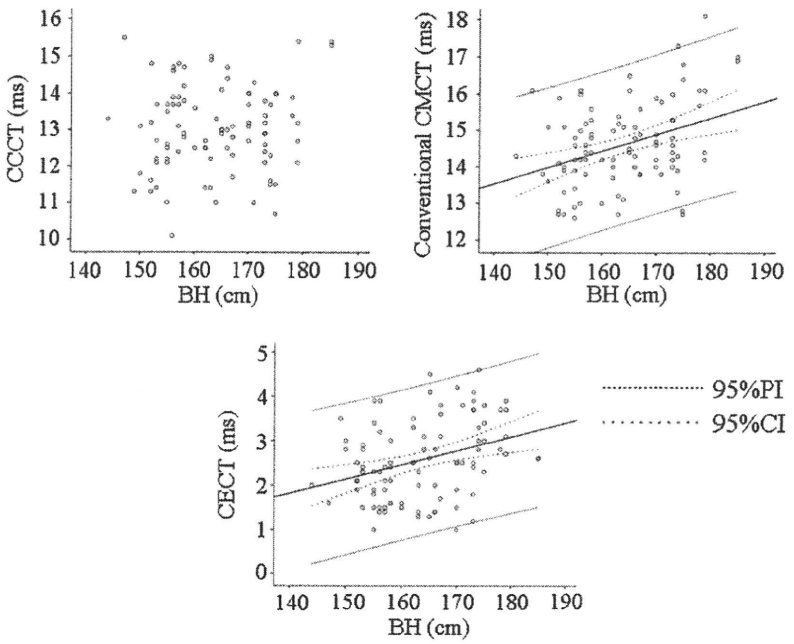

Fig. 4. Relation between each conduction time and body height. The CCCT is not significantly correlated with body height ($p = 0.298$). A significant and positive linear relation was found between the conventional CMCT and body height ($p < 0.001$; conventional CMCT = 0.045 × body height + 7.166, $R = 0.366$). Similarly, a significant correlation was found for CECT ($p = 0.001$; latency = 0.032 × body height − 2.602, $R = 0.331$). PI, prediction interval; CI, confidence interval.

versial. Ugawa et al. reported that the cortical–L1 conduction time measured using high-voltage electrical stimulation was not significantly correlated with body height (Ugawa et al., 1989b). In contrast, Claus reported that the cortical–L1 conduction time measured using transcranial magnetic stimulation and high-voltage electrical stimulation had a significant correlation with body height (Claus, 1990). The results in this study were similar to that in the former report. One plausible explanation of this discrepancy might be the difference in the body height of subjects. The average (range) of body height in the paper of Ugawa et al. was about 163 (151–178) cm and that in Claus was about 173 (156–191) cm. The body height in this study was almost same (164 cm) as that in the paper of Ugawa et al. The difference in body height seems to be due to the difference between Japanese and European peoples. Whatever the difference, this study demonstrates that the CCCT is relatively independent of body height compared to the conventional CMCT and CECT.

The relative independence of the CCCT from the body height might be mainly explained by the disproportion between growths in length of the spinal cord and the vertebral column (Kunitomo, 1918; Vettivel, 1991). The spinal cord length does not elongate proportionally to body height, although the cauda equina elongates concomitantly with the spine growth proportionally to body height. Large variability of the conduction velocity of the corticospinal tracts between subjects might also explain the lack of significant relation between CCCT and body height. Indeed, the conduction velocity in awake human estimated by Ugawa et al. (1995) ranged from 62.0 to 79.0 m/s, and that in anesthetized human by Fujiki et al., (1996) ranged from 50.5 to 72.7 m/s (Ugawa et al., 1995; Fujiki et al., 1996).

One point of caution related to this method is the MEP amplitude. The MEPs evoked by L1 level stimulation were often smaller than those by L5 level stimulation in normal subjects, which suggests that an amplitude comparison between L1 and L5 level stimulation is not useful for evaluation of the conduction block within the cauda equina even though the latencies are good parameters for evaluation of motor conduction. Another point of caution is the difference of CCCT between target muscles. If another muscle is selected, the normal value of CCCT should be made for each target muscle.

In conclusion, we propose that the MATS coil is useful for the accurate evaluation of corticospinal tract function for leg muscles.

Acknowledgments

This work was supported by the Daiwa Anglo–Japanese Foundation, by Research Project Grants-in-aid for Scientific Research No. 17590865 (R.H.) and No. 18590928 (Y.T.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, by grants from the Research Committee on rTMS treatment of movement disorders, the Ministry of Health and Welfare of Japan (17231401) and the Research Committee on Dystonia, the Ministry of Health and Welfare of Japan, by a grant from the Committee for the study of Human Exposure to EMF, Ministry of Internal Affairs and Communications, and by a Research Grant from the Magnetic Health Science Foundation and Telecommunications.

References

Chen R, Cros D, Curra A, Di Lazzaro V, Lefaucheur JP, Magistris MR, et al. The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2008;119:504–32.

Chu NS. Motor evoked potentials with magnetic stimulation: correlations with height. Electroencephalogr Clin Neurophysiol 1989;74:481–5.

Claus D. Central motor conduction: method and normal results. Muscle Nerve 1990;13:1125–32.

Eisen AA, Shtybel W. Clinical experience with transcranial magnetic stimulation. Muscle Nerve 1990;13:995–1011.

Epstein CM, Fernandez-Beer E, Weissman JD, Matsuura S. Cervical magnetic stimulation. The role of the neural foramen. Neurology 1991;41:677–80.

Fujiki M, Isono M, Hori S, Ueno S. Corticospinal direct response to transcranial magnetic stimulation in humans. Electroencephalogr Clin Neurophysiol 1996;101:48–57.

Furby A, Bourriez JL, Jacquesson JM, Mounier-Vehier F, Guieu JD. Motor evoked potentials to magnetic stimulation: technical considerations and normative data from 50 subjects. J Neurol 1992;239:152–6.

Kunitomo K. The development and rejection of the tail end of the caudal end of the spinal cord in the human embryo. Contrib Embryol 1918;26:161–98.

Maccabee PJ, Lipitz ME, Desudchit T, Golub RW, Nitti VW, Bania JP, et al. A new method using neuromagnetic stimulation to measure conduction time within the cauda equina. Electroencephalogr Clin Neurophysiol 1996;101:153–66.

Maegaki Y, Maeoka Y, Takeshita K. Magnetic stimulation of the lumbosacral vertebral column in children: normal values and possible sites of stimulation. Electroencephalogr Clin Neurophysiol 1997;105:102–8.

Matsumoto H, Seki N, Yamamoto T, Oshima K, Asai T, Motokura T, et al. A case of asymmetric demyelinating neuropathy in a patient with chronic graft-versus-host disease. Rinshoshinkeigaku 2005;45:748–53 [in Japanese].

Matsumoto H, Octaviana F, Hanajima R, Terao Y, Yugeta A, Hamada M, et al. Magnetic lumbosacral motor root stimulation with a flat, large round coil. Clin Neurophysiol 2009a;120:770–5.

Matsumoto H, Octaviana F, Terao Y, Hanajima R, Yugeta A, Hamada M, et al. Magnetic stimulation of the cauda equina in the spinal canal with a flat, large round coil. J Neurol Sci 2009b;284:46–51.

Matsumoto H, Hanajima R, Terao Y, Yugeta A, Hamada A, Shirota Y, et al. Prominent cauda equina involvement in patients with chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Sci 2010;290:112–4.

Matsumoto L, Hanajima R, Matsumoto H, Ohminami S, Terao Y, Tsuji S, et al. Supramaximal responses can be elicited in hand muscles by magnetic stimulation of the cervical motor roots. Brain Stimulat, in press. doi:10.1016/j.brs.2009.09.001.

Mills KR, McLeod C, Sheffy J, Loh L. The optimal current direction for excitation of human cervical motor roots with a double coil magnetic stimulator. Electroencephalogr Clin Neurophysiol 1993;89:138–44.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Dimitrijević MR, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994;91:79–92.

Ruohonen J, Panizza M, Nilsson J, Ravazzani P, Grandori F, Tognola G. Transverse-field activation mechanism in magnetic stimulation of peripheral nerves. Electroencephalogr Clin Neurophysiol 1996;101:167–74.

Terao Y, Ugawa Y, Sakai K, Uesaka Y, Kohara N, Kanazawa I. Transcranial stimulation of the leg area of the motor cortex in humans. Acta Neurol Scand 1994;89:378–83.

Terao Y, Ugawa Y, Hanajima R, Machii K, Furubayashi T, Mochizuki H, et al. Predominant activation of I1-waves from the leg motor area by transcranial magnetic stimulation. Brain Res 2000;859:137–46.

Ugawa Y, Shimpo T, Mannen T. Central motor conduction in cerebrovascular disease and motor neuron disease. Acta Neurol Scand 1988a;78:297–306.

Ugawa Y, Kohara N, Shimpo T, Mannen T. Central motor and sensory conduction in adrenoleukomyeloneuropathy, cerebrotendinous xanthomatosis, HTLV-1-associated myelopathy and tabes dorsalis. J Neurol Neurosurg Psychiatry 1988b;51:1069–74.

Ugawa Y, Genba K, Shimpo T, Mannen T. Physiologic analysis of central motor pathways – simultaneous recording from multiple relaxed muscles. Eur Neurol 1989a;29:135–40.

Ugawa Y, Rothwell JC, Day BL, Thompson PD, Marsden CD. Magnetic stimulation over the spinal enlargements. J Neurol Neurosurg Psychiatry 1989b;52:1025–32.

Ugawa Y, Genba-Shimizu K, Kanazawa I. Electrical stimulation of the human descending motor tracts at several levels. Can J Neurol Sci 1995;22:36–42.

Vettivel S. Vertebral level of the termination of the spinal cord in human. J Anat 1991;179:149–61.

Movement Disorders
Vol. 25, No. 14, 2010, pp. 2413–2419
© 2010 Movement Disorder Society

Cerebellar Dysfunction in Progressive Supranuclear Palsy: A Transcranial Magnetic Stimulation Study

Yuichiro Shirota, MD,[1]* Masashi Hamada, MD, PhD,[1] Ritsuko Hanajima, MD, PhD,[1] Yasuo Terao, MD, PhD,[1] Hideyuki Matsumoto, MD,[1] Shinya Ohminami, MD,[1] Shoji Tsuji, MD, PhD,[1] and Yoshikazu Ugawa, MD, PhD[2]

[1]*Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, Tokyo, Japan*
[2]*Department of Neurology, School of Medicine, Fukushima Medical University, Fukushima, Japan*

Abstract: Progressive supranuclear palsy (PSP) rarely shows cerebellar signs and symptoms even though the cerebellar dentate nuclei are involved pathologically. This study evaluates cerebellar function using transcranial magnetic stimulation (TMS) to determine whether subclinical cerebellar involvement is present in PSP patients. We studied 11 patients with PSP, 11 patients with Parkinson's disease (PD), and 10 age-matched controls. Patients were examined with their usual medications and in their relative on state. Motor evoked potentials (MEPs) were recorded from the hand muscle. Cerebellar function was evaluated using suppressive effects of TMS over the cerebellum on MEPs elicited by TMS over the contralateral motor cortex, which we call cerebellar inhibition (CBI). Interstimulus intervals (ISIs) of 4 to 8 ms were used, and the time course of CBI was analyzed. The CBI was reduced in PSP patients. By contrast, the CBI was normal in PD patients in their on state. Although the CBI in their off state should be examined in future studies, the results described herein suggest that Purkinje cells or the dentato–thalamo–cortical pathway assessed by CBI is involved in PSP. Our results are compatible with the pathological findings showing severe dentate nucleus degeneration in PSP patients. © 2010 Movement Disorder Society

Key words: progressive supranuclear palsy; cerebellum; transcranial magnetic stimulation

INTRODUCTION

Progressive supranuclear palsy (PSP) is a syndrome that is typically characterized by postural instability and supranuclear gaze palsy.[1] Although a recent study reported pathologically confirmed PSP patients developing cerebellar ataxia as the initial and principal symptom,[2] clinical signs of cerebellar dysfunction are usually considered rare. In contrast, involvement of the cerebellar dentate nucleus has been well documented to be the cardinal neuropathological findings in PSP.[1] With this background, neurophysiological evaluation of cerebellar functions in PSP would be an interesting approach to clarify the presence of subclinical cerebellar dysfunctions, but such investigations have not been well documented.

Transcranial magnetic stimulation (TMS) is a noninvasive technique to stimulate the human brain. Cerebellar function can be studied using the paired-pulse paradigm; a preceding TMS over the cerebellum decreased the size of motor evoked potentials (MEPs) elicited by TMS over the contralateral primary motor cortex (M1) at interstimulus intervals (ISIs) of 5 to 7 ms.[3] The suppressive effect is likely to be derived from activation of Purkinje cells that inhibit or disfacilitate the dentato–thalamo–cortical pathway. For descriptive purposes only, in this article, we refer to this inhibition as cerebellar inhibition (CBI).[4]

This study evaluated cerebellar function using this technique in PSP patients. For comparison, we also studied patients with Parkinson's disease (PD), in which some brain structures common to PSP are involved.

*Correspondence to: Yuichiro Shirota, Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, Tokyo, Japan E-mail: yshirota-tky@umin.ac.jp

Potential conflict of interest: Nothing to report.

Received 14 January 2010; Revised 4 March 2010; Accepted 11 May 2010

Published online 3 September 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23298

METHODS

Participants

We studied 11 patients with probable PSP according to the National Institute of Neurological Disorders and Stroke and the Society for PSP, (NINDS-SPSP) criteria,[5] 11 patients with PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria,[6] and 10 healthy right-handed healthy volunteers (Table 1). No participants had any contraindication to TMS.[7] No patients showed pyramidal signs or cerebellar ataxia. All participants gave their written informed consent. This study was approved by the Institutional Review Board. Severity of the disease was assessed using the Hoehn and Yahr staging and the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Table 1). Dopaminergic medications were expressed as levodopa (L-dopa) equivalent daily dose (LEDD) as reported elsewhere[8]: 1 mg of pergolide = 1 mg of pramipexole = 5 mg of ropinirole = 10 mg of bromocriptine = 100 mg of L-dopa.

Recording

A surface electromyogram (EMG) was recorded from the first dorsal interosseous (FDI) muscle using a belly tendon montage on the more affected side with larger summed score of items 23 to 25 of the UPDRS Part III in PD and PSP patients, and on the right side in healthy subjects. Responses input to an amplifier (Biotop; GE Marquette Medical Systems, Japan) through filters set at 100 Hz and 3 kHz were digitized and stored in a computer for later offline analyses (TMS bistim tester; Medical Try System, Japan).

TABLE 1. *Clinical features and basic electrophysiological values*

	PSP	PD	Control	*P* value
Female: male (*n*)	4: 7	4: 7	9: 1	
Age at exam[a] (yr)	72.7 ± 7.8	68.4 ± 8.7	64.0 ± 6.4	0.06
Disease duration[a] (yr)	4.5 ± 2.7	15.9 ± 9.7		0.001
Hoehn and Yahr stage (*n*)				0.06
2	0	5		
3	6	3		
4	4	3		
5	1	0		
UPDRS III[b]	27 (9–75)	22 (13–51)		0.77
Test MEP size[a] (mV)	0.52 ± 0.15	0.62 ± 0.22	0.50 ± 0.16	0.27
CMCT[a] (ms)	6.3 ± 0.38	6.5 ± 0.72	6.7 ± 0.64	0.45

[a]Values are shown as mean ± SD.
[b]Values are shown as median (range).
PSP, progressive supranuclear palsy; PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale; MEP, motor evoked potential; CMCT, central motor conduction time.

Transcranial Magnetic Stimulation

For TMS over the cerebellum (conditioning stimulus, CS), a double-cone coil (110 mm mean diameter) was centered over the midpoint between the inion and the mastoid process ipsilateral to the recording side. Current in the coil was directed downward (that is, upward current was induced in the cerebellum).[3] The M1 was stimulated using a round coil (90 mm mean diameter) centered over the vertex (test stimulus, TS). Current in the coil was directed anteroposteriorly over the target M1 (posteroanterior current in the target M1). Monophasic TMS pulses were delivered using two magnetic stimulators (Magstim 200; The Magstim).

EXPERIMENTAL DESIGN

The CBI was examined as described previously.[3] We first determined the active motor threshold (AMT) for pyramidal tract activation at the brainstem with the double-cone coil centered over the inion.[9] CS was fixed at an intensity of 95% AMT and given at 4, 5, 6, 7, and 8 ms before the test stimulus. The intensity of the TS was adjusted to elicit MEPs of 0.5 mV on average when given alone. The experiment was performed with the target muscle relaxed, as confirmed by an oscilloscope monitor. Seven trials recorded for each ISI (i.e., conditioned trials) were randomly intermixed with 10 trials in which TS was delivered alone (i.e., unconditioned trials) with an intertrial interval of 10 s. When recording was contaminated by voluntary EMG, such trials were discarded from the analyses. When necessary, we briefly stopped the session to maintain the resting state of the target muscle. We also evaluated the central motor conduction time (CMCT), as described previously.[10] The patients on medications were studied when they were in the relative on state; that is, they took their medications as usual, and the experiments were performed ~2 hours after their morning or noon dose.

Data analyses

We used one-way analysis of variance (ANOVA) for comparisons of the following parameters among the groups (i.e., PSP, PD, and controls): the age at examination, test MEP size, and CMCT. Student's *t* test was used to compare the disease duration, and Mann-Whitney U test was used to compare the Hoehn and Yahr stages and UPDRS Part III scores between the

TABLE 2. *Clinical features of each patient*

Case No.	Age (yr)	Disease duration (yr)	H & Y stage	UPDRS part III	UPDRS item 20 (rest tremor)	UPDRS item 21 (postural tremor)	LEDD (mg)
PSP 1	61	5	3	19	0	0	0
PSP 2	76	7	4	40	0	1	300
PSP 3	57	1	3	29	0	0	0
PSP 4	78	4	3	9	0	0	0
PSP 5	84	4	3	9	0	0	0
PSP 6	73	3	3	14	0	0	0
PSP 7	71	7	4	45	0	0	100
PSP 8	75	2	4	45	0	0	0
PSP 9	78	2	3	20	0	0	0
PSP 10	77	5	4	27	0	0	0
PSP 11	70	10	5	75	0	0	300
PD 1	72	19	3	25	3	0	405
PD 2	52	9	2	20	0	0	750
PD 3	75	3	2	15	0	0	0
PD 4	81	10	4	36	5	2	500
PD 5	64	23	3	22	0	0	700
PD 6	70	21	4	51	7	2	515
PD 7	72	3	2	19	1	1	200
PD 8	60	35	2	15	0	0	975
PD 9	66	12	2	13	0	0	425
PD 10	79	24	4	36	0	0	350
PD 11	61	16	3	28	5	0	625

H & Y stage, Hoehn and Yahr stage; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease, PSP, progressive supranuclear palsy; UPDRS, unified Parkinson's disease rating scale.

two disease groups. To evaluate the time course of CBI among groups, the ratio of the mean peak-to-peak amplitude of the conditioned MEPs to that of unconditioned MEPs was calculated for each ISI in each subject. These individual mean ratios from all subjects in each group were then averaged to produce a grand mean ratio for that group. We analyzed the CBIs in different groups using two-way repeated measures ANOVA with GROUP (PSP, PD, or control) as the between-subject factor and with ISI as the within-subject factor. Bonferroni's post hoc tests were used for additional analyses.

To further investigate the relations between CBI and other demographic or clinical features, average size ratio (ASR) was calculated for each participant by averaging the MEP ratio across ISIs of 5 to 7 ms.[11] The correlation of age with the ASR was tested for each group of the subjects using linear regression analyses. Possible relations between the CBI and disease severity in the patient groups were analyzed in two manners. First, one-way ANOVA was conducted for each patient group to analyze effect of Hoehn and Yahr stage. Second, the correlation between ASR and UPDRS part III score was investigated using linear regression analyses. Difference in the ASR between PD patients with and without tremor was studied using the Student's *t* test. Influence of the dopaminergic medication in PSP patients was assessed by comparing the mean ASR of the PSP patients with medications to that of the PSP patients without medications, using the Student's *t* test. We did not conduct such analyses for PD patients, because all but one patient was taking dopaminergic medication.

A P-value < 0.05 was considered significant. Data were analyzed using a commercial software (*SPSS* for Windows ver. 13; SPSS, Chicago, IL, USA).

RESULTS

No significant age difference was found among groups, but it tended to be higher in the PSP group. Disease duration differed significantly between PD and PSP (Table 1). Neither the amplitude of test MEP size nor CMCT differed significantly among groups (Table 1). Test stimulus intensity expressed as %maximal stimulator output (%MSO) was 55.6% ± 11.9% (mean ± standard deviation; range 38–72%) in the PSP group, 51.6% ± 17.1% (range 28–80%) in the PD group, and 55.4% ± 16.6% (range 39–90%) in the healthy controls. AMT for pyramidal tract activation at the brainstem was 54.3% ± 11.6% MSO (range 38–70%) in the PSP group, 63.2% ± 19.1% (range 38–100%) in the PD group, and 45.4% ± 13.5% (range 27–70%) in the healthy controls.

Table 2 shows clinical details of the PSP and PD patients. Three PSP patients were on dopaminergic medication.

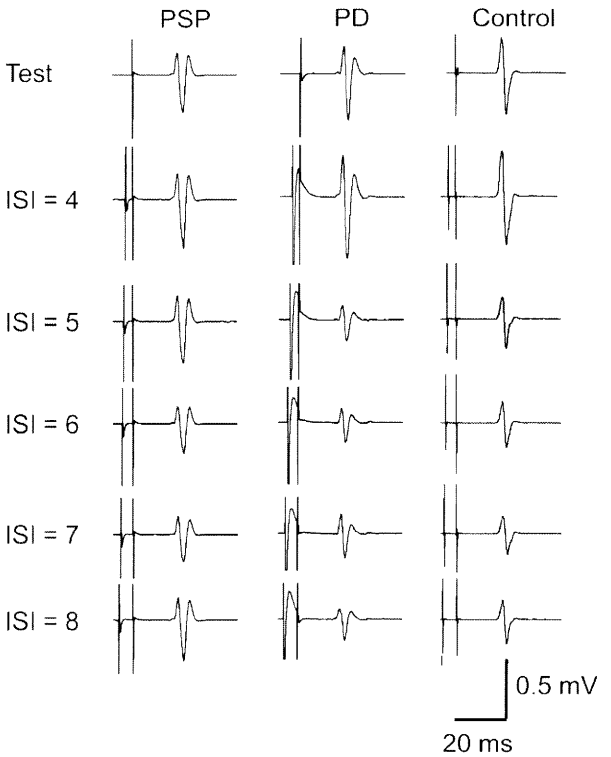

FIG. 1. Representative responses from a single subject of each group. Traces show averaged motor evoked potentials (MEPs) from one PSP patient, one PD patient, and one healthy volunteer. The top row shows unconditioned responses (averaged over 10 trials). The lower rows demonstrate conditioned responses for each ISI (averaged over seven trials). In a PSP patient, the suppression was reduced at ISIs of 6 and 7 ms. No suppression was present at ISIs of 5 and 8 ms. In contrast, MEPs were inhibited at ISIs of 5 to 8 ms in a PD patient and a healthy volunteer.

Figure 1 presents representative responses in a single participant from each group. In a healthy volunteer, the conditioned response at an ISI of 4 ms was similar in size to the unconditioned response. In contrast, the conditioned MEPs were smaller than the unconditioned MEP at ISIs of 5 to 8 ms. Similar results were obtained in a PD patient, indicating normal CBI. In a PSP patient, in contrast, the inhibition at ISIs of 5 to 8 ms was reduced. The mean time courses of CBI are depicted in Figure 2. They also demonstrated reduced CBI in PSP patients. The statistical comparisons disclosed an effect of GROUP (F (2,29) = 7.703, P = 0.002) and an effect of ISI (F (4,116) = 7.206, P < 0.001). Post hoc analysis revealed that PSP showed reduced CBI than PD (P = 0.005) or controls (P = 0.008), but no significant difference between PD and controls. Furthermore, a significant difference between PSP and PD was found at ISIs of 5, 6, and 7 ms (P = 0.011, 0.029, and 0.005, respectively). No significant difference was found between PD and controls at any ISIs.

We found no significant correlation between the CBI assessed by ASR and age in any of the groups (R^2 = 0.034, P = 0.61 in the control group, R^2 = 0.012, P = 0.75 in the PSP group, and R^2 = 0.001, P = 0.90 in the PD group). One-way ANOVA with regard to the Hoehn and Yahr stages revealed significant main effect of disease severity on CBI in the PSP group (P = 0.007, Fig. 3A), but not in the PD group (P = 0.70, Fig. 3B). Furthermore, we found a significant correlation between the ASR and UPDRS part III score in the PSP group (R^2 = 0.76, P < 0.001, Fig. 3C), but not in the PD group (R^2 = 0.006, P = 0.81, Fig. 3D). We found normal CBI in PD patients, irrespective of the presence or absence of tremor. ASR was 0.66 ± 0.08 in PD patients with tremor; and 0.60 ± 0.16 in those without (P = 0.49). CBI was abnormally reduced (ASR 0.90) in one PSP patient showing tremor (patient No. PSP 2 in Table 2). The ASR of PSP patients with medication was 1.14 ± 0.29, and that of PSP without

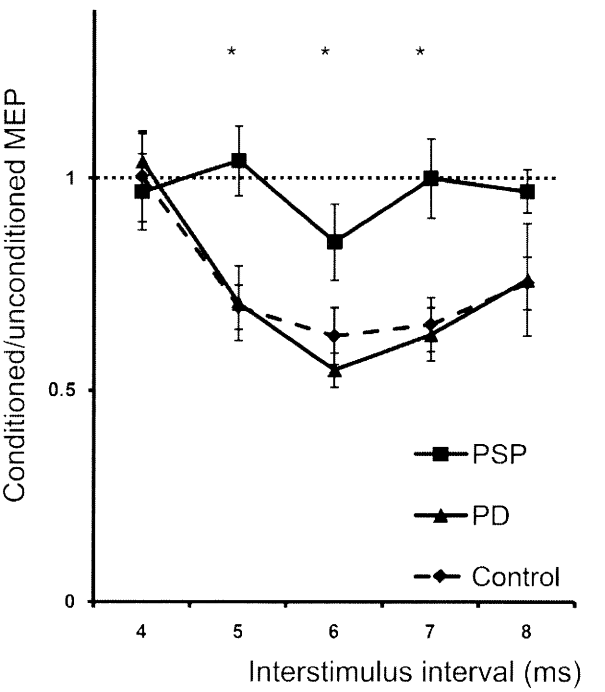

FIG. 2. Mean time courses of CBI in each group. The averaged time courses of CBI showed decreased CBI in a PSP group (rectangles) and normal CBI at ISIs of 5 to 8 ms in a PD group (triangles). A control group is shown by diamonds. The abscissa denotes ISI. The ordinate shows the MEP size ratio. Error bars represent SE. * indicates statistical significance between PSP and PD (P < 0.05 with Bonferroni's correction).

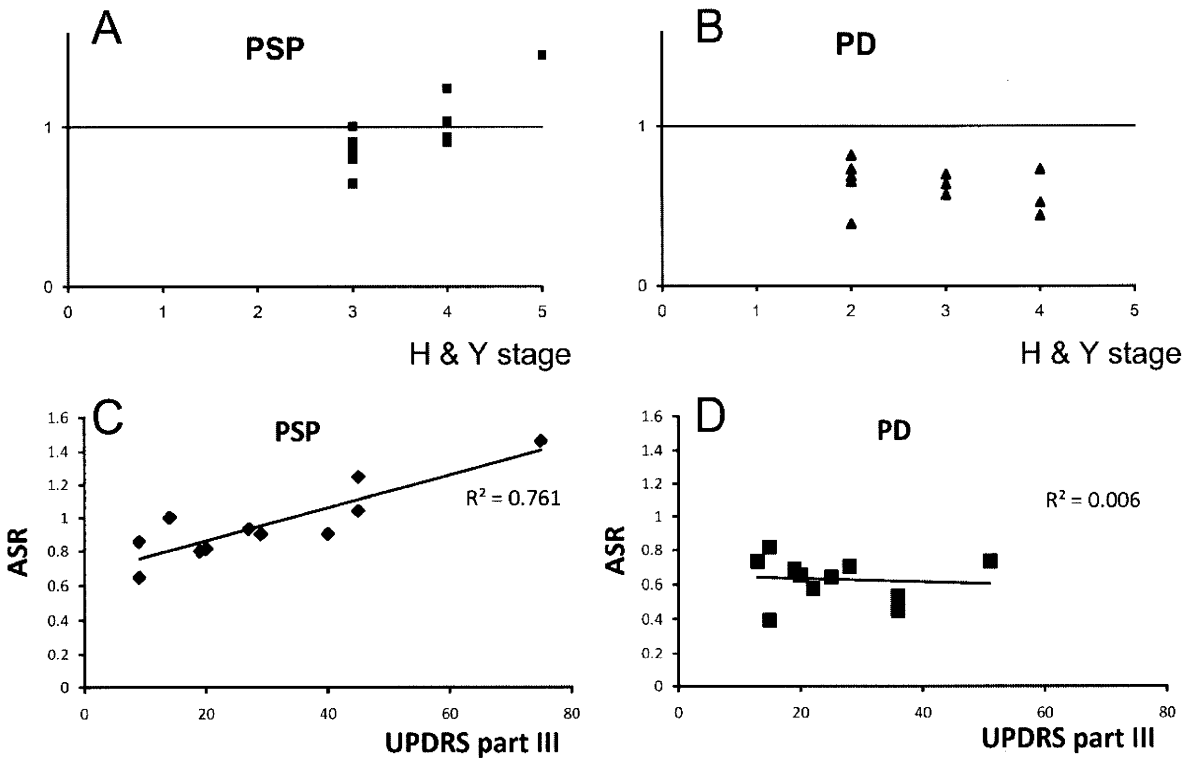

FIG. 3. Correlations between the degree of CBI and disease severity. (**A,B**) The degree of CBI expressed as average size ratio (ASR) was plotted against Hoehn and Yahr stage (H & Y stage) for each patient for each disease group. In the PD group (B), ASR is similar among the H & Y stages of 2 to 4. In contrast, PSP patients with higher H & Y stage showed more decreased CBI, that is, larger ASR (A). (**C,D**) For each patient, ASR was plotted against UPDRS part III total score. In PSP patients (C), there is a significant correlation between ASR and UPDRS part III total score ($R^2 = 0.76$, $P < 0.001$). PD patients (D) did not show any significant correlation ($R^2 = 0.006$, $P = 0.81$).

medication was 0.89 ± 0.19. They did not significantly differ from each other ($P = 0.14$).

DISCUSSION

The results showed that CBI was significantly reduced in PSP patients, although it was normal in PD patients. TMS over the cerebellum has been proposed to activate Purkinje cells that inhibit the dentate nucleus, which in turn engenders suppression of contralateral M1[3]. Consequently, the present results suggest that Purkinje cells or the dentato–thalamo–cortical pathway is involved in PSP patients, although no clinical cerebellar sign was observed.

Our results are consistent with previous pathological and radiological findings of PSP. Pathologically, the cerebellar dentate nucleus and superior cerebellar peduncle (SCP), which connects the cerebellar dentate nucleus with the thalamus, are severely involved in PSP.[1,2,12] A study using magnetic resonance imaging also demonstrated atrophy of the SCP quantitatively.[13] It is also consistent with a recent report that 3 of 22 pathologically confirmed PSP patients showed cerebellar ataxia as an initial and cardinal symptom.[2]

Our present results also agree with the following issues. It has been proposed recently that PSP should be divided into several subtypes[14]: Richardson's syndrome (RS) is the classical type, as reported in the original article. PSP-parkinsonism (PSP-P) resembles idiopathic PD in some respects such as asymmetric symptoms at onset, presence of tremor, lack of supranuclear gaze palsy at an early stage, and moderate responsiveness to L-dopa. Dentate nucleus degeneration was severer in RS than in PSP-P.[15] Because our patients were all classified as RS based on the clinical criteria, the significant reduction in CBI revealed in this study is compatible with such pathological findings. Whether the CBI of PSP-P is different from that of RS warrants further investigation.

Can dysfunction of neural systems other than the cerebellum or some other confounding factors account for the present findings? Four possibilities might be

discussed. First, given that PSP patients sometimes show severe corticospinal tract degeneration and frontal lobe degeneration,[16] dysfunction of the corticospinal tract or M1 might be responsible for our findings. However, the lack of pyramidal sign in the PSP patients suggested that this possibility is less likely. Second, some other changes in the motor cortex excitability, which might be revealed by investigations of motor threshold, short-interval intracortical inhibition, or intracortical facilitation, could possibly have an influence on the present results. Third, dopaminergic medications which may affect motor cortex excitability[17] might be responsible for the present findings. However, the PSP patients showed reduced CBI irrespective of medication. Thus, this leads us to conjecture that dopaminergic drugs had no significant influence on the degree of CBI in PSP. Considering the fact that PD patients took more dopaminergic medications, however, we cannot exclude a possibility that PD patients without medication or in their off state may have abnormal CBI. Finally, there was a trend for difference in age among groups. But, this factor is again unlikely to explain the reduced CBI in PSP patients because we did not find any significant correlation between CBI and age. These issues raised above should be addressed in more detail in future studies because our sample size may be too small to draw any firm conclusions.

CBI was reduced in PSP, but none of our patients showed cerebellar symptoms and signs. Why do PSP patients rarely show limb ataxia even though cerebellar structures are involved? A plausible explanation is that other symptoms of PSP such as akinesia or rigidity would mask clinical cerebellar signs. Indeed, cerebellar dysfunction is sometimes masked by parkinsonian symptoms.[11]

In the present study, PSP patients tended to be clinically severer than PD patients. Can disease severity affect the results? First, in PD patients, we did not find any relation between CBI and disease severity; patients with different Hoehn and Yahr stages showed similar ASR (Fig. 3B), and UPDRS part III did not correlate with ASR (Fig. 3D). In contrast, more advanced PSP patients showed larger ASR, that is, more abnormal CBI (Fig. 3A,C). These results suggest that neural structure which is affected in PSP but not in PD can explain the reduced CBI shown here. One of the candidates for such neural structures may be the cerebellum. Further studies, however, are needed to confirm the possible relation between CBI and disease severity in PSP.

A shortcoming of our study is that the diagnosis was based solely on clinical findings and was not confirmed pathologically. The clinical criteria we used, however, can diagnose PSP or PD with a high positive predictive value.[5] Another issue relates to the technical procedure. Although we have monitored participant's voluntary EMG activity using oscilloscope and discarded the trials contaminated by voluntary EMG, we did not record the degree of EMG activity quantitatively. Then, some small difference in the muscle state may explain the present results. In future studies, this point may need to be controlled more quantitatively.

In conclusion, although the PSP patients showed no clinical cerebellar signs, the results described herein suggest that Purkinje cells or the dentato–thalamo–cortical pathway assessed by CBI is involved in PSP. Our results are compatible with the pathological findings showing severe dentate nucleus degeneration in PSP patients.

Financial Disclosures: This work was supported by Research Project Grants-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan; grant from the Support Center for Advanced Telecommunications Technology Research; the Research Committee on rTMS Treatment of Parkinson disease from the Ministry of Health, Labour and Welfare of Japan (H20-023); the Research Committee on Dystonia, the Ministry of Health, Labour and Welfare of Japan; the Committee of the Study of Human Exposure to Electromagnetic Fields, Ministry of Internal Affairs and Communications; the Life Science Foundation of Japan; the Magnetic Health Science Foundation; and the Global COE Program (Comprehensive Center of Education and Research for Chemical Biology of Diseases) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Author Roles: Shirota—Research Project: Conception, Organization, Execution; Statistical Analysis: Design, Execution; Manuscript: Writing of the first draft, Review and Critique. Hamada—Research Project: Conception, Organization, Execution; Statistical Analysis: Design, Review and Critique; Manuscript: Review and Critique. Hanajima—Research Project: Conception, Organization, Execution; Manuscript: Review and Critique. Terao—Research Project: Organization, Execution; Statistical Analysis: Review and Critique; Manuscript: Review and Critique. Matsumoto—Research Project: Execution; Manuscript: Review and Critique. Ohminami—Research Project: Execution; Manuscript: Review and Critique. Tsuji—Research Project: Conception, Organization; Statistical Analysis: Review and Critique; Manuscript: Review and Critique. Ugawa—Research Project: Conception, Organization, Execution; Statistical Analysis: Review and Critique; Manuscript: Review and Critique.

REFERENCES

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. Arch Neurol 1964;10:337–343.
2. Kanazawa M, Shimohata T, Toyoshima Y, et al. Cerebellar involvement in progressive supranuclear palsy: a clinicopathological study. Mov Disord 2009;24:1312–1318.

3. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol 1995;37:703–713.
4. Daskalakis ZJ, Paradiso GO, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. Exploring the connectivity between the cerebellum and motor cortex in humans. J Physiol 2004;557: 689–700.
5. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. Neurology 1996;47:1–9.
6. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinic-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55:181–184.
7. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. Electroencephalogr Clin Neurophysiol 1998;108:1–16.
8. Herzog J, Volkmann J, Krack P, et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 2003;18:1332–1337.
9. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation of corticospinal pathways at the foramen magnum level in humans. Ann Neurol 1994;36:618–624.
10. Chen R, Cros D, Curra A, et al. The clinical diagnostic utility of transcranial magnetic stimulation: report of a IFCN committee. Clin Neurophysiol 2008;119:504–532.
11. Ugawa Y, Terao Y, Hanajima R, et al. Magnetic stimulation over the cerebellum in patients with ataxia. Electroencephalogr Clin Neurophysiol 1997;104:453–458.
12. Tsuboi Y, Slowinski J, Josephs KA, Honer WG, Wszolek ZK, Dickson DW. Atrophy of superior cerebellar peduncle in progressive supranuclear palsy. Neurology 2003;60:1766–1769.
13. Paviour DC, Price SL, Stevens JM, Lees AJ, Fox NC. Quantitative MRI measurement of superior cerebellar peduncle in progressive supranuclear palsy. Neurology 2005;64:675–679.
14. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol 2009;8:270–279.
15. Williams DR, Holton JL, Strand C, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. Brain 2007;130:1566–1576.
16. Josephs KA, Katsuse O, Beccano-Kelly DA, et al. Atypical progressive supranuclear palsy with corticospinal tract degeneration. J Neuropath Exp Neurol 2006;65:396–405.
17. Strafella AP, Valzania F, Nassetti SA, et al. Effects of chronic levodopa and pergolide treatment on cortical excitability in patients with Parkinson's disease: a transcranial magnetic stimulation study. Clin Neurophysiol 2000;111:1198–1202.

J Neurophysiol 104: 1382–1391, 2010.
First published May 26, 2010; doi:10.1152/jn.00164.2010.

Influence of Short-Interval Intracortical Inhibition on Short-Interval Intracortical Facilitation in Human Primary Motor Cortex

Yuichiro Shirota,[1] Masashi Hamada,[1] Yasuo Terao,[1] Hideyuki Matsumoto,[1] Shinya Ohminami,[1] Toshiaki Furubayashi,[2] Setsu Nakatani-Enomoto,[2] Yoshikazu Ugawa,[2] and Ritsuko Hanajima[1]

[1]*Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, Tokyo; and* [2]*Department of Neurology, School of Medicine, Fukushima Medical University, Fukushima, Japan*

Submitted 9 February 2010; accepted in final form 22 May 2010

Shirota Y, Hamada M, Terrao Y, Matsumoto H, Ohminami S, Furubayashi T, Nakatani-Enomoto S, Ugawa Y, Hanajima R. Influence of short-interval intracortical inhibition on short-interval intracortical facilitation in human primary motor cortex. *J Neurophysiol* 104: 1382–1391, 2010. First published May 26, 2010; doi:10.1152/jn.00164.2010. Using the paired-pulse paradigm, transcranial magnetic stimulation (TMS) has revealed much about the human primary motor cortex (M1). A preceding subthreshold conditioning stimulus (CS) inhibits the excitability of the motor cortex, which is named short-interval intracortical inhibition (SICI). In contrast, facilitation is observed when the first pulse (S1) is followed by a second one at threshold (S2), named short-interval intracortical facilitation (SICF). SICI and SICF have been considered to be mediated by different neural circuits within M1, but more recent studies reported relations between them. In this study, we performed triple-pulse stimulation consisting of CS-S1-S2 to further explore putative interactions between these two effects. Three intensities of CS (80–120% of active motor threshold: AMT) and two intensities of S2 (120 and 140% AMT) were combined. The SICF in the paired-pulse paradigm exhibited clear facilitatory peaks at ISIs of 1.5 and 3 ms. The second peak at 3 ms was significantly suppressed by triple-pulse stimulation using 120% AMT CS, although the first peak was almost unaffected. Our present results obtained using triple-pulse stimulation suggest that each peak of SICF is differently modulated by different intensities of CS. The suppression of the second peak might be ascribed to the findings in the paired-pulse paradigm that CS mediates SICI by inhibiting later I waves such as I3 waves and that the second peak of SICF is most probably related to I3 waves. We propose that CS might inhibit the second peak of SICF at the interneurons responsible for I3 waves.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a useful tool to stimulate the human brain noninvasively (Day et al. 1989). A single electrical stimulation of the primary motor cortex (M1) elicits periodic, multiple discharges or multiple descending volleys in the corticospinal tract in animals (Patton and Amassian 1954). Similarly, TMS over M1 elicits multiple descending volleys in humans (Day et al. 1989; Di Lazzaro et al. 1998a). The first response is called a D (direct) wave; the later waves are designated as I (indirect) waves. The I waves follow the D wave periodically at intervals of ~1.5 ms and are named I1–I3 waves in the order of their latency. The D wave is probably evoked by direct activation of the pyramidal tract neurons or their axon, and I waves are considered to be produced by activation of interneurons within M1, which in turn activate pyramidal tract neurons (Patton and Amassian 1954). A single pulse TMS evokes I waves preferentially (Day et al. 1989; Nakamura et al. 1997).

Furthermore, the paired-pulse paradigm enables us to investigate inhibitory and facilitatory circuits within M1 (Kujirai et al. 1993; Tokimura et al. 1996; Ziemann et al. 1998) probably by modulating different components of I waves. Short-interval intracortical inhibition (SICI) can be elicited by a conditioning stimulus (CS) followed by a test stimulus (S1) (Di Lazzaro et al. 1998b; Hanajima et al. 1998; Kujirai et al. 1993; Ziemann et al. 1996b). At interstimulus intervals (ISIs) of 1–5 ms, the motor evoked potential (MEP) produced by S1 is inhibited by CS. Furthermore, at ISIs of 2–4 ms, SICI is evident for the I3 wave, and to a lesser extent, the I2 wave but not for the I1 wave (Di Lazzaro et al. 1998b; Hanajima et al. 1998). The SICI at these ISIs are considered to reflect synaptic inhibition within M1 (Fisher et al. 2002; Hanajima et al. 2003; Roshan et al. 2003), which is mediated by gamma-aminobutyric acid (GABA) (Kujirai et al. 1993; Ziemann et al. 1996a). Interestingly, variation in the CS intensity results in the U-shaped SICI curve with the most enhanced SICI occurring at CS intensity of 90–110% active motor threshold (AMT) (Orth et al. 2003; Peurala et al. 2008; Ziemann et al. 1996b).

By contrast, short-interval intracortical facilitation (SICF) is elicited by a test stimulus (S1) followed by a second pulse (S2) set at around the resting motor threshold (RMT) (Tokimura et al. 1996). Three peaks of facilitation were observed: ISIs of 1.1–1.5, 2.3–2.9, and 4.1–4.4 ms (Ziemann et al. 1998). Because the intervals between the successive peaks are ~1.5 ms, SICF is considered to represent an interaction between I waves; in fact, we previously showed that additional I2 waves were elicited at the first peak of SICF (Hanajima et al. 2002). Another study showed that the S1 and S2 pulses interacted along the later I wave pathway (Ilic et al. 2002). According to the notion that the later I wave pathway consists of chains of interneurons (Amassian et al. 1987), both authors propose that the second pulse excites the interneurons that are hyperexcitable or subliminally depolarized in the presence of S1. Although the information available is insufficient, the second or the third peak of SICF might represent additional production of later I waves; e.g., I3 or I4 waves are elicited additionally at the second or the third peak of SICF. These two peaks become greater when the intensity of the S2 increases (Chen and Garg 2000).

The SICI and SICF are commonly considered to be mediated by different neural circuits (Chen and Garg 2000; Ortu et al.

Address for reprint requests and other correspondence: Y. Shirota, Dept. of Neurology, Div. of Neuroscience, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-Ku, Tokyo 113-8655, Japan (E-mail: yshirota-tky@umin.ac.jp).

0022-3077/10 Copyright © 2010 The American Physiological Society

Downloaded from jn.physiology.org on February 2, 2011

2008), but their effects converge on the pyramidal tract neurons or some interneurons to elicit MEP. Thus we can speculate that there is some interaction between these effects. In fact, some studies reported some relations between SICI and SICF using the paired-pulse paradigm. Peurala et al. (2008) demonstrated that measurement of SICI was contaminated by SICF when CS of higher intensity was used. Similarly, Ortu and colleagues (2008) showed that they can only assess net inhibition or facilitation by the paired-pulse paradigm because SICI and SICF were mixed when stimulus intensity became higher.

More recently, to further elucidate the putative interaction between SICI and SICF, Wagle-Shukla et al. (2009) used the triple-pulse stimulation of CS, S1, and S2. They showed that CS facilitated the peaks of SICF (Wagle-Shukla et al. 2009). Although they studied the third peak of SICF intensively, only one stimulus intensity was used for S2 and the other peaks were tested using one stimulus intensity for CS and for S2. Because the stimulus intensity and ISIs are crucial for the paired-pulse paradigm, the same might hold true in the triple-pulse paradigm. Therefore we studied a wider range of time course of SICF using several stimulus intensities for CS and S2 to clarify stimulus intensity dependency of the effect of CS on SICF under the triple-pulse paradigm. Our original hypothesis is that each peak of SICF would be modulated differently by a preceding CS and CS intensity would affect this modulation.

METHODS

Participants

Participants were 10 right-handed healthy volunteers [1 woman, 9 men; 27–46 yr old, 36.2 ± 6.6 (SD) yr old], who gave their written informed consent to participate in the experiments. No participant had neurological, psychiatric, or other medical problem, or had any contra-indication to TMS (Rossi et al. 2009; Wassermann 1998). The protocol was approved by the Ethics Committee of the University of Tokyo Hospital and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Recordings

Participants were seated on a comfortable chair. MEPs were recorded from the right first dorsal interosseous muscle (FDI). Pairs of Ag/AgCl surface cup electrodes (9 mm diam) were placed over the muscle belly (active) and the metacarpophalangeal joint of the index finger (reference). Responses were input to an amplifier (Biotop; GE Marquette Medical Systems) through filters set at 100 Hz and 3 kHz; they were then digitized and stored in a computer for later off-line analyses (TMS Bistim Tester; Medical Try System).

TMS

TMS was given over the hand area of the motor cortex using a hand-held figure-eight coil (9 cm external diameter at each wing; Magstim, Whitland, Dyfed, UK) placed tangentially over the scalp with the handle pointing backward at ~45° laterally, which is perpendicular to the central sulcus. Monophasic TMS pulses were delivered using a magnetic stimulator (Magstim 200^2; Magstim). The optimal site for eliciting MEPs in the right FDI muscle (i.e., hot spot) was determined before each experiment. The hot spot was defined as the site at which the largest responses were elicited. This position was marked using a blue pen on the scalp for repositioning the coil. Placing the coil over this position, the RMT was determined as the lowest intensity that evoked a response of ≥50 μV in the relaxed FDI in ≥5 of 10 consecutive trials (Rossini et al. 1994). The AMT was defined as the lowest intensity that evoked a small response (>100 μV) when the participant maintained a slight contraction of the right FDI (5–10% of the maximum voluntary contraction) observing an oscilloscope monitor, in >5 of 10 consecutive trials. The experiments were performed separately on several days, and RMT and AMT were determined every experimental day.

Paired- and triple-pulse stimulation procedures

Paired- or triple-pulse stimuli were delivered using two or three magnetic stimulators (Magstim 200^2; Magstim) connected with a specially designed combining module (Magstim). This device com-

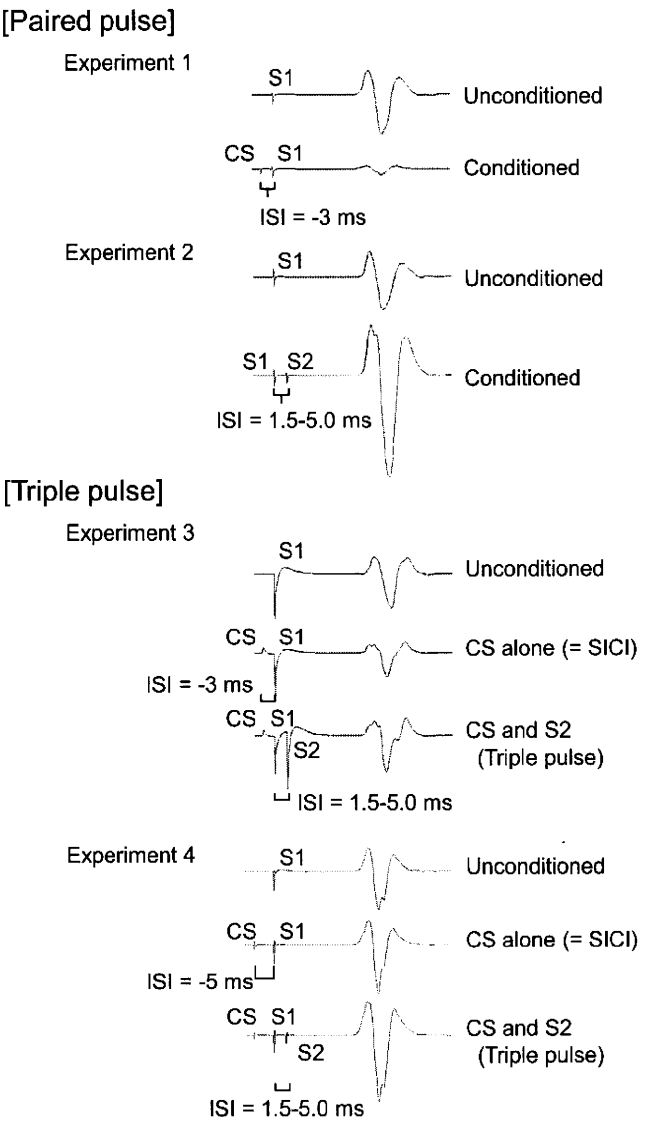

FIG. 1. Experimental procedures. The experimental design is exhibited schematically. In the 1st 2 experiments using paired-pulse stimulation (i.e., *experiments 1* and *2*), conditioned responses are compared with unconditioned ones. In *experiment 1*, conditioning stimulus (CS) is followed by the 1st pulse (S1) to examine short-interval intracortical inhibition (SICI). *Experiment 2* used S1 followed by the 2nd pulse (S2) to study short-interval intracortical facilitation (SICF). The other 2 experiments (*experiments 3* and *4*) constitute triple-pulse stimulations of CS-S1-S2 compared with paired-pulse stimulations of CS-S1 (SICI paradigm). Interstimulus intervals (ISIs) between CS and S1 take negative values such as −3 and −5 ms because they precede S1.

Downloaded from jn.physiology.org on February 2, 2011