

## Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation

FUMIKO MAEDA, JULIAN P. KEENAN and ALVARO PASCUAL-LEONE

**Background** Neuroimaging studies of major depressive disorder (MDD) indicate interhemispheric differences in prefrontal cortical activity (right greater than left).

**Aims** To investigate whether there are any interhemispheric differences of motor cortical excitability in MDD.

**Method** Eight patients with treatment-refractory MDD off medication were assessed for the severity of their depression, and transcranial magnetic stimulation studies (bilateral motor threshold and paired-pulse studies) were conducted. Eight normal controls were also studied.

**Results** MDD patients showed significant interhemispheric differences in motor threshold and paired-pulse curves, both of which showed lower excitability on the left hemisphere. Such differences were absent in controls.

**Conclusions** Our findings may aid the further understanding of the neurophysiology underlying MDD.

**Declaration of interest** This study was supported in part by the Cellular Science Research Foundation, Yoshida Science Foundation, Stanley Vada Foundation, National Alliance for Research in Schizophrenia and Depression, and the National Institute of Mental Health (RO1MH57980).

A number of neuroimaging studies have suggested that patients with mood disorders have interhemispheric asymmetries in brain activity, particularly in the dorso-lateral prefrontal cortex with the left hemisphere being hypoactive (Baxter *et al*, 1989; George *et al*, 1999). However, such imaging studies do not provide specific physiological information regarding inhibitory *v.* facilitatory modulation in brain activity. For the motor cortex, transcranial magnetic stimulation (TMS) allows the non-invasive study of cortical excitability. Few studies have investigated cortical excitability using TMS in patients with depression. Samii *et al* (1996) and Shajahan *et al* (1999), combining TMS to the left hemisphere and an exercise paradigm, reported reduction in post-exercise cortical excitability in depression relative to normal subjects. We hypothesised, given the findings from neuroimaging studies, that there may be interhemispheric asymmetries in cortical excitability even in the absence of preactivation, and we therefore examined motor cortical excitability with TMS using measurements of motor threshold and paired-pulse excitability.

### METHOD

The study was approved by the local institutional review board, and informed written consent was obtained from all participants.

### Subjects

#### Patients

Eight patients were recruited (five males, three females; age range 19–78 years; mean age 46.8 years; seven right-handed, one left-handed) from a community-based outpatient clinic. All patients met criteria for unipolar recurrent major depressive disorder (MDD) according to the Structured Clinical Interview for DSM-III-R (SCID; Spitzer *et al*, 1987) and DSM-IV (American Psychiatric Association, 1996), in which the

diagnosis was established by a trained psychiatrist. All patients had been treated unsuccessfully with at least three different antidepressant medications at sufficiently high doses and for at least six weeks during the current major depressive episode. The absence of neurological disorders and contraindications to TMS (Wassermann, 1998) was confirmed by a trained neurologist. After patients' medications were withdrawn, there was a two-week wash-out period prior to participation in the study.

#### Normal controls

We recruited eight healthy volunteers (six males, two females; age range 21–75 years; mean age 44.9 years; all right-handed). All were naïve to TMS. Screening interviews confirmed that none had any psychiatric or medical history. None were on chronic medications. All had normal neurological examinations and none had contraindications for TMS.

#### TMS procedure

Subjects were seated in a comfortable reclining chair so that the whole body, including both arms, was at rest. Subjects were instructed to keep their hands still and as relaxed as possible. A tightly fitting Lycra swimming cap was placed on the head to mark the site of stimulation, which was identified as the scalp position at which TMS induced motor-evoked potentials (MEPs) of maximal peak-to-peak amplitude in the target muscle. Four disposable self-adhesive electrodes (Nicolet Biomedical, WI) were placed on the belly and the tendon of the abductor pollicis brevis (APB) muscles bilaterally. Two circular ground electrodes with a diameter of 30 mm were placed on the forearm bilaterally and linked to a common ground. MEPs were collected by a Dantec Counterpoint electromyograph with an amplification of 1.0 mV and a band pass of 20–1000 Hz (Dantec, Skovlunde, Denmark). Following preamplification, the signal was digitised by a CED 1404 interface (Cambridge Electronic Design, Cambridge, UK; sampling rate 2 kHz) and stored in a personal computer for off-line analysis.

TMS was performed with a commercially available 70 mm figure-of-eight coil using two magnetic stimulators (Magstim 200), which were linked through a Bistim module (Magstim Company, Carmarthen, UK). The optimal sites

for evoking responses from right and left APB muscle (when stimulating the left and right hemispheres, respectively) were determined. The coil was positioned tangentially to the surface of the head, and the handle was placed along a sagittal axis pointing occipitally. In this position, the induced current in the brain predominantly activates corticospinal neurons transsynaptically (Werhahn *et al*, 1994). The motor threshold was defined as the minimal intensity of stimulation capable of inducing MEPs of more than 50  $\mu$ V peak-to-peak amplitude in at least six out of ten trials. The threshold determination was made during complete muscle relaxation. Muscle relaxation was documented by electromyogram and audio recording for least 200 ms prior to TMS.

The paired-pulse TMS study followed the method of Kujirai *et al* (1993). The conditioning stimulus was applied at 80% of the subject's motor threshold and was confirmed to induce no MEPs. The test stimulus was applied at approximately 130% of the subject's motor threshold and was adjusted to evoke MEPs of approximately 0.8 mV peak-to-peak amplitude ( $\pm 0.2$  mV). The interstimulus intervals (ISIs) used in this study were 1, 3, 6, 8, 10 and 12 ms for the patient group. The experiment was set up in blocks of 50 trials. In each block, the order of the trials was random. The 50 trials consisted of five trials for each different ISI and ten trials each of conditioning stimulus alone and test stimulus alone. There was an eight-second interval between each trial. The study of each patient included four blocks of trials per hemisphere. The stimuli were triggered and continuous data were collected by a CED Micro 1401 interface (Cambridge Electronic Design, Cambridge, UK).

The order in which the hemispheres were studied was randomised across subjects.

After obtaining the results of the MDD group, a similar study was conducted on the normal controls in order to test whether our findings of interhemispheric asymmetry might be related to the pathophysiology of depression. The study design was similar to that of the patient group except that the ISIs in the paired-pulse study were limited to 1, 6 and 12 ms. These ISIs were chosen to test the validity of the results for the patients who revealed a significant interhemispheric difference in intracortical excitability at 6 ms ISI but not at 1 and 12 ms ISI.

## Neuropsychological measures

The patients' severity of depression was assessed with the Hamilton Rating Scale for Depression (HRSD, 28 items; Hamilton, 1960) and the Beck Depression Inventory (BDI; Beck & Beamcoderifer, 1974) by laboratory staff members who had been checked for interrater reliability.

## Data analysis

The motor threshold (see above) was determined for each subject and for each hemisphere. An asymmetry index defined as percentage difference in the motor threshold between right and left hemispheres was calculated.

For the paired-pulse data, ten MEPs recorded for each subject at each ISI were averaged. These scores were then compared to the amplitude of the MEPs to the test stimulus alone. For each ISI, we computed a percentage difference from the test stimulus value for each subject. We first performed comparisons within the groups (patients with depression and controls). Following the within-group comparisons, percentage difference scores between the left and right hemispheres were computed at the 1, 6, and 12 ms levels. These scores were used to compare differences between patients and controls. All data were analysed with SPSS version 6.0/9.0 (SPSS, 1998).

## RESULTS

All subjects tolerated the study well without unexpected complications. The only side-effect of TMS was a mild transient headache in one patient. The headache was resolved promptly with mild analgesia (paracetamol).

### Baseline depression

The mean HRSD score was 30.5 (s.d.=4.41), and the mean BDI score was 21.5 (s.d.=11.55) for the MDD group. We found a correlation between the two ratings ( $r=0.80$ ,  $P<0.02$ ). Hence, HRSD scores were used for further analysis.

### Motor threshold

For the MDD group, the mean motor threshold was 41.13% (s.d.=7.79%) of maximum output of the magnetic stimulator for the left hemisphere and 37.63% (s.d.=4.84%) for the right hemisphere. The average percentage difference

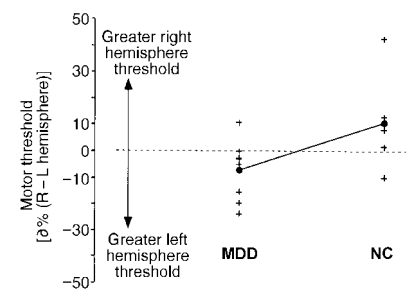
between the hemispheres was  $-7.30\%$  (s.d.=11.41%), indicating a higher left hemisphere motor threshold.

For the control group, the mean motor threshold was 48.29% (s.d.=13.40%) for the left hemisphere and 52.71% (s.d.=12.88%) for the right hemisphere. The average percentage difference was 11.02% (s.d.=16.0%, indicating a greater right hemisphere motor threshold). Data were not available for one of the control subjects, so these results represent the findings for seven controls.

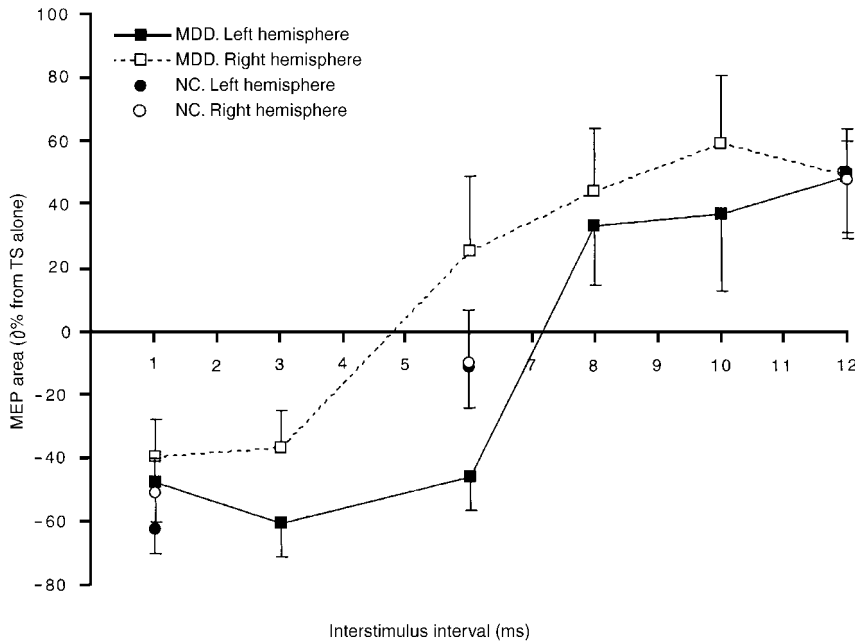
Comparing the interhemispheric percentage differences in motor thresholds, there was a significant difference between the two groups ( $t(13)=-2.581$ ,  $P<0.03$ ) (Fig. 1). The strength of this effect as indexed by  $\epsilon^2$  was 0.339. While this indicated that there were differences between the groups, we wished to determine whether asymmetry truly differed from zero in either group. Two corrected ( $\alpha=0.025$ ) single-group  $t$ -tests were performed. In both the MDD group ( $t(7)=-1.811$ ,  $P<0.05$ ) and the control group ( $t(6)=1.823$ ,  $P<0.05$ ), the asymmetry indices did not differ from zero.

### Paired-pulse curve

First, the differences across the ISIs and between the hemispheres in the MDD group (Fig. 2) were compared. A  $2 \times 6$  repeated-measures analysis of variance (ANOVA) revealed that there was no significant interaction between hemispheres and ISI ( $F(5,35)=1.44$ ,  $P>0.05$ ;  $\epsilon^2=0.171$ ) and no main effect for hemisphere ( $F(1,7)=3.36$ ,  $P>0.05$ ). However, there was a main effect for ISI ( $F(5,35)=17.18$ ,  $P<0.0005$ ;  $\epsilon^2=0.711$ ). Bonferroni corrected *post hoc* comparisons ( $\alpha=0.003$ ) revealed that 1 ms ISI results



**Fig. 1** Interhemispheric difference in motor threshold for the major depressive disorder (MDD) and normal control (NC) groups ( $P<0.03$ ).



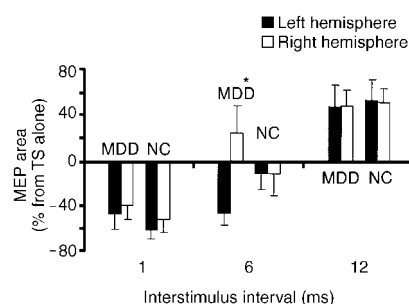
**Fig. 2** Paired-pulse curves for the major depressive disorder (MDD) and normal control (NC) groups. Bars indicate standard errors.

were significantly different from the 10 and 12 ms ISI results. The 3 ms ISI results were significantly different from the 8, 10 and 12 ms ISI results.

Next the control group results across the 3 ISIs (1, 6 and 12 ms) contrasting the left and the right hemispheres (Fig. 2) were compared. Employing a  $2 \times 3$  (hemisphere  $\times$  time) repeated-measures ANOVA, there was no significant interaction between the variables ( $F(2,14)=0.890$ ,  $P>0.05$ ;  $\epsilon^2=0.016$ ). There was no main effect for hemisphere ( $F(1,7)=0.859$ ,  $P>0.05$ ;  $\epsilon^2=0.005$ ). However, there was a main effect for ISI ( $F(2,14)=29.98$ ,  $P<0.0005$ ;  $\epsilon^2=0.811$ ). All ISIs were

significantly different from each other using Bonferroni comparisons ( $\alpha=0.017$ ).

We then compared the MDD and control groups at 1, 6 and 12 ms (Fig. 3). There was a significant interaction between the hemispheres and ISI ( $F(2,14)=7.66$ ,  $P<0.006$ ;  $\epsilon^2=0.523$ ). Comparing the groups across the three ISIs using Bonferroni-corrected comparisons ( $\alpha=0.017$ ) at 6 ms ISI, there was a difference between the MDD group ( $M=-1.05$ ,  $s.d.=62.54$ ) and the control group ( $M=-0.2$ ,  $s.d.=2.60$ ;  $t(7)=5.23$ ,  $P<0.001$ ;  $\epsilon^2=0.796$ ), such that the motor cortical excitability of the right hemisphere was greater than that of the left for the MDD group but not for the control group.



**Fig. 3** Comparisons between the major depressive disorder (MDD) group and the normal control (NC) group when paired pulses were applied at 1, 6 and 12 ms interstimulus intervals. Bars indicate standard errors.  $*P<0.001$ .

### Correlation between severity of depression and motor cortical excitability

The influence of each hemisphere at each ISI was examined in order to determine whether there was a correlation with HRSD scores. Paired-pulse changes in the left hemisphere correlated at 10 ms ISI ( $r=0.773$ ,  $P<0.03$ ). This positive relationship indicated that as left hemisphere excitability increased at 10 ms, depression scores also increased. In the right hemisphere, there was no correlation with HRSD scores at any value of ISI (all  $P>0.05$ ).

To determine whether asymmetry played a role, we subtracted the right from the left hemisphere percentage differences and compared them with HRSD scores. Asymmetry did not correlate with baseline HRSD scores.

Finally, the average of the inhibitory ISIs (1 and 3 ms) and the excitatory ISIs (10 and 12 ms) was calculated. Using the same asymmetry index, these scores were correlated with the HRSD scores. The average of 10 and 12 ms ISIs correlated with HRSD scores ( $r=0.844$ ,  $P<0.008$ ). As right hemisphere excitability increased in relation to left hemisphere activity, depression scores decreased.

## DISCUSSION

### Suggested mechanisms of motor threshold and paired-pulse techniques

Motor threshold studies reflect neuronal membrane excitability, which is mainly dependent on ion channel conductivity (Hodgkin & Huxley, 1952; Ziemann *et al*, 1998a).

Paired-pulse TMS studies investigate intracortical excitability (Pascual-Leone *et al*, 1998). The effects obtained depend on the intensity of the conditioning and test stimuli and on the ISI (Pascual-Leone *et al*, 1998). These intensities influence the effects, because different circuits are recruited by different intensities of stimulation. The ISI influences the results because the time constants of the activated circuits may differ. At very short ISIs ( $<1$  ms), neural time constants of the stimulated elements may be studied; at ISIs of 1–4 ms, interactions between I-wave inputs to the corticospinal neurons may be studied; and at ISIs of 1.5–20 ms, intracortical inhibitory and facilitatory circuits may be studied. All these effects appear to be cortically mediated (Kujirai *et al*, 1993; Ziemann *et al*, 1996), and intracortical inhibition (at ISIs of 1–4 ms) and facilitation (at ISIs of 8–12 ms) appear to be due to activation of separate circuits (Ziemann *et al*, 1996). Inhibition seems to reflect the activity of inhibitory interneurons or inhibitory connections between cortical output cells (Wassermann *et al*, 1996). Facilitation seems to be partially due to facilitatory interaction between I-waves, and is thought to take place in the motor cortex at or upstream from the

corticospinal neuron (Ziemann *et al*, 1998b).

The effects of different disorders and medications on the inhibitory and facilitatory phases of the paired-pulse curve suggest that  $\gamma$ -aminobutyric acid-(GABA)-ergic, dopaminergic and glutamatergic mechanisms are involved. Medications that enhance GABAergic activity have been shown to increase the degree of intracortical inhibition and decrease intracortical facilitation evoked by paired TMS stimuli at ISIs of approximately 8–12 ms (Ziemann *et al*, 1998a; Werhahn *et al*, 1998). Conversely, in Parkinson's disease, the dopamine deficiency is associated with reduced intracortical inhibition at short ISIs (<5 ms) (Berardelli *et al*, 1996). Dopaminergic drugs have been shown to enhance intracortical inhibition in normal subjects (Ziemann *et al*, 1998a). Furthermore, studies suggest that an early phase of relative facilitation in the paired-pulse curve at ISIs of approximately 3 ms as well as intracortical facilitation (ISIs of 8–12 ms) may be related to glutamatergic excitatory intracortical modulation (Ziemann *et al*, 1998a).

### Other disorders that show abnormalities in motor cortical excitability

In addition to the studies on Parkinson's disease, other disorders have been investigated using the paired-pulse technique. Patients with writer's cramp have shown a reduction in the inhibitory effects on the symptomatic side during muscle activation (Chen *et al*, 1997). Patients with restless legs syndrome have shown a reduction in intracortical inhibition of both foot and hand muscles, suggesting that its origin may be subcortical (Tergau *et al*, 1999). Patients with cerebellar degeneration have shown a reduced intracortical facilitation, which supports the idea that the cerebellum physiologically exerts a facilitatory influence on the motor cortex (Liepert *et al*, 1998).

### Interhemispheric asymmetry in motor cortical excitability in depression

In this study, MDD patients showed a significant interhemispheric difference in motor cortical excitability, with the left hemisphere having lesser and the right hemisphere having greater excitability

### CLINICAL IMPLICATIONS

- Interhemispheric asymmetry in motor cortical excitability may be related to the pathophysiology of depression.
- Transcranial magnetic stimulation (TMS) is a useful tool for demonstrating abnormalities in inhibitory/facilitatory cortico-cortical/cortico-subcortical circuits.
- Physiological measurements with TMS provide useful supplementary findings to neuroimaging studies in neuropsychiatric disorders.

### LIMITATIONS

- The relevance of motor cortex abnormalities to depression is unknown.
- A larger sample size is needed to confirm this abnormality in depression.
- Different types of depression, both medication-responsive and refractory, need to be studied.

FUMIKO MAEDA, MD, Laboratory for Magnetic Brain Stimulation, Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Cambridge, MA and Department of Neuropsychiatry, Keio University School of Medicine, Tokyo; JULIAN P. KEENAN, PhD, Laboratory for Magnetic Brain Stimulation, Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Cambridge, MA; ALVARO PASCUAL-LEONE, PhD, Laboratory for Magnetic Brain Stimulation, Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Cambridge, MA and Institute for Bioengineering, Miguel Hernandez University, Alicante, Spain

Correspondence: Dr A. Pascual-Leone, 330 Brookline Ave. KS452, Boston, MA 02215, USA. Tel: 617-667-0203; Fax: 617-975-5322; e-mail: ap Leone@caregroup.harvard.edu

(First received 11 August 1999, final revision 17 January 2000, accepted 19 January 2000)

than in controls. However, it is unclear what the underlying pathophysiological mechanisms are. The paired-pulse study revealed significant interhemispheric differences only at ISI of 6 ms. This is the time when the switch from intracortical inhibition to facilitation usually takes place. This switch is presumably related to a change in the balance between GABAergic and glutamatergic influences. The role played by depression is unclear. A plausible explanation for our findings might be that by comparison with the right hemisphere, the left hemisphere in MDD patients during a medication-resistant major depressive episode has relatively low glutamatergic influence or excessive GABAergic tone. Recently, Larisch *et al* (1999) have reported an abnormally low serotonin release in patients with a treatment-unresponsive major depressive episode. Such abnormalities, which may involve more than a single neurotransmitter system, may explain our findings.

The most basic parameter of motor excitability is motor threshold. In our study, we found a significant interhemispheric difference in motor thresholds between patients with MDD and controls. Recent neuropharmacological studies have indicated that the motor threshold reflects neuronal membrane excitability, which is mainly dependent on ion channel conductivity (Ziemann *et al*, 1998a). This is different from paired-pulse studies that mainly reflect transmitter-related effects. It is interesting that both motor excitability parameters, although different in mode of action, showed interhemispheric differences.

### Future studies

The relationship between depressive symptoms and interhemispheric differences in motor cortical excitability found in our study is novel, and caution is necessary in the interpretation of these results until a

larger sample is studied. Nevertheless, the findings provide new insights regarding the cortical pathophysiology of MDD. It may be interesting not only to examine this effect in a larger number of patients but also to examine patients with MDD before and after remission from various antidepressant treatments.

## ACKNOWLEDGEMENTS

We thank Aisling S. Warde, Zoë Stinchfield, Dawn Mechanic and Thomas Kauffman for research assistance, and Drs Bernard Vaccaro, Shirlene Sampson and Robert Birnbaum for their evaluation of the patients.

## REFERENCES

- American Psychiatric Association (1994)** *Diagnostic and Statistical Manual of Mental Disorders* (4th edn, revised) (DSM-IV). Washington, DC: APA.
- Baxter, L. R., Schwartz, J. M., Phelps, M. E., et al (1989)** Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, **46**, 243–250.
- Beck, A. T. & Beamcoderifer, A. (1974)** Assessment of depression: the depression inventory. In *Psychological Measurements in Psychopharmacology: Modern Problems of Pharmacopsychiatry*, Vol. 7 (eds P. Pichot & R. Oliver-Martin). Basel: Karger.
- Berardelli, A., Rona, S., Inghilleri, M., et al (1996)** Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. *Brain*, **119**, 71–77.
- Chen, R., Wassermann, E. M., Canos, M., et al (1997)** Impaired inhibition in writer's cramp during voluntary muscle activation. *Neurology*, **49**, 1054–1059.
- George, M. S., Lisanby, S. H., Sackeim, H. A. (1999)** Transcranial magnetic stimulation. Applications in neuropsychiatry. *Archives of General Psychiatry*, **56**, 300–311.
- Hamilton, M. (1960)** A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.
- Hodgkin, A. L. & Huxley, A. (1952)** Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *Journal of Physiology*, **116**, 449–472.
- Kujirai, T., Caramia, M. D., Rothwell, J. C., et al (1993)** Corticocortical inhibition in human motor cortex. *Journal of Physiology*, **471**, 501–519.
- Larisch, R., Hamacher, K., Klimke, A., et al (1999)** Measurement of serotonin release in depressive patients *in vivo*: initial experiences using PET, [<sup>18</sup>F]altanserin and the serotonin reuptake inhibitor clomipramine. *Neuroimage*, **9** (suppl.), 656.
- Liepert, J., Wessel, K., Schwenkreis, P., et al (1998)** Reduced intracortical facilitation in patients with cerebellar degeneration. *Acta Neurologica Scandinavica*, **98**, 318–323.
- Pascual-Leone, A., Tormos, J. M., Keenan, J. P., et al (1998)** Study and modulation of human cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology*, **15**, 333–343.
- Samii, A., Wassermann, E. M., Ikoma, K., et al (1996)** Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue or depression. *Neurology*, **47**, 1410–1414.
- Shajahan, P. M., Glabus, M. F., Gooding, P. A., et al (1999)** Reduced cortical excitability in depression. Impaired post-exercise motor facilitation with transcranial magnetic stimulation. *British Journal of Psychiatry*, **174**, 449–454.
- Spitzer, R. L., Williams, J. B. & Gibbon, J. (1987)** *Structured Clinical Interview for DSM-III-R – Patient Edition* (SCID-P). New York: New York State Psychiatric Institute.
- SPSS (1998)** *SPSS for Windows Base System User's Manual. Release 9.0*. Chicago, IL: SPSS Inc.
- Tergau, F., Wischer, S. & Paulus, W. (1999)** Motor excitability in patients with restless legs syndrome. *Neurology*, **52**, 1060–1063.
- Wassermann, E. M. (1998)** 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. *Electroencephalography and Clinical Neurophysiology*, **108**, 1–16.
- , **Samii, A., Mercuri, B., et al (1996)** Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles. *Experimental Brain Research*, **109**, 158–163.
- Werhahn, K. J., Fong, J. K., Meyer, B. U., et al (1994)** The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. *Electroencephalography and Clinical Neurophysiology*, **93**, 138–146.
- , **Forderreuther, S. & Straube, A. (1998)** Effects of the serotonin 1B/1D receptor agonist zolmitriptan on motor cortical excitability in humans. *Neurology*, **51**, 896–898.
- Ziemann, U., Rothwell, J. C. & Ridding, M. C. (1996)** Interaction between intracortical inhibition and facilitation in human motor cortex. *Journal of Physiology*, **496**, 873–881.
- , **Steinhoff, B. J., Tergau, F., et al (1998a)** Transcranial magnetic stimulation: its current role in epilepsy research. *Epilepsy Research*, **30**, 11–30.
- , **Tergau, F., Wassermann, E. M., et al (1998b)** Demonstration of facilitatory I-wave interaction in the human motor cortex by paired transcranial magnetic stimulation. *Journal of Physiology*, **511**, 181–190.