Transcranial Magnetic Stimulation (TMS) in Controlled Treatment Studies: Are Some "Sham" Forms Active?

Colleen K. Loo, Janet L. Taylor, Simon C. Gandevia, Benjamin N. McDarmont, Philip B. Mitchell, and Perminder S. Sachdev

Background: *Carefully designed controlled studies are essential in further evaluating the therapeutic efficacy of transcranial magnetic stimulation (TMS) in psychiatric disorders. A major methodological concern is the design of the "sham" control for TMS. An ideal sham would produce negligible cortical stimulation in conjunction with a scalp sensation akin to real treatment. Strategies employed so far include alterations in the position of the stimulating coil, but there has been little systematic study of their validity. In this study, we investigated the effects of different coil positions on cortical activation and scalp sensation.*

Methods: *In nine normal subjects, single TMS pulses were administered at a range of intensities with a "figure eight" coil held in various positions over the left primary motor cortex. Responses were measured as motor-evoked potentials in the right first dorsal interosseus muscle. Scalp sensation to TMS with the coil in various positions over the prefrontal area was also assessed.*

Results: *None of the coil positions studied met the criteria for an ideal sham. Arrangements associated with a higher likelihood of scalp sensation were also more likely to stimulate the cortex.*

Conclusions: *The choice of a sham for TMS involves a trade-off between effective blinding and truly inactive "stimulation." Further research is needed to develop the best sham condition for a range of applications.* Biol Psychiatry 2000;47:325–331 © *2000 Society of Biological Psychiatry*

Key Words: Transcranial magnetic stimulation, brain, psychiatry, treatment, motor cortex, prefrontal cortex

Introduction

In recent years, transcranial magnetic stimulation (TMS) has shown potential as a treatment for psychiatric disorders (George et al 1996). It is a noninvasive method of brain stimulation that uses strong magnetic fields to induce small electrical currents in the cerebral cortex, depolarizing neurons. The potential of TMS to influence cerebral function has been demonstrated in a number of ways. Transcranial magnetic stimulation of the motor cortex has been reported to increase the excitability of some cortical neurons when delivered at high frequency (10 Hz, 20 Hz; Pascual-Leone et al 1994) or to depress excitability at low frequencies (1 Hz; Wassermann et al 1996). These effects lasted several minutes after a single session of stimulation. Functional imaging studies have shown changes in regional cerebral blood flow during TMS (e.g., Fox et al 1997; Paus et al 1997, 1998). Transcranial magnetic stimulation has also been linked with downregulation of β-adrenoreceptors in the rat cortex (Fleischmann et al 1996) and effects on astroglial gene expression in mice (Fujiki and Steward 1997). Thus, there are several putative mechanisms by which TMS may exert a therapeutic effect in psychiatric disorders. Research studies have examined the efficacy of TMS in treating depression (as an alternative to electroconvulsive therapy; e.g., George et al 1997; Kolbinger et al 1995; Pascual-Leone et al 1996), mania (Grisaru et al 1998b), obsessive–compulsive disorder (Greenberg et al 1997), and posttraumatic stress disorder (Grisaru et al 1998a; McCann et al 1998).

Controlled studies have used either stimulation at a different cerebral site (Greenberg et al 1997; Grisaru et al 1998b) or a "sham" form of TMS (George et al 1997; Klein et al 1999; Kolbinger et al 1995; Pascual-Leone et al 1996) as a control condition. There are difficulties with both these types of control stimulation. Stimulation at other sites (e.g., vertex, occiput, cerebellum) may produce confounding psychiatric effects, either locally derived or by effects on the verum treatment site via indirect pathways. For example, functional imaging studies have demonstrated effects of TMS on cerebral

From the Schools of Psychiatry (CKL, BNM, PBM, PSS), Physiology and Pharmacology (JLT), and Medicine (SCG), Faculty of Medicine, University of New South Wales; Department of Psychiatry (CKL), Mood Disorders Unit (PBM), and Neuropsychiatric Institute (PSS), Prince of Wales Hospital; and Prince of Wales Medical Research Institute (JLT, SCG), Sydney, Australia.

Address reprint requests to Dr. Colleen Loo, Dept. of Psychiatry, Prince of Wales Hospital, High and Avoca Streets, Randwick NSW 2031, Australia.

Received May 19, 1999; revised October 6, 1999; accepted October 13, 1999.

0006-3223/00/$20.00
PII S0006-3223(99)00285-1

sites far from the site of stimulation (e.g., Fox et al 1997). The alternative, sham TMS, has rarely been studied in terms of its design and cortical effects.

We propose that an "ideal" sham for TMS would have the following characteristics: 1) placement on the subject's head of a TMS coil identical to that used for treatment to obtain visual and tactile parity with "real" treatment; 2) comparable scalp sensation arising from stimulation of superficial nerves and muscles; 3) similar acoustic artifact of TMS, time locked to the scalp sensation; and 4) no physiologic effect on the cortex. Achieving this ideal would be particularly important in crossover studies. However, this ideal is difficult to attain, as any magnetic stimulus delivered from the same coil in contact with the scalp and powerful enough to produce scalp sensation is also likely to depolarise cortical neurons.

A number of different forms of sham TMS were used in the controlled studies cited above. These mostly involved variations in the position of the stimulating coil relative to the scalp, resulting in differences in the intensity and direction of currents induced in cortical tissue (cf. different arrangements shown over the motor cortex in Figure 1). Pascual-Leone et al (1996) and George et al (1997) used a figure-eight coil placed tangential to the scalp for real treatment and with its lateral edge touching the scalp at 45° for sham treatment (as in Figure 1B; personal communication from both authors). Such an arrangement was reported not to produce evoked potentials or to cause measurable changes in cerebral glucose metabolism when used over the motor cortex (George et al 1997). However, patients may have been alert to any subjective differences with sham stimulation, given the crossover design of these trials. Klein et al (1999) used a circular coil, tangential for real TMS and "perpendicular to the scalp surface without direct contact" for sham treatment. Scalp sensation was not mentioned and was presumably absent in this arrangement. Kolbinger et al (1995) used a tangential circular coil for both treatments but reduced the machine output to a very low level (0.05 T) for sham TMS. This was sufficient to induce an acoustic artifact (which would have been much reduced in intensity) but is unlikely to have produced any scalp sensation.

All of the authors of the studies above found significant differences between the outcomes of real and sham treatment. However, in our own double-blind, controlled study in depressed patients we failed to find a significant difference between real and sham TMS treatment, with both groups demonstrating improvement (Loo et al 1999). We concluded that this improvement (about 25%) was probably because of "nonspecific" clinical factors, but we could not rule out the possibility that the sham procedure

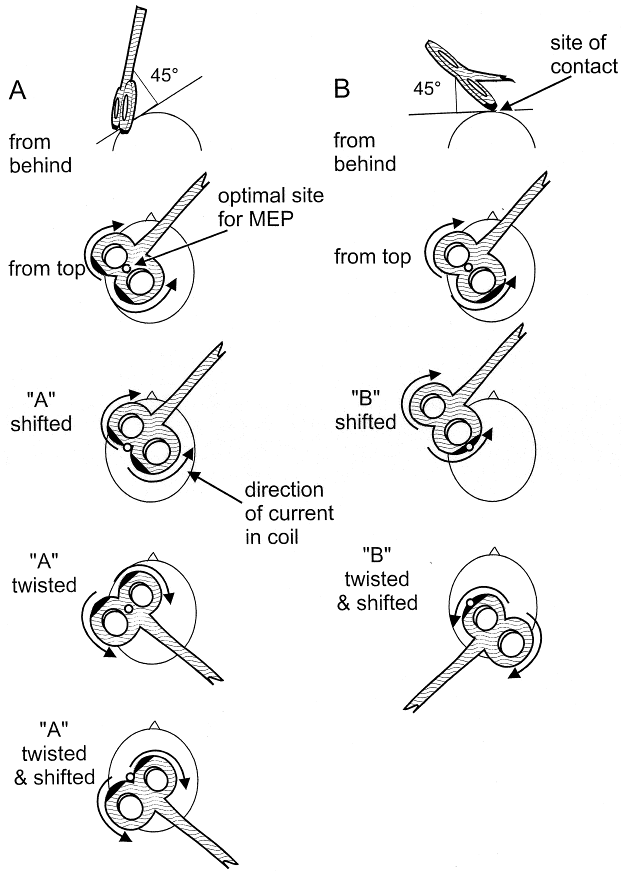

Figure 1. Orientation of the magnetic coil on the head in seven sham conditions. In conditions A, the figure-eight magnetic coil was tilted at 45° from a tangent to the head so that the front edge of the coil remained in contact with the head. The upper left diagram shows a view of the back of a subject's head with the coil positioned on the left side. A line marks a tangent to the curve of the head. The rest of A are views of the top of the subject's head with the nose indicating anterior. In A, the coil is positioned so that its center is over the optimal site (open circle) for evoking a motor-evoked potential in the right first dorsal interosseus muscle. The black edges indicate where the coil is in contact with the head. Arrows indicate the direction of current flow in the coil. Lower A diagrams show the coil *shifted* so that the edge in contact with the head is over the optimal site for stimulation, *twisted* so that current flow in the coil is in a different orientation to the head, and *twisted and shifted.* In conditions B, the coil is tilted at 45° to a tangent to the curve of the head so that one side of the coil (marked black) remains in contact with the head. As with A, the upper diagram shows a view of the back of the head and the lower diagrams are views of the top of the head.

used (figure-eight coil with front edge touching the scalp at 45°, as in Figure 1A), while being weaker than real treatment, did in fact deliver a clinically meaningful stimulation. In this study, we sought to investigate this issue further.

Regrettably, little is known about the relative intensity of cortical stimulation resulting from various coil positions. Lisanby et al (1998) measured the electrical currents induced in cerebral electrodes implanted in live, nonhuman primates while stimulation was applied with a figure-eight coil in various positions. Variations from a tangential position reduced the magnitude of induced currents by 25–73%. How this translates into physiologic effects is not readily apparent, as neuronal depolarization is determined by a complex set of factors apart from the magnitude of induced currents. These include the direction of currents relative to neuronal orientation (Amassian et al 1992) and the conductivity of surrounding tissue (Barker 1991). The effects of coil orientation and position on cortical stimulation therefore require study in human subjects. In the current investigation, seven coil positions were studied (Figure 1) to encompass the common variations reported in published studies and further the search for an ideal sham. While the prefrontal cortex remains the focus of interest in psychiatric disorders, our study was limited to the motor cortex because of the practical advantage the latter offers in the ability to measure evoked responses in peripheral muscles.

Since subjective sensation is an important component of any sham treatment, we also administered single TMS pulses over the left dorsolateral prefrontal area, a common treatment site in psychiatric studies (e.g., Pascual-Leone et al 1996), to determine the relative degree of scalp sensation produced by different coil positions.

Methods and Materials

Subjects

Nine normal adult subjects (four male, two left-handed, aged 25–45 years) participated in the study with informed consent and institutional ethics committee approval. Subjects were seated comfortably throughout the study with the right hand resting on a support. The electromyogram (EMG) was recorded from the right first dorsal interosseus (FDI) muscle through surface electrodes. The EMG was amplified and filtered (20 Hz–1 kHz) and recorded to disk through a laboratory interface (CED 1902, Micro 1401, Sigavg software, Cambridge Electronic Design, Cambridge, UK).

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation was delivered over the hand area of the left primary motor cortex using a 70-mm figure-eight coil and a Magstim (Carmarthenshire, Wales, UK) Rapid machine. Initially, with the coil held tangential to the scalp, the optimal position and orientation (current direction) for evoking a motor response (motor-evoked potential [MEP]) in the right FDI muscle were found for each subject. Threshold stimulus intensity (T) was determined as the lowest intensity at which 10 consecutive stimuli yielded ≥5 MEPs with a peak-to-peak amplitude of ≥50 μV with the subject at rest (Figure 2 , top left). Transcranial magnetic stimulation was delivered with the coil in seven sham positions (Figure 1). As a subject's arousal level and motor threshold vary over time (unpublished observations), the seven stimulation conditions and a second motor threshold measurement were conducted in random order. In addition, subjects were encouraged to converse briefly after each 10 stimuli to maintain a consistent level of arousal.

Stimulation at Rest

Subjects were blind to the order of sham stimulations. For each sham condition, an initial set of 10 stimuli was given at twice threshold (2 T) stimulus intensity. Sets of 10 stimuli at lower intensities (1.75 T, 1.5 T, and 1.25 T) were then administered until an intensity at which no MEPs were apparent was reached. Within each set, stimuli were given at 5-sec intervals. The number of MEPs (with a peak-to-peak amplitude of ≥50 μV) per set was recorded. This number was later confirmed with offline measurements of all trials.

Stimulation during Voluntary Contraction

Further testing was done for three sham conditions that had either been used in controlled studies or were considered likely to deliver a higher level of stimulation (Figure 1 conditions A, B shifted, and B twisted and shifted). Stimuli were given while the subject maintained a weak contraction of the right FDI muscle. Because the ongoing muscle activity created a noisy background from which to identify the response to the stimulus (compare left and right halves of Figure 2), we set a criterion of ≥100 μV peak-to-peak amplitude for MEPs during contraction.

Scalp Sensation during Prefrontal Stimulation

Single TMS pulses were administered over the left dorsolateral prefrontal area, defined as 5 cm anterior to the motor cortex hand area. Subjects reported the presence or absence of scalp sensation with stimuli of intensity T with the coil in various positions: tangential, front edge at 45° (Figure 1A), and lateral edge at 45° (Figure 1B).

Results

Motor thresholds (T) for the subjects ranged between 38% and 66% of maximal stimulator output and did not change significantly during the course of the experiment (paired *t* test, $p = .29$). Two subjects had thresholds above 60% of maximal stimulator output and could therefore only be tested at levels up to 1.5 T.

Stimulation at Rest

Of the seven sham conditions, the only condition which evoked appreciable motor responses in any subject was that with the front edge touching at 45° (Figure 1A). With the coil in this position, two subjects had five or more responses with a stimulus intensity of 2 T and another

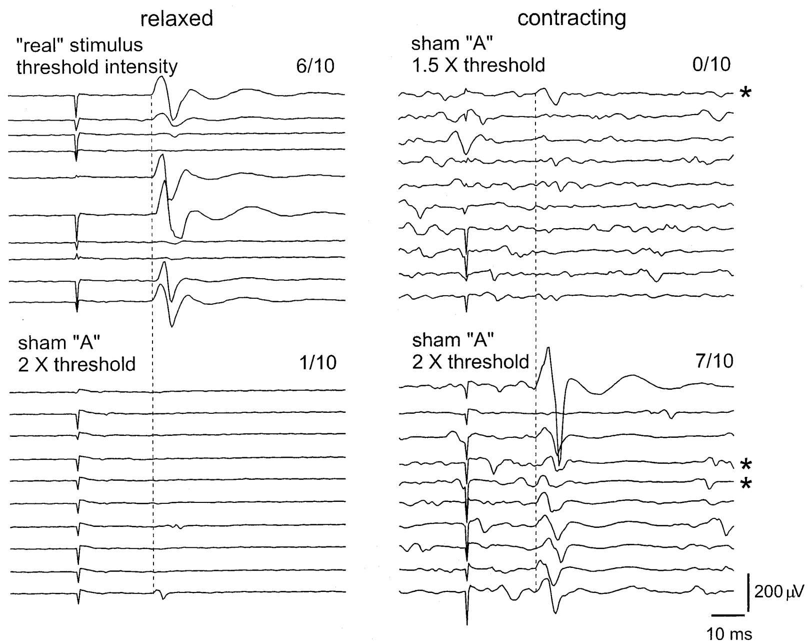

Figure 2. Electromyogram (EMG) traces from a single subject. Each of the four panels shows the EMG recorded from the right first dorsal interosseus muscle during a set of 10 stimuli. Each trace shows an EMG recorded from 20 msec before to 100 msec after a stimulus. A stimulus artifact marks the time of stimulation in most traces. The traces on the left were recorded while the subject remained relaxed and those on the right during a weak contraction of the muscle. The dotted lines mark the onset of motor-evoked potentials (MEPs). The top left panel shows responses to real (tangential) stimulation over the motor cortex at a threshold intensity (T). In six out of 10 of the traces, responses reach the criterion of 50 μV peak-to-peak amplitude. The lower left panel shows responses to stimulation of twice the intensity (2 T) but with the coil in sham position A. There is one MEP from 10 stimuli. In traces on the right, the ongoing muscle contraction means that the response is more difficult to identify compared to the background activity and a criterion of 100 μV peak-to-peak amplitude was used. With an intensity of 2 T (lower right panel), stimulation in sham position A elicited MEPs in seven out of 10 traces. Stimuli of 1.5 T (upper right panel) evoked no responses. *Traces in which responses were probably present but failed to reach the amplitude criterion.

three subjects had at least one response. For the other conditions, there were negligible responses (not more than one subject with one MEP), even at a stimulation intensity equivalent to 2 T. Table 1 shows the median and range of the number of MEPs evoked by 10 stimuli in each sham condition.

Stimulation during Voluntary Contraction

Again, the sham condition that produced the most responses was that with the front edge touching at 45° (Figure 1A). Whereas one to three MEPs were elicited in three of the nine subjects by stimulation in the "B twisted and shifted" position, and two MEPs in only one subject in "B shifted," MEPs were elicited in the contracting muscle in eight of the nine subjects by the A sham. Occasional MEPs could be elicited by stimulation with an intensity as low as 1.25 T. Figure 2 shows the EMG responses to real (tangential) TMS and sham stimulation in condition A for one subject during relaxation and voluntary muscle contraction. Group results (median and range) for condition A are shown in Table 2 .

Scalp Sensation during Prefrontal Stimulation

With single pulses at intensity T, all subjects reported a scalp sensation with tangential stimulation, four of the

Table 1. Number of Motor Responses Evoked in Relaxed First Dorsal Interosseus Muscle by 10 Magnetic Stimuli of Intensity 2 × Motor Threshold[a]

Coil position[b]	Median	Range
A	1	0–10
A shifted	0	0–1
A twisted	0	0–0
A twisted and shifted	0	0–0
B	0	0–0
B shifted	0	0–1
B twisted and shifted	0	0–0

[a]Or maximum machine output if threshold >50% maximum.
[b]See Figure 1 and text for description of the coil positions.

Table 2. Number of Motor Responses Evoked in Relaxed and Contracting First Dorsal Interosseus Muscle by 10 Magnetic Stimuli with Coil in Position A[a]

Stimulus Intensity (× threshold)	Relaxed median (range)	Contracting median (range)
1.0	—	0 (0–1)
1.25	—	1 (0–3)
1.5	0.5 (0–1)	2 (0–8)
1.75	2 (0–4)	6 (2–10)
2.0	1 (0–10)	6.5 (4–10)

[a]See Figure 1 and text for description of the coil positions.

nine subjects with stimulation with the front edge at 45° (A), and one of the nine with stimulation with the lateral edge at 45° (B).

Discussion

Stimulation over the motor cortex was used as a test for the functional efficacy of TMS with a figure-eight stimulating coil held in various positions. Stimulation conditions were tested with the target muscle at rest and during voluntary contraction, as the latter increases both the likelihood that a stimulus will activate neurons in the cortex and that any descending volley evoked by the stimulus will activate enough spinal motoneurons to provide a detectable response in the muscle (e.g., Hess et al 1987; Mazzocchio et al 1994). Thus, stimulation during contraction is a more sensitive test of the effects of TMS on the motor cortex than stimulation at rest and can evoke MEPs at stimulus levels that produce no response at rest.

Research groups using a figure-eight coil have generally held its front edge at 45° (as in Figure 1A) or its lateral edge at 45° (as in Figure 1B) for sham treatment. This study demonstrated that condition A delivered a higher level of stimulation and was also more likely to produce a scalp sensation. The level of activation elicited in A was still low compared to a tangential coil placement (i.e., as in real TMS treatment). For most subjects, stimulation at 2 T (at rest) failed to produce a response (defined as ≥ 5 responses per set of 10 stimuli). In other words, raising the coil as in A reduced the stimulation level to less than 50% for most subjects. Since sham TMS in treatment studies is usually given at the same level as real TMS, close to the subject's motor threshold (T), this is unlikely to represent an effective dose, though the possibility cannot be excluded. When stimulation was given during voluntary contraction, the majority of subjects had $>5/10$ responses, even at 1.75 T. If there is an analogous condition in the prefrontal cortex to voluntary contraction in the motor cortex, then this form of sham may in fact be delivering a clinically relevant stimulus.

In our recently completed double-blind, parallel design, controlled study of 18 depressed patients (Loo et al 1999), sham A given at 110% motor threshold proved to be an effective blind, with subjects being unable to distinguish sham from real TMS. We found that the intensity of prefrontal scalp sensation varied greatly between individuals, though all subjects receiving sham TMS experienced some scalp sensation. Those in the sham group who went on to have open real treatment did report far greater scalp sensation with the latter. Therefore, while sham condition A was adequate to achieve blinding in our parallel-design study, it may not be good enough in a crossover design.

Positions B delivered a much lesser degree of cortical stimulation (minimal even in the presence of voluntary contraction) but were also less likely to be associated with scalp sensation. Thus B, while having the advantage of being less "active," is more likely to be perceived by the subject as inactive treatment.

Theoretically, strategies for reducing cortical stimulation while preserving the scalp sensation of TMS include moving the coil over the scalp away from the treatment site (cf. shifted arrangements in Figure 1) and rotating the coil over the scalp (cf. twisted arrangements in Figure 1). Shifting the coil reduces its effective stimulation, as seen in A and "A shifted" (Table 1). This finding implies that the geometric center of the (figure eight) coil still delivers more stimulation at a cortical level than the edge of the coil touching the scalp, even though the former is not in contact with the scalp when the coil is raised at 45°. This is an important consideration when using active coils in sham designs. Twisting the coil has been shown to markedly affect the degree of motor cortex activation when the coil is held tangentially, since current direction relative to neuronal orientation strongly determines depolarization (Mills et al 1992). The effect was not evident in this study, where the coil was held at 45° to the scalp; however, this strategy may be important in other sham designs (e.g., where the coil is tangential but the stimulator output level is decreased).

There are a number of caveats in the interpretation of our results and their application to sham designs in psychiatric treatment studies. First, motor and prefrontal cortex may differ in their responses to magnetic stimulation owing to differences in cortical cytoarchitecture and neuronal connections. Thus TMS thresholds for the two areas may be different and prefrontal cortical response may not be as distinctly a threshold phenomenon as it is in the motor cortex.

Second, there are other factors to consider in the effects of TMS apart from a threshold response. A subthreshold sham may still affect cortical functioning. This phenomenon has been demonstrated in the motor cortex, where a subthreshold conditioning stimulus can alter the response to a subsequent suprathreshold stimulus (e.g., Kujirai et al 1993; Nakamura et al 1995). An analogous phenomenon may occur in the prefrontal cortex. In the motor cortex, a background voluntary contraction increased the likelihood of an MEP response to a stimulus of given intensity. Likewise, certain mental states or tasks may similarly "prime" the prefrontal cortex, producing a response to TMS which is otherwise "subthreshold."

Third, shifting the coil in this study reduced the likelihood of activating the small area of motor cortex controlling a hand muscle, but this may have a negligible effect in the prefrontal cortex if similar mental state changes can be induced by stimulation of a number of sites within a far larger area. Likewise, twisting the coil may make little difference if target prefrontal neurons (i.e., those putatively responsible for mental state changes) are not oriented such as to be preferentially depolarized by currents in a particular direction (in contrast to the motor cortex).

Fourth, the effects of single TMS pulses were examined in our study, whereas most treatment studies apply repeated TMS pulses, often at high frequency, to a single cortical site. We chose to use single pulses because MEP responses to a train of pulses are more difficult to interpret, particularly in the presence of voluntary contraction; however, it is likely that both neuronal depolarization and subjective scalp sensation would differ with TMS at different frequencies.

A further area of investigation would be coil arrangements at 90° to the scalp. We concentrated on 45° arrangements because our experience has been that scalp sensation is far less likely with the coil at 90° (unpublished observations); however, since the geometry of the stimulating field is not symmetrical around a figure-eight coil (Ueno et al 1988), it may well be that coil positions with scalp sensation but minimal cortical activation could be found.

In conclusion, none of the coil positions investigated above met all the criteria for an ideal sham. The choice of a particular position for sham TMS will be determined by the design of the study and, in particular, the importance of blinding. In psychiatric treatment studies using a crossover design, scalp sensations are particularly important. Yet the need for a truly inactive sham has to be recognized, and it must be acknowledged that previously published studies may well have used a partially active placebo. Further research is needed to explore alternative approaches to designing a sham for TMS, including the development of specially designed coils for this purpose. These strategies will gain from applying functional neuroimaging techniques to investigate the real effects of sham stimulation.

This study was supported by the Australian National Health and Medical Research Council Mood Disorders Unit Program Grant No. 993208, private donations from Mr. Peter Joseph (Director, Bankers Trust, Australia) and Mr. William Loewenthal (Company Director), and a part-time Research Fellowship from the New South Wales Institute of Psychiatry (CKL).

References

Amassian VE, Eberle L, Maccabee PJ, Cracco RQ (1992): 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* 85:291–301.

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

Fleischmann A, Sternheim A, Etgen A, Li C, Grisaru N, Belmaker R (1996): Transcranial magnetic stimulation downregulates β-adrenoreceptors in rat cortex. *J Neural Transm* 103:1361–1366.

Fox P, Ingham R, George MS, Mayberg H, Ingham J, Roby J, et al (1997): Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport* 8:2787–2791.

Fujiki M, Steward O (1997): High frequency transcranial magnetic stimulation mimics the effects of ECS in upregulating astroglial gene expression in the murine CNS. *Mol Brain Res* 44:301–308.

George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, et al (1997): Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry* 154:1752–1756.

George MS, Wassermann EM, Post RM (1996): Transcranial magnetic stimulation: A neuropsychiatric tool for the 21st century. *J Neuropsychiatry Clin Neurosci* 8:373–382.

Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, Altemus M, et al (1997): Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry* 154:867–869.

Grisaru N, Amir M, Cohen H, Kaplan Z (1998a): Effect of transcranial magnetic stimulation in posttraumatic stress disorder: A preliminary study. *Biol Psychiatry* 44:52–55.

Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH (1998b): Transcranial magnetic stimulation in mania: A controlled study. *Am J Psychiatry* 155:1608–1610.

Hess CW, Mills KR, Murray NMF (1987): Responses in small hand muscles from magnetic stimulation of the human brain. *J Physiol (Lond)* 388:397–419.

Klein E, Kreinin I, Chistyakov A, Korean D, Mecz L, Marmur S, et al (1999): Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: A double blind controlled study. *Arch Gen Psychiatry* 56:315–320.

Kolbinger HM, Höflich G, Hufnagel A, Möller H-J, Kasper S (1995): Transcranial magnetic stimulation (TMS) in the treatment of major depression: A pilot study. *Hum Psychopharmacol* 10:305–310.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al (1993): Corticocortical inhibition in human cortex. *J Physiol (Lond)* 471:501–519.

Lisanby S, Luber B, Schroeder C, Osman M, Finck D, Jalinous R, et al (1998): Intracerebral measurement of rTMS and ECS induced voltage in vivo. *Biol Psychiatry* 43:100S.

Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S (1999): A double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry* 156:946–948.

Mazzocchio R, Rothwell JC, Day BL, Thompson PD (1994): Effect of tonic voluntary activity on the excitability of human motor cortex. *J Physiol (Lond)* 474:261–267.

McCann UD, Kimbrell TA, Morgan CM, Anderson T, Geraci M, Benson BE, et al (1998): Repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Arch Gen Psychiatry* 55:276–279.

Mills KR, Boniface SJ, Schubert M (1992): Magnetic brain stimulation with a double coil: The importance of coil orientation. *Electroencephalogr Clin Neurophysiol* 85:17–21.

Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H, Takano H, Nakatoh S (1995): Intracortical facilitation and inhibition after paired magnetic stimulation in humans under anaesthesia. *Neurosci Lett* 199:155–157.

Pascual-Leone A, Rubio B, Pallardó F, Catalá MD (1996): Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 347:233–237.

Pascual-Leone A, Valls-Sole J, Wassermann E, Hallett M (1994): Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 117:847–858.

Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC, et al (1997): Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *J Neurosci* 17:3178–3184.

Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC, et al (1998): Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. *J Neurophysiol* 79:1102–1107.

Ueno S, Tashiro T, Harada K (1988): Localised stimulation of neural tissues in the brain by means of a paired configuration of time-varying magnetic fields. *J Appl Physiol* 64:5862–5864.

Wassermann E, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, et al (1996): Use and safety of a new repetitive transcranial magnetic stimulator. *Electroencephalogr Clin Neurophysiol* 101:412–417.