International Journal of Neuropsychopharmacology (2002), **5**, 73–103. Copyright © 2002 CINP
DOI: 10.1017/S1461145702002791

REVIEW ARTICLE

Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis

Tal Burt[1,2,4], Sarah H. Lisanby[1,2] and Harold A. Sackeim[1,2,3]

[1] *Department of Biological Psychiatry, New York State Psychiatric Institute, New York, USA*
Departments of [2] *Psychiatry and* [3] *Radiology, College of Physicians and Surgeons of Columbia University, New York, NY, USA*
[4] *Pfizer Inc., New York, NY*

Abstract

Transcranial magnetic stimulation (TMS) is a technology that allows for non-invasive modulation of the excitability and function of discrete brain cortical areas. TMS uses alternating magnetic fields to induce electric currents in cortical tissue. In psychiatry, TMS has been studied primarily as a potential treatment for major depression. Most studies indicate that slow-frequency repetitive TMS (rTMS) and higher frequency rTMS have antidepressant properties. A meta-analysis of controlled studies indicates that this effect is fairly robust from a statistical viewpoint. However, effect sizes are heterogeneous, and few studies have shown that rTMS results in substantial rates of clinical response or remission, and the durability of antidepressant effects is largely unknown. We review in detail rTMS studies in the treatment of depression, as well as summarize treatment studies of mania, obsessive–compulsive disorder, post-traumatic stress disorder, and schizophrenia. We also review the application of TMS in the study of the pathophysiology of psychiatric disorders and summarize studies of the safety of TMS in human subjects.

Received 15 October 2001; Reviewed 18 November 2001; Revised 4 December 2001; Accepted 5 December 2001

Key words: Cortical excitability, depression, ECT, meta-analysis, psychiatric disorders, transcranial magnetic stimulation.

Introduction

Transcranial magnetic stimulation (TMS) is a technology that allows for discrete non-invasive probing and modulation of cortical excitability and function (Lisanby et al., 2000). TMS uses alternating magnetic fields to induce electric currents in cortical tissue in specific brain regions. Depending on the stimulation parameters, cortical excitability may be increased or decreased, and the changes may be transient or possibly may last for weeks. In addition, depending on the location and parameters of the stimulation and the physiology of the underlying cortical tissue, different changes in behaviour may ensue, including the enhancement or interference with cognitive performance (Boroojerdi et al., 2001; Grafman et al., 1994). These effects hold great promise in the study of brain function and patterns of neural connectivity in normal and pathological states, and also, possibly, in the diagnosis and treatment of neuropsychiatric disorders (Belmaker and Fleischmann, 1995; Brandt et al., 1997; Conca et al., 1996; George et al., 1996a, 1999; George and Wassermann, 1994; Grisaru, 1994; Haag et al., 1997; Hasey, 1999; Kammer and Spitzer, 1996; Kirkcaldie et al., 1997a,b; Markwort et al., 1997; Nemeroff, 1996; Pascual-Leone et al., 1999; Paus, 1999; Post et al., 1997, 1999; Pridmore and Belmaker, 1999; Puri and Lewis, 1996; Reid et al., 1998; Sackeim, 1994, 2000; Tormos et al., 1999; Zyss, 1992; Zyss and Krawczyk, 1996).

Address for correspondence: Dr T. Burt, Department of Biological Psychiatry, New York State Psychiatric Institute, Unit 126, 1051 Riverside Drive, New York, NY 10032, USA.
Tel.: 212 733-2308 *Fax*: 212 309-4280
E-mail: tal.burt@columbia.edu

Historical perspective

The first use of magnetic stimulation to elicit changes in behaviour was conducted by d'Arsonval in the late 19th century (d'Arsonval, 1896; Geddes, 1991). Given device output limitations and the low intensity of the magnetic field produced, d'Arsonval could only elicit the experience of phosphenes (i.e. perception of light flickers), due to the low discharge threshold in the retina. It was only in 1985 that Barker and colleagues developed a device capable of producing depolarization in cortical areas, and proposed the use of TMS for clinical purposes (Barker et al., 1985). In the first years following its introduction, TMS was almost exclusively used by neurologists for non-invasive exploration of the human cortex. Hoflich et al. (1993) was the first published study of TMS in psychiatric patients,

reporting modest antidepressant effects of repetitiveTMS (rTMS) administered to two depressed patients.

Mechanism and technique

Two electromagnetic principles underlie the mechanism of TMS. The first is the generation of a magnetic field using an alternating electric current (Ampère's Law), and the second is the generation of an electric current using an alternating magnetic field (Faraday's Law). These two principles are enacted sequentially in the two steps that comprise the TMS mechanism (Malmivuo and Plonskey, 1995). First, an insulated metal coil is placed on the scalp and an alternating electric current in the coil generates an alternating magnetic field perpendicular in orientation to the current flow in the coil. Secondly, the alternating magnetic field that passes unimpeded through the scalp and skull induces a secondary electric current in the brain tissue underlying the external coil. The direction of current flow in the brain is parallel to that in the coil, but opposite in direction. A detailed description of TMS parameters and technique is available elsewhere (Lisanby et al., 2000).

Magnetic pulses may be administered individually ('single-pulse' TMS), or in pairs that are few milliseconds apart ('paired-pulse' TMS), or repetitively for a train of many seconds or minutes (rTMS). In the latter case, the stimulation is described by the number of pulses per second or frequency (in Hz). Slow rTMS is typically described as repetitive stimulation using a frequency $\leqslant 1$ Hz. The term, fast-frequency rTMS, is usually reserved for stimulation frequencies > 1 Hz. The magnetic pulse is further described, typically by its intensity in percentage relative to the motor threshold (MT) of the individual. The MT is the lowest intensity of stimulation that when applied to the motor cortex causes a standard contraction of a muscle [typically the first dorsal interosseous (FDI) or abductor pollicus brevis (APB) muscles] in at least 5 of 10 consecutive trials. In addition, when rTMS is administered the number of pulse trains per daily session is typically described, as well as the inter-train interval, the number of daily sessions, the site of stimulation and the geometry (type) of coil used (e.g. round, figure-of-eight, double-cone) and the orientation of the coil relative to the site on the scalp.

Most TMS today is delivered to humans in the context of research protocols. Individuals to whom rTMS is administered are usually fully awake and sitting and sessions last 20 min to 1 h. If multiple sessions are required they usually occur daily on consecutive weekdays for a number of weeks. Concurrent electroencephalographic (EEG) and electromyographic (EMG) monitoring are common in this investigational stage, and imaging with positron emission tomography (PET), single photon emission tomography (SPECT), and functional magnetic resonance imaging (fMRI) are occasionally added to the protocols (Bohning et al., 1999; Catafau et al., 2001; Paus, 1999; Zheng, 2000)

Effects of TMS on brain cortical tissue

rTMS can be used either to modulate brain cortical parameters (e.g. excitability, blood flow, receptor density, and hormone levels) or to study brain characteristics (e.g. localization of brain function and connectivity, effects of medications on cortical excitability). This section will describe the evidence supporting these uses.

TMS as a tool used to alter brain cortical parameters for treatment or research purposes

TMS can modulate brain cortical parameters when trains of stimuli are administered in rapid succession to discrete brain regions (rTMS). Virtually all TMS applications that have a therapeutic rather than investigative goal use slow-frequency rTMS ($\leqslant 1$ Hz) or fast-frequency (> 1 Hz) rTMS, rather than single-pulse TMS in an attempt to modify the cortical parameters that are believed to be associated with an underlying psychopathology.

Effects on cortical excitability and regional cerebral blood flow (rCBF)

TMS can modify brain cortical excitability and rCBF (Bohning et al., 1999, 2000; Catafau et al., 2001; Chen et al., 1997a; Fox et al., 1997; Izumi et al., 1997; Meyer et al., 1994; Nakamura et al., 1997; Oliviero et al., 1999; Paus, 1999; Paus et al., 1997, 1998; Teneback et al., 1999; Wassermann et al., 1998; Zheng, 2000). In some of this work, high-frequency rTMS (e.g. > 1 Hz) produced a local increase in local rCBF (e.g. in the area under the coil), while low-frequency rTMS (e.g. $\leqslant 1$ Hz) produced a local decrease in cortical excitability that lasted after the stimulation had terminated (Chen et al., 1997a; Nakamura et al., 1997). It also appears that decreased excitability is a correlate of decreased blood flow and metabolism and may occur at a distance from the primary site of excitation (Wassermann et al., 1998). Perhaps more interestingly, improvement of depressed symptoms has been associated in some studies with changes in prefrontal and paralimbic blood flow after rTMS (Catafau et al., 2001; Teneback et al., 1999; Zheng, 2000). Hamano et al. (1993), however, failed to replicate changes in rCBF in 3 normal volunteers after maximum-intensity rTMS. Paus et al. (1998) observed that high-

frequency rTMS led to a paradoxical decrease in CBF in areas under the coil (motor cortex), in contrast to previous findings when stimulating over the frontal eye fields (Paus et al., 1997). They postulated an activation of an inhibitory system in the underlying motor cortex was the cause of this observation. However, almost all imaging studies, using PET or fMRI found increased neuronal activation in sites under the coil, regardless of stimulation frequency.

Several authors have suggested that the cellular mechanisms involved in long-term potentiation (LTP) and long-term depression (LTD) subserve the effects that outlast the duration of the stimulation (Chen et al., 1997a; Wang et al., 1996, 1999). Kimbrell et al. (1999) described a working hypothesis stipulating that high-frequency rTMS, like LTP, increases synaptic efficacy, while low-frequency rTMS reduces it. Consistent with this speculation was their finding of a differential antidepressant response to rTMS as a function of baseline cerebral glucose metabolism. Pre-treatment global hypometabolism was associated with positive clinical response to 10 Hz rTMS to the left dorsolateral prefrontal cortex (LDLPFC) and pre-treatment global hypermetabolism was associated with response to 1 Hz rTMS at this same site. However, there has yet to be a convincing demonstration that rTMS impacts on LTP and/or LTD and that these effects are frequency dependent. In contrast, there have been repeated demonstrations that a course of electroconvulsive shock (ECS) in animals results in attenuation of LTP (Anwyl et al., 1987; Stewart and Reid, 2000).

Neuroendocrine effects

rTMS over prefrontal regions led to increase in thyroid-stimulating hormone (TSH), but not prolactin, in 10 healthy volunteers (George et al., 1996b) and reversal of the dexamethazone suppression test (DST) with symptomatic remission in 6 of 12 consecutively treated depressed patients (Pridmore, 1999; Reid and Pridmore, 1999). Szuba et al. (2001) randomized 14 medication-resistant depressed patients to a single session of sham or real rTMS (10 Hz, 100% MT, 20 trains over 10 min). Patients receiving real but not sham rTMS showed significant improvement in mood immediately following the stimulation and an increase in TSH. These observations support the hypothesis that rTMS can exert physiological effects consistent with antidepressant effects at areas that are distant to the primary stimulation area. In other words, despite the focality of stimulation and restriction of rTMS induced current to cortical tissue, there may be may be significant effects on subcortical structures through patterns of connectivity.

Effects on cognitive functioning

Several studies have demonstrated the effects of rTMS on learning and short-term memory. These cognitive functions are frequently abnormal in psychiatric disorders, notably, in depression and schizophrenia (Stern and Sackeim, In Press). Depending on the location and stimulation parameters, rTMS has been found to either improve or disrupt cognitive functioning, although most effects have been disruptive and have concentrated on stimulation during task performance (Claus et al., 1999; Grafman et al., 1994; Grafman and Wassermann, 1999; Kessels et al., 2000; Mull and Seyal, 2001; Pascual-Leone and Hallett, 1994; Robertson et al., 2001; Sabatino et al., 1996). These observations are important in demonstrating that brain cortical tissue has anatomically specific cognitive functions that can be externally modulated. It would be interesting to observe whether in psychiatric patients modulation of cognitive functions using rTMS can occur in isolation of effects on mood, volition, or other core psychiatric symptoms. It should be noted, however, that all modulation of cognitive function with rTMS has occurred only during or shortly after stimulation. There are few data suggesting that that rTMS leads to a more long-term effect on cognition (Flitman et al., 1998; Little et al., 2000).

TMS in animal models of mental illness

Animal models have been instrumental in demonstrating lasting effects of rTMS on brain cortical tissue. Specifically, numerous studies have demonstrated similarities between the effects of rTMS and the effects of ECS in animal models of depression (Belmaker and Grisaru, 1998; Ben-Shachar et al., 1997; Fleischmann et al., 1995, 1996, 1999; Fujiki and Steward, 1997; Zyss et al., 1996, 1997, 1999). Like ECS, Belamker and Grisaru (1998) found that rTMS led to enhancement of apomorphine-induced stereotypy, reduction of immobility time in the Porsolt swim test, and increases in seizure threshold for subsequent stimulation. They also reported evidence that rTMS led to a reduction in β-adrenergic receptor density in cortical areas, but not the hippocampus. Also in line with the effects of ECS (Duman and Vaidya, 1998; Gombos et al., 1999), our group found that daily rTMS in rats leads to an increase in hippocampal mossy fibre sprouting (Lisanby SH, Arango V, Underwood MD, Dwork AJ, Sackeim HA, unpublished observations). In contrast Ben-Shachar et al. (1997, 1999) demonstrated alterations induced by rTMS after 10 d of treatment that differed from previous findings. β-Adrenergic receptors were significantly up-regulated in the frontal cortex, and down-regulated in the striatum. 5-HT-2 receptors were down-regulated in the frontal cortex, but no changes were observed in benzodia-

zepine receptors. Thus, it is possible that rTMS exerts an effect through a unique mechanism of action unlike other antidepressants.

TMS as a tool used to study brain cortical parameters and psychopathology

Through the study of cortical excitability in the natural state, psychopathological states, and under the effects of different medications and interventions, TMS can be used to study the function and excitability of brain regions, the pathways connecting them, the effects of neurotransmitter systems on behaviour and perception, and provide a guide for evolving pharmacological or instrumental interventions (e.g. rTMS, ECT, vagus nerve stimulation, deep brain stimulation, and psychosurgery) (Pascual-Leone et al., 1998). Most commonly, studies of cortical excitability have involved the production of motor-evoked potentials (MEPs) in the FDI or APB muscle through single- or paired-pulse TMS of the contralateral motor cortex using a variety of stimulation paradigms. The different paradigms such as the silent period, paired-pulse inhibition and facilitation, input–output curves, and the threshold of motor response are believed to be able to discriminate different neuronal pathway or neurotransmitter systems (Ziemann et al., 1995, 1996a–c, 1997b, 1998). These paradigms are described in greater detail elsewhere (Lisanby et al., 2000).

Cortical excitability in Tourette's disorder and obsessive–compulsive disorder (OCD)

There has been relatively few investigations using these paradigms to study the pathophysiology of psychiatric disorders. In 20 patients with Tourette's disorder compared to 21 healthy controls, Ziemann et al. (1997a) found that MT and peripheral motor excitability were normal, but the cortical silent period following a TMS-evoked response was shortened and the intracortical inhibition reduced in the paired-pulse paradigm. A subgroup analysis revealed that these abnormalities were seen mainly when tics were present in the EMG target muscle or in patients without neuroleptic treatment. These findings suggested that tics in Tourette's disorder result from either a subcortical disturbance affecting the motor cortex through disinhibited afferent signals or from impaired inhibition directly at the level of the motor cortex.

OCD shares features with Tourette's disorder, and the two conditions are often co-morbid. Greenberg et al. (1997, 2000) studied 16 OCD patients and 11 healthy age-matched volunteers using rTMS paradigms similar to Ziemann et al. (1997a). They found that like the findings in Tourette's syndrome and focal dystonia, OCD patients had significantly decreased intracortical inhibition at interstimulus intervals from 2 to 5 ms. They also found decreased active and resting MEP threshold in the OCD patients, another indication of increased cortical excitability. Neither abnormality appeared medication related. The decreases in intracortical inhibition and MT were greatest in OCD patients with co-morbid tics, but remained significant in patients without tics.

Cortical excitability in depression

Samii et al. (1996) studied the effects of exercise on the magnitude of MEPs, another measure of cortical excitability, elicited by TMS. The study was conducted in 18 normal subjects, 12 patients with chronic fatigue syndrome, and 10 depressed patients. Post-exercise cortical excitability was significantly reduced in patients with chronic fatigue syndrome and in depressed patients compared to normal subjects. Shajahan et al. (1999a,b) reported that depressed patients show reduced post-exercise facilitation when compared to recovered depressed patients. They hypothesized that modulation of cortical excitability may be impaired during the depressive state, i.e. a state-dependent phenomenon. There have yet to be reports of abnormalities in major depression using classic TMS paradigms that assess cortical excitability, such as MT, paired-pulse inhibition, duration of the silent period following an evoked response, etc.

Cortical excitability in schizophrenia

Abarbanel et al. (1996) demonstrated increase MEP amplitude after TMS to the motor cortex, an observation that is consistent with theories of decreased γ-aminobutyric acid (GABA) activity and increased cortical excitability in schizophrenia. However, they noted that results should be interpreted in the context of a study conducted in medicated patients with secondary rigidity and tremor, both of which might affect MEP amplitude. Davey et al. (1997) reported no difference in threshold of MEPs or their latency in 9 drug-naive schizophrenic patients when compared to patients on neuroleptic medication. Puri et al. (1996) reported differences between 9 drug-free schizophrenic patients and normal controls. The latency of MEPs following TMS was significantly shorter in the schizophrenic patients and could be attributed to a relative lack of corticospinal inhibition of motor responses. Thus, the initial evidence suggests increased cortical excitability in the motor cortex of patients with schizophrenia and should be followed by studies using other TMS paradigms to confirm this observation.

Cortical excitability in attention deficit hyperactivity disorder (ADHD)

Ucles et al. (1996) studied a group of 15 children aged 3–7 yr suffering from ADHD, and a control group of 23 age-matched normal children using computerized EEG and TMS in combination. With TMS, a marked difference in right/left stimulation was obtained in the ADHD group ($p < 0.001$). Coupled with abnormal EEG findings, the authors concluded that these results suggest delayed myelination at the brainstem reticular formation and at the corticospinal pathway as part of a widespread dysfunction.

Cortical excitability in Alzheimer's Disease (AD)

Perretti et al. (1996) studied MEPs in the APB and tibialis anterior (TA) muscles elicited by TMS to the motor cortex in 15 patients with AD. An abnormally higher MEP threshold in APB, frequently associated with absence of the MEP in relaxed TA muscles, was found in 40% of patients, almost all of whom were in the more severe stages of the disease. Only 20% of patients showed an increase in central motor conduction time, while 64% had a shortening of the central silent period in the APB muscle. The authors concluded that these results suggest that loss and/or dysfunction of motor cortex neurons, including pyramidal cells and inhibitory interneurons may occur in AD patients even before clinical signs become apparent.

TMS in psychogenic paralysis

By inducing MEPs after motor cortex TMS, the integrity of the corticospinal tract was confirmed and several cases of psychogenic paralysis identified. This obviated the need for more invasive procedures (Janssen et al., 1995; Mullges et al., 1991).

Cortical excitability and personality

Wassermann et al. (2001) conducted the first study of the relations between TMS measures of cortical excitability and scores on personality dimensions among healthy control subjects. They used the NEO Personality Inventory Revised (NEO-PI-R) which has shown strong longitudinal retest reliability, cross-cultural invariance and strong genetic loading for specific dimensions (Costa and McCrae, 2000; Herbst et al., 2000). The NEO-PI-R produces 5 'super-factors' labelled to neuroticism, agreeableness, conscientiousness, extraversion and openness. In 46 volunteers, Wassermann et al. (2001) assessed MT and paired-pulse inhibition and facilitation. There were no relations between personality scores and MT. In contrast, neuroticism showed a robust association ($p = 0.0006$) with the ratio of the amplitude of conditioned to unconditioned MEPs at all interstimulus intervals in the paired-pulse paradigm. Individuals high in neuroticism had increased ratios throughout the periods usually associated with paired-pulse inhibition and facilitation. This indicated increased cortical excitability in individuals high on a personality dimension associated with depression and other negative affects (e.g. anxiety). Pharmacological studies have shown that GABA agonists reduce the amplitude of conditioned MEPs throughout the short (inhibitory) and long (facilitory) intervals in the paired-pulse paradigm (e.g. Ziemann et al., 1996b,c). This may suggest a link between reduced evoked GABAergic function and anxiety-proneness in normal individuals.

Cortical excitability and sleep

Hess et al. (1987) demonstrated an increase in motor amplitudes to TMS during REM sleep when compared to baseline. They suggested that there is an increase in cortical excitability during REM sleep. Stalder et al. (1995) demonstrated increased variability of muscular response during REM sleep. Pre-treatment with rTMS was shown to delay the first REM sleep period on average by 17 min and prolong the non-REM–REM cycle length. Importantly, these rTMS-induced changes in REM sleep variables are similar to findings observed after pharmacological and ECT treatment of depression. Some have suggested that the capability of rTMS to affect circadian and ultradian biological rhythms might contribute to its antidepressant action (Cohrs et al., 1998).

rTMS and mood alterations in healthy volunteers

George et al. (1996b) administered rTMS on different days to the right or left prefrontal cortex (PFC), midfrontal cortex, occipital cortex, or cerebellum in 10 healthy volunteers. Decreased happiness was reported after left prefrontal rTMS and decreased sadness after right prefrontal rTMS. Stimulation of all three prefrontal regions, but not the occipital or cerebellar regions, was associated with increases in serum TSH. There was no effect on serum prolactin. The effects on mood were slight and only detectable in statistical analysis of visual analogue ratings. They were not subjectively reported. Pascual-Leone et al. (1996a) also studied the effects of rTMS of different scalp positions on mood in 10 normal volunteers. Left prefrontal rTMS resulted in a significant increase in 'sadness' ratings and a significant decrease in 'happiness' ratings as compared with right prefrontal and midfrontal cortex stimulation. Again, the changes in mood were slight and only detectable by small but consistent changes in self-ratings. In both studies subjects

did not appear to be conscious of mood changes and the time-course of the mood effects relative to stimulation differed considerably in the reports by George et al. (1996b) and Pascual-Leone et al. (1996a).

Recently, Mosimann et al. (2000) attempted to replicate the mood effects in 25 male normal volunteers. Using a sham-controlled cross-over design, active rTMS (20 Hz, 2 s train duration, 40 trains, 100% MT) was delivered over the LDLPFC. They were unable to demonstrate any mood changes in visual analogue ratings after either sham or active stimulation. Since all previous work on mood effects in normal volunteers used high-frequency rTMS, Grisaru et al. (2001) examined the effects of slow TMS (1 Hz) delivered with a figure-of-eight, 9-cm coil to the left and right DLPFC (110% MT, 500 stimuli). Examination of slow rTMS was particularly important since there is evidence that slow-frequency rTMS to the RDLPFC has antidepressant properties (see below). In this cross-over study of 18 healthy volunteers both active and sham stimulation conditions were used and mood effects were assessed 5, 30, and 240 min after stimulation using visual analogue scales. There were no significant effects on mood or sleep with active stimulation. Thus, at least with the rTMS parameters examined so far, it is unlikely that this form of stimulation has a consistent or robust effect on the mood of normal volunteers.

Using a different paradigm, Tormos et al. (1997) studied the changes in excitability of corticospinal projections evoked by self-induced sad and happy thoughts. Corticospinal excitability was probed using focal, single-pulse TMS applied to the optimal scalp position for evoking MEPs in the contralateral FDI muscle. Fourteen right-handed subjects were studied while counting mentally, thinking sad thoughts, or thinking happy thoughts. In each of these three conditions, TMS was applied in each subject randomly 20 times to the right and 20 times to the left hemisphere. Sad thoughts resulted in a significant facilitation of the MEPs evoked by left-hemispheric stimulation, while happy thoughts facilitated MEPs evoked by right-hemispheric TMS, but decreased the amplitude of those evoked by left-hemispheric TMS. These results were interpreted to further illustrate the role of lateralized neural systems in the regulation of mood (Davidson, 1995; Lisanby and Sackeim, 2000; Sackeim et al., 1982). The fact that affectively laden thoughts influence motor cortex excitability is an unexpected finding and requires replication.

TMS in the treatment of psychiatric disorders

Since Zyss (1992) first suggested the use of TMS as a non-invasive treatment for psychiatric disorders, numerous trials have been conducted in psychiatric patients. Major depressive disorder has received the most extensive investigation, but trials in patients with bipolar disorder, OCD, post-traumatic stress disorder (PTSD), schizophrenia, catatonia, Tourette's disorder and Alzheimer's disorder have also been conducted. Although most applications have used subconvulsive rTMS, Sackeim (1994) and Lisanby et al. (2001b,c) have argued that convulsive magnetic stimulation, magnetic seizure therapy (MST) (see below), may have significant advantages over ECT.

Methodological issues in the use of rTMS in therapeutic trials

There have been a large series of open and controlled trials investigating the potential of both low-frequency rTMS ($\leqslant$ 1 Hz) and high-frequency rTMS ($>$ 1 Hz) to alleviate the symptoms of major depression. The initial open studies often stimulated at the vertex using non-focal round coils (see Tables 1 and 2). Almost all recent work, including the controlled studies (see Tables 3–6) have concentrated on stimulation over the left or right DLPFC, typically using more focal, figure-of-eight coils. The method to determine location of DLPFC was introduced by George et al. (1995). This method involves determining the optimal site of stimulation over the motor cortex to elicit MEPs in the APB. The coil is then moved 5 cm forward from this site on a parasagittal plane and presumed to be over the DLPFC (e.g. Brodmann area 9) and the magnetic stimulus intensity for the treatment trial is typically set as a percentage of the MT (see Tables 2, 4, 6). This method for determining coil positioning is clearly inexact, as it does not account for individual differences in brain size and anatomy. MRI-guided three-dimensional stereotactic methods have been used in basic research to provide more precise coil positioning relative to specific anatomic locations (Paus et al., 1997, 1998; Paus and Wolforth, 1998), but has yet to be applied in therapeutic trials. A recent comparison of the standard method of coil positioning with the use of a MRI-guided frameless stereotatic method demonstrated that in only 7 of 22 subjects the DLPFC was targeted correctly over Brodmann area 9. In the remaining 15 subjects, the centre of the coil was more dorsally located, over the premotor cortex (Herwig et al., 2001).

Another source of potential artifact is the presumption of a strong association between the MT, determined as the lowest magnetic stimulus intensity for single pulses to elicit MEPs in the APB or FDI in 5 out 10 trials, and the intensity needed to produce the requisite physiological response in the DLPFC using repetitive trains of magnetic pulses (rTMS). Since distance of the cortex from the coil is the major determinant of local induced current density

Table 1. Open TMS studies in major depression: therpaeutic effects and effect size

Study	Treatment	*n*	Depression type	Percent change in HRSD	s.d.	Effect Size (*d*)	Lower	Upper	*p* value
Hoflich et al. (1993)	Vertex TMS	2	MDD	10.3	14.6	0.71	−6.22	7.03	0.52
George et al. (1995)	LDLPFC rTMS	6	1 MDD/5 BPD	26.5	19.6	1.35	−1.63	3.79	0.02
Grisaru et al. (1995)	Motor TMS	10	5 MDD/3 BPD/2 schizoaffective depressed	na (see comments; Table 2)	na	na	na	na	na
Geller et al. (1997)	LPFC and RPFC TMS	10	6 MDD/3 BPD/1 schizoaffective depressed	na (see comments; Table 2)	na	na	na	na	na
Epstein et al. (1998)	LDLPFC rTMS	32	25 MDD/3 BPD	52.0	46.4	1.12	0.31	1.87	0.0001
Figiel et al. (1998)	LDLPFC rTMS	56	53 MDD/3 BPD	44.4	25.0[a]	1.78	1.12	2.39	0.0001
Feinsod et al. (1998)	RDLPFC TMS	14	MDD	30.8	35.8	0.86	−0.42	2.03	0.01
Menkes et al. (1999)	RF TMS	8	MDD/dysthymia	42.4	37.4	1.13	−0.94	2.91	0.02
Pridmore (1999)	LDLPFC rTMS	12	MDD	na (see comments; Table 2)	na	na	na	na	na
Pridmore et al. (1999)	LDLPFC rTMS	22 patients in 24 episodes	MDD with melancholia	58.1[b]	29.5	1.97	0.85	2.95	0.0000
Triggs et al. (1999)	LDLPFC rTMS	10	MDD	40.5	25.0[a]	1.62	−0.29	3.21	0.0009
Eschweiler et al. (2000)	LDLPFC rTMS ($n = 14$) and RDLPFC TMS ($n = 2$)	16 (all later received ECT)	MDD and schizoaffective depressed	na (see comments; Table 2)	na	na	na	na	na
Cohen et al. (unpubl. obs.)	Bilateral TMS: LDLPFC rTMS followed by RDLPFC TMS	10	MDD	28.3	29.8	0.95	−0.71	2.42	0.02

LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; LPFC, left prefrontal cortex; RPFC, right prefrontal cortex.

[a] Indicates that the s.d. was estimated.

[b] In Pridmore et al. (1999), the outcome measure was change in Montgomery–Åsberg (MADRS) scores.

Table 2. Open TMS studies in major depression: patient characteristics, treatment parameters and comments

Study	Treatment	Age	Medication		Stimulus intensity	Pulse freq. (Hz)	Train duration (s)	Number of trains	Pulses per session	Total sessions	Comments
			Resist	Free							
Hoflich et al. (1993)	Vertex TMS	42.0	Yes	No	105–130% MT	0.3	na	na	250	10	One patient had slight improvement.
George et al. (1995)	LDLPFC rTMS	46.5	Yes	4/6	80% MT	20	2	20	800	5+	Two robust responders.
Grisaru et al. (1995)	Motor TMS	39.4	na	No	2 T	0.017	3600	1	60	1	Outcome assessed after single session; 4 mild improvement, 1 worse, 5 no change.
Geller et al. (1997)	LPFC and RPFC TMS	39.4	na	No	2.5 T	0.033	900	1	30	1	Outcome assessed after single session; 3 immediate lifting of mood; 2 possible improvement; 1 worsening, 4 no change.
Epstein et al. (1998)	LDLPFC rTMS	40.0	Yes	Yes	110% MT	10	5	10	250	5	Age $<$ 65, 4 dropouts, rTMS resulted in HRSD $<$ 10 in 50% of sample. 8/10 with previous favourable response to ECT responded to rTMS (HRSD $<$ 10). Non-responders older than rTMS responders.
Figiel et al. (1998)	LDLPFC rTMS	59.9	53/56	50/56	110% MT	10	5	10	500	5	Sample overlaps with Epstein study, but includes new sample $\geqslant$ 65. Results calculated on 50 patients who completed study. Only 23% of $>$ 65 responded; 56% of those $<$ 65 responded ($<$ 60% HRSD reduction with maximal post score of 16). Only 2 of 8 patients (25%) with psychotic depression responded.
Feinsod et al. (1998)	RDLPFC TMS	58.0	na	4/14	1 T, 0.1 ms	1	60	2	120	10	By CGI 6 of 14 (42.9%) MDD patients showed marked improvement.
Menkes et al. (1999)	RF TMS	33.3	No	No	100% MT	0.5	40	5	800	8	Included 6 healthy controls who had no change in HRSD score (mean 0.7).

Pridmore (1999)	LDLPFC rTMS	57	Yes	No	90–100% MT	10	5	20	1000	10–14	All 12 patients were dexamethasone test (DST) non-suppressors at baseline. 6 of 12 normalized the DST after rTMS. These 6 had strong clinical improvement (MADRS decreased from 31 to 9; 70.0%) and maintained their response for at least 4 wk. The remaining 6 patients showed at best moderate improvement that was not sustained.
Pridmore et al. (1999)	LDLPFC rTMS	52.5	Yes	5/24	90–100% MT	10	5	25	1250	12–14	Patients were characterized as melancholic by CORE criteria. Only 3 went on to receive ECT. In 19 of 24 episodes (79.2%) MADRS scores decreased by $< 50\%$. The mean time from treatment to relapse was 20 wk.
Triggs et al. (1999)	LDLPFC rTMS	52.0	9/10	Yes	80% MT	20	2	40	2000	10	5/10 had at least 50% reduction in HRSD. Motor-evoked potential threshold decreased during treatment in 9/10.
Eschweiler et al. (2000)	LDLPFC RTMS ($n = 14$), RDLPFC TMS ($n = 2$)	50.0	Un-known	Un-known	LDLPFC: 90–100% MT; RDLPFC: 130% MT	LDLPFC: 10; RDLPFC: 1	LDLPFC: 5–6.5; RDLPFC: 50	LDLPFC: 20; RDLPFC: 20	LDLPFC: 1000–1300; RDLPFC: 1000	5–15	38% of patients were responders with CGI scores indicating much or very much improved. Non-responders and patients who relapsed received RUL ECT after an average of 143 ± 153 d; 12 of 16 responded to ECT. This induced all 6 TMS responders. The 4 ECT non-responders did not respond to earlier TMS ($p < 0.05$).
Cohen et al. (unpubl. obs.)	Bilateral TMS: LDLPFC rTMS and RDLPFC TMS	45	Yes	No	LDLPFC: 100% MT; RDLPFC: 100% MT	LDLPFC: 20; RDLPFC: 1	LDLPFC: 1.5; RDLPFC 60	LDLPFC: 20; RDLPFC: 2	LDPFC: 600; RDLPFC: 120	5–10	4/10 (40%) patients showed a 50% reduction in HRSD scores, but changes in CGI and self-ratings were slight. There was a trend for younger patients to have stronger therapeutic response.

Table 3. Randomized, controlled TMS trials in major depression: therapeutic outcome and effect size

Study	Design	Group 1	N1	% HRSD change	s.d.	Group 2	N2	% HRSD change	s.d.	Effect (*d*)	Lower	Upper	Total (*n*)	*p* value
Kolbinger et al. (1995) [1]	Parallel	Above threshold rTMS (vertex)	5	16.0	19.9	Sham	5	5.7	33.4	0.34	−1.14	1.82	10	0.567
Kolbinger et al. (1995) [2]	Parallel	Below threshold rTMS (vertex)	5	35.5	17.8	Sham	5	5.7	33.4	1.01	−0.60	2.61	10	0.116
Conca et al. (1996)	Parallel	TMS (8 sites: frontal, temporal and parietal) + medication	12	57.5	25.0[a]	Medication only	12	32.4	25.0[a]	0.97	0.07	1.87	24	0.003
Pascual-Leone et al. (1996b) [1]	Cross-over	LDLPFC rTMS	17	48.0	30.0	LDLPFC sham	17	2.0	17.0	1.76	0.49	3.03	17	0.002
Pascual-Leone et al. (1996b) [2]	Cross-over	RDLPFC rTMS	17	2.0	20.0	RDLPFC sham	17	2.0	20.0	0.00	−1.04	1.04	17	1.000
George et al. (1997) [1]	Parallel	LDLPFC rTMS	7	23.9	23.1	Sham	5	−15.2	30.9	1.36	−0.15	2.87	12	0.031
George et al. (1997) [2]	Cross-over	LDLPFC rTMS	5	5.6	26.0	Sham	7	−15.8	22.5	0.83	−0.56	2.21	12	0.158
Avery et al. (1999)	Parallel	LDLPFC rTMS	4	42.5	20.0[a]	Sham	2	10.0	15.0[a]	1.38	−1.68	4.43	6	0.118
Kimbrell et al. (1999) [1]	Cross-over	LDLPFC rTMS (20 Hz)	10	−26.2	63.9	LDLPFC TMS (1 Hz)	10	18.8	21.6	−0.99	−2.59	0.61	10	0.120
Kimbrell et al. (1999) [2]	Cross-over	LDLPFC rTMS (20 Hz)	3	24.7	10.0	Sham	3	0.9	17.5	0.32	−5.54	6.18	3	0.632

Klein et al. (1999b)	Parallel	RDLPFC TMS	35	46.9	33.1	Sham	32	−7.9	33.1	0.69	0.19	1.19	67	0.007
Loo et al. (1999)	Parallel	LDLPFC rTMS	9	20.0	25.0[a]	Sham	9	22.7	25.0[a]	−0.11	−1.11	0.89	18	0.822
Padberg et al. (1999) [1]	Parallel	LDLPFC rTMS	6	5.6	9.5	Sham	6	−5.9	21.2	0.70	−0.63	2.03	12	0.254
Padberg et al. (1999) [2]	Parallel	LDLPFC TMS	6	19.5	14.0		6	−5.9	21.2	1.41	−0.03	2.85	12	0.035
Stikhina et al. (1999)	Parallel	LDLPFC TMS + psychotherapy	15	62.4	25.0[a]	Sham + psychotherapy	14	14.5	25.0[a]	1.65	0.75	2.55	29	0.000
Berman et al. (2000)	Parallel	LDLPFC rTMS	10	31.5	23.4	Sham	10	−0.2	31.7	1.14	0.12	2.15	20	0.020
Eschweiler et al. (2000)	Cross-over	LDLPFC rTMS	10	24.2	43.1	Sham	10	−9.2	43.1	1.77	0.05	3.50	10	0.023
George et al. (2000) [1]	Parallel	LDLPFC rTMS (20 Hz)	10	26.4	28.7	Sham	10	21.2	16.0	0.21	−0.73	1.16	20	0.623
George et al. (2000) [2]	Parallel	LDLPFC rTMS (5 Hz)	10	48.1	19.2	Sham	10	21.2	16.0	1.46	0.37	2.54	20	0.003
Garcia-Toro et al. (2001)	Parallel	LDLPFC rTMS	17	26.0	20.0[a]	Sham	18	12.6	15.0[a]	0.76	0.05	1.47	35	0.031
Lisanby et al. (2001d) [1]	Parallel	LDLPFC rTMS + sertraline	12	20.7	24.9	Sham + sertraline	12	13.3	34.6	0.24	−0.61	1.09	24	0.554
Lisanby et al. (2001d) [2]	Parallel	RDLPFC TMS + sertraline	12	19.5	26.1	Sham + sertraline	12	13.3	34.6	0.20	−0.65	1.04	24	0.625
Manes et al. (2001)	Parallel	LDLPFC rTMS	10	36.6	25.0[a]	Sham	10	31.7	25.0[a]	0.19	−0.75	1.14	20	0.670

LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; Effect (*d*), effect size of difference between Group 1 and Group 2; Lower and Upper are estimates of lower and upper 95% confidence intervals for the effect size.

Figures within brackets following the study's authors refer to specific comparisons within a study.

[a] Indicates that the s.d. was estimated.

Table 4. Randomized, controlled TMS studies: patient characteristics and treatment parameters

Study	Design	Age	Medication resistant	Medication free	TMS intensity	Pulse frequency (Hz)	Train duration (s)	No. of trains	Total pulses per session	No. of sessions
Kolbinger et al. (1995) [1]	Parallel	49.0	Unknown	No	110% MT	0.25–0.50	na	1	250	5
Kolbinger et al. (1995) [2]	Parallel	49.0	Unknown	No	90% MT	0.25–0.50	na	1	250	5
Conca et al. (1996)	Parallel	42.7	Unknown	No	1.9 T	0.17	30	8	40	10–14
Pascual-Leone et al. (1996b) [1]	Cross-over	48.6	All	No	90% MT	10	10	20	2000	5
Pascual-Leone et al. (1996b) [2]	Cross-over	48.6	All	No	90% MT	10	10	20	2000	5
George et al. (1997) [1]	Parallel	42.0	All	9/12	80% MT	20	2	20	800	10
George et al. (1997) [2]	Cross-over	42.0	All	9/12	80% MT	20	2	20	800	10
Avery et al. (1999)	Parallel	44.5	All	2/6	80% MT	10	5	20	1000	10
Kimbrell et al. (1999) [1]	Cross-over	42.1	All	7/10	80% MT	20	2	20	800	10
Kimbrell et al. (1999) [2]	Cross-over	45.1	All	2/3	80% MT	20	2	20	800	10
Klein et al. (1999)	Parallel	59.0	Most	24/70	110% MT	1	60	2	120	10
Loo et al. (1999)	Parallel	48.3	Most	5/18	110% MT	10	5	30	1500	10
Padberg et al. (1999) [1]	Parallel	51.2	All	2/12	90% MT	10	5	5	250	5
Padberg et al. (1999) [2]	Parallel	51.2	All	2/12	90% MT	0.3	83	10	250	5
Stikhina et al. (1999)	Parallel	37.5	Some	Yes	0.015 T	40	600	2	4800	10
Berman et al. (2000)	Parallel	Unknown	Most	Yes	80% MT	20	2	20	800	10
Eschweiler et al. (2000)	Cross-over	57.0	Unknown	No	90% MT	10	10	20	2000	10
George et al. (2000) [1]	Parallel	44.5	Most	Yes	100% MT	20	2	40	1600	10
George et al. (2000) [2]	Parallel	45.4	Most	Yes	100% MT	5	8	40	1600	10
Garcia-Toro et al. (2001)	Parallel	50.8	All	No	90% MT	20	2	30	1200	10
Lisanby et al. (2001d) [1]	Parallel	48.2	Most	All recd 50 mg sertraline	110% MT	10	8	20	1600	10
Lisanby et al. (2001d) [2]	Parallel	45.9	Most	All recd 50 mg sertraline	110% MT	1	1600	1	1600	10
Manes et al. (2001)	Parallel	60.7	All	Yes	80% MT	20	2	20	800	5

MT, Motor threshold.
Figures within brackets following the study's authors refer to specific comparisons within a study.

Table 5. Randomized trials contrasting rTMS and ECT in major depression: therapeutic effects and effects size

Study	Treatment groups	Design	*n*	Depression type	Percent change in HRSD	s.d.	Effect (*d*)	Lower	Upper	Group difference in *p* value
Grunhaus et al. (2000)	LDLPFC rTMS	Open and randomized	20	MDD (11 psychotic)	40.3	na	0.54	−0.11	1.19	0.09
	12 RUL ECT only; 8 RUL and BL ECT		20	MDD (10 psychotic)	60.6	na				
Pridmore et al. (2000)	LDLPFC rTMS	Single-masked raters and randomized	16	11 MDD, 5 BPD	55.6	30.2	0.33	−0.40	1.06	0.40
	RUL ECT		16	15 MDD, 1 BPD	66.4	33.6				
Grunhaus et al. (unpubl. obs.)	LDLPFC rTMS	Single-masked raters and randomized	20	MDD (non-psychotic)	45.5	na	0.04	−0.60	0.68	0.10
	13 RUL ECT only; 7 RUL and BL ECT		20	MDD (non-psychotic)	48.2	na				

LDLPFC, left dorsolateral prefrontal cortex; RUL, right unilateral ECT; BL, bilateral ECT; MMD, major depressive disorder; BPD, bipolar depressed; Effect (*d*), effect size of difference between ECT and rTMS groups. Lower and Upper are estimates of lower and upper 95% confidence intervals for the effect size.

and has shown a relationship to MT (McConnell et al., 2001), factors such as cortical atrophy will introduce variability in the distance between the coil and the motor cortex and the coil and the DLPFC. The use of the MT to determine intensity of stimulation over the DLPFC was introduced as a safety precaution (Wassermann, 1998), as highly intense rTMS has elicited seizures in a few normal volunteers (e.g. Chen et al., 1997b; Pascual-Leone et al., 1992b). Unfortunately, a behavioural index of the effects of rTMS over the DLPFC, like the elicitation of a MEP, has yet to be established. Were there such a behavioural or physiological marker, more precise determination of rTMS parameters might be possible.

There are other sources of potential artifact in rTMS therapeutic trials and basic studies due to the large number of parameters involved in delivery of rTMS (i.e. device, waveform, coil type, size and orientation, stimulus intensity, pulse frequency, train duration, inter-train interval, number of trains, number of treatment sessions, etc.). Kammer et al. (2001) demonstrated marked differences in MT as a function of device type (Dantec Magpro, Magstim 200 and Magstim Rapid), biphasic vs. monophasic waveform, and coil orientation. For example, normalized Magstim thresholds were consistently higher than Dantec thresholds by a factor of 1.3. Monophasic pulses resulted in lower thresholds when coil orientation resulted in induced current flow in a posterior–anterior direction in motor cortex. However, this was not the case for biphasic pulses. These sources of variability make it difficult to compare different studies using different equipment and techniques in terms of therapeutic effects. Unlike ECT, where overall charge relative to seizure threshold has shown robust relations with efficacy and cognitive effects (McCall et al., 2000; Sackeim et al., 1993, 2000), no single measure has been derived to characterize the overall intensity of rTMS and, for the reasons mentioned above, it is unlikely that any such measure would be of value in cross-study comparisons.

In controlled, double-masked trials, another concern is the characteristics of the control condition. Sham rTMS has frequently been used as a comparison to 'active' rTMS. An ideal sham condition would involve tilting the coil so that it results in the same acoustic artifact as active rTMS and the same peripheral sensations in the scalp (stimulation of extracranial muscles), with minimal current density in brain. However, under these conditions the operator would not be masked to real and sham conditions. A variety of sham coil orientations have been use in clinical trials. A common orientation had been to place a figure-of-eight coil 45° from a tangent to the head. Using this sham condition, Loo et al. (1999) found no difference between active and sham rTMS in antidepressant effects, with both conditions resulting in substantial reductions in Hamilton Rating Scale for Depression (HRSD) scores. Subsequently, Loo et al. (2000) tested various sham orientations in their capacity to elicit MEPs

Table 6. Randomized trials contrasting rTMS and ECT in major depression: patient characteristics, treatment parameters, and comments

Study	Age	Medication resistant	Medication free	Stimulus intensity	Pulse freq. (Hz)	Train duration (s)	No. of trains	Pulses per session	Total sessions	Comments
Grunhaus et al. (2000)	58.4	5/15	Clonazepam 1–2 mg/d)	90% MT	10	2 (8 patients) 6 (12 patients)	20	400–1200	20	Psychotic MDD patients had a superior response to ECT than rTMS (73.3 vs. 27.5% reductions in HRSD, $p = 0.005$). Non-psychotic patients showed comparable reductions with ECT and rTMS (44.8 vs. 53.2%). The degree of symptomatic improvement in non-psychotic patients was unusual for an ECT trial.
	63.6	10/10	No	2.5 × seizure threshold and increased progressively					9.6 (range 7–14)	
Pridmore et al. (2000)	44.0	All	No	100% MT	20	2	30–35	1200–1400	10–14	ECT was superior to rTMS in multivariate analyses across depression measures ($p = 0.04$), with the difference most marked for the Beck Depression Inventory (BDI) (69.1 vs. 45.5% improvement, $p = 0.03$). However, no difference noted on change in HRSD. An equivalent number of patients in each group (11 of 16) achieved remission criteria (final HRSD < 8).
	41.5	All	No	504 mC				30	12.2 ± 3.4	
Grunhaus et al. (unpubl. obs.)	57.6	na	Lorazepam (up to 3 mg/d)	90% MT	10	6	10	1200	20	ECT and rTMS were equivalent in efficacy in all depression measures. 12 of 20 ECT patients met response criteria (50% decrease in HRSD or a final rating < 10 and a final GAF < 60; 11 of 20 rTMS patients met response criteria. As in the previous study by Grunhaus et al. (2000) the degree of improvement was unusually low for an ECT sample.
	61.4	na	Lorazepam (up to 3 mg/d)	2.5 × seizure threshold and increased progressively					10.3 ± 3.1 (range 4–13)	

when placed over motor cortex. The 45° tangential orientation had the lowest threshold for FDI MEP elicitation, implying that it resulted in the greatest current density in brain. We replicated these behavioural results in humans. Furthermore, in a non-human primate with indwelling electrodes we demonstrated that the 45° positioning with the two wings of the figure-of-eight coil in tangential orientation resulted in only 24% less induced voltage over the PFC than active rTMS. In contrast, three other types of sham orientations (one-wing 45° and 90° and two-wing 90° tilt) induced much lower voltage in the brain than active rTMS (67–73% reductions) (Lisanby et al., 2001a). Thus, some sham conditions may have active properties.

It is not known whether the sham orientations that induce the least current density reliably mimic the peripheral effects of active rTMS. Furthermore, any sham condition in which the coil is tilted relative to the head may also defeat the blind if patients are familiar with rTMS research. A solution to this problem has been developed, but yet to be reported in a clinical trial. 'Placebo' figure-of-eight coils have been constructed in which the orientation of current flow in each wing results in cancellation of the magnetic field. In other cases, special shielding of the coil is used. While these coils can be held in the same position and orientation as in the active condition, allowing for masking of both the patient and the personnel delivering rTMS, it is questionable whether such coils will result in the same peripheral sensations as active rTMS, and perhaps defeat the mask. Therefore, while progress is being made in developing more valid sham conditions, this problem, particularly with respect to masking, is not fully resolved. This is a particular concern for studies using a cross-over design where we have shown that patients can readily discriminate between active and sham rTMS (Boylan et al., 2001).

rTMS in the treatment of major depression: meta-analyses

Meta-analyses of effect size and analyses of the magnitude of therapeutic effects of rTMS were conducted for three categories of studies in depressed patients: open and uncontrolled trials, sham or otherwise controlled trials, and comparisons of rTMS and ECT. For each study, the percentage change in HRSD scores and in one instance (Pridmore et al., 1999) Montgomery–Åsberg Depression Rating Scale (MADRS) scores are reported. Each of these values are accurate, based on computations on raw data or information provided in the original reports. In the tables, an effect size is reported for each study, as well as the 95% lower and upper confidence intervals. This effect size corresponds to Cohen's *d*, the difference between group means in therapeutic effects divided by the pooled S.D. (Cohen, 1988). The effect size is accurate for each study, based on either raw computation of the data per subject or derivation from reported *F*, *t*, or *p* values. In some instances, the S.D. for the percentage change in depression ratings was not available. In some cases these were derived from *F* values or *t* values, assuming equal variance between the groups. In other cases, the S.D. was estimated from figures. When no information was available an S.D. value, most commonly 25.00 was assumed. These estimated values are demarcated in the tables, and represent a conservative estimate of the variability, given the findings across studies.

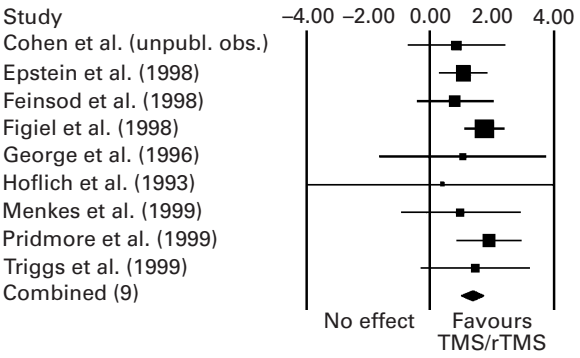

Figure 1. Effect size (*d*) and 95% confidence intervals for open and uncontrolled studies of TMS and rTMS in the treatment of depression. The size of the boxes is proportional to the sample size. The overall combined effect size is indicated by a diamond.

The meta-analyses used software developed by Borenstein and Rothstein (1999). Weighted mean effects sizes combining across studies are reported for both Cohen's *d* and Hedges' adjusted *g* (Hasselblad and Hedges, 1995; Hedges and Olkin, 1985). Weighting was based both on a function of study sample size and precision of the effect size estimate. The Hedges' *g* statistic provides a more conservative estimate of combined effect size. The statistical significance of the pooled effect sizes was tested with random effects models, since it should not be assumed that all studies derived from the same population with the same characteristics. Finally, heterogeneity in effect sizes across studies was tested with the *Q* statistic, which provides a χ^2 value for the degree of dispersion of effect size across studies.

TMS in the treatment of depression: uncontrolled trials

Tables 1 and 2 summarize the open and uncontrolled studies of rTMS in the treatment of major depression. Across the 9 studies that reported quantitative changes in depression scores (Figure 1) the weighted effect size

(Cohen's d) was 1.37, corresponding to a large statistical effect. Across these studies, the point estimate for the unadjusted Cohen's d was 1.47 [S.E. = 0.16, $t(8) = 9.39$, $p < 0.0001$]. For Hedges' adjusted g, the point estimate was 1.37 [S.E. = 0.18, $t(8) = 7.58$, $p < 0.0001$]. There was no evidence of heterogeneity in effect size for either Cohen's d [$Q(8) = 6.69$, $p = 0.57$] or Hedges' g [$Q(8) = 5.41$, $p = 0.71$]. As seen in Figure 1 all the open studies had effect sizes indicating antidepressant effects of slow or fast rTMS, accounting for the lack of effect size heterogeneity. The sample reported by Epstein et al. (1998) overlapped with the larger sample reported by Figiel et al. (1998). Excluding the Epstein et al. (1998) study, the effect size for the remaining 8 studies (Cohen's d) increased to 1.45.

Despite the impressive consistency and size of this effect, the degree of therapeutic change across these studies was relatively modest. The average reduction in HRSD or MADRS scores (unweighted mean) was only 37.03% (S.D. = 29.23). Relatively few patients in these studies would meet standard criteria for response, let alone remission. Thus, the open studies suggest that slow or fast rTMS have antidepressant properties, but that the clinical significance of this effect is uncertain. Since these studies were open, and the procedure is intricate and involves considerable patient interaction, it is conceivable that some portion of the improvement observed reflected placebo or other non-specific effects.

It may be noteworthy that the study conducted by Pridmore et al. (1999) yielded the greatest effect size and degree of improvement. This study was restricted to patients with major depression who met the CORE criteria for melancholia (Hickie et al., 1996). This approach may have created greater patient sample homogeneity and high CORE scores, indicative of motor retardation, have shown positive predictive value with respect to ECT response (Hickie et al., 1990, 1996). In contrast, Figiel et al. (1998) observed that elderly patients and patients with psychotic depression had a particularly poor response to rTMS.

The majority of the open studies used rTMS (> 1 Hz) over the LDLPFC. The rationale for this approach, first used by George et al. (1995), was based on brain-imaging findings suggesting that the LDLPFC is especially low in functional activity in major depression (Baxter et al., 1985, 1989; Sackeim and Prohovnik, 1993; Soares and Mann, 1997). This perspective assumes that high frequency stimulation will enhance the excitability and normalize activity in this region. Other work used low frequency TMS (< 1 Hz) delivered to the RDLPFC (Eschweiler et al., 2000; Feinsod et al., 1998; Klein et al., 1999). The presumption underlying this approach is that the fundamental problem is in hemispheric imbalance (Lisanby and Sackeim, 2000; Sackeim et al., 1982), with slow-frequency TMS reducing overactivity in right PFC regions and fast-frequency TMS enhancing underactivity in left PFC regions. Approximately 20 functional imaging studies have demonstrated inverse correlations between severity of depressive symptomatology and PFC functional activity (George et al., 1994; Sackeim and Prohovnik, 1993; Soares and Mann, 1997), but asymmetry has been observed only in a minority of studies. Nonetheless, based on this perspective, almost all open and controlled work with rTMS has used fast frequencies over the left hemisphere and slow frequencies over the right hemisphere. It has been attempted to take advantage of both effects, delivering 20 Hz stimulation to the LDLPFC followed by 1 Hz stimulation to the RDLPFC, essentially mimicking a form of bilateral stimulation (Cohen C, Akande BO, Maccabee PJ, Amasian V, unpublished observations). The magnitude of therapeutic change in this study was quite modest (28.3% reduction HRSD scores). Mitchell has also conducted a similar study in Australia with bilateral stimulation with modest therapeutic effects (Mitchell P, personal communication: July 2001).

TMS in the treatment of depression: sham and other controlled trials

Tables 3 and 4 present the sham- or otherwise controlled studies of TMS and rTMS in the treatment of depression. A number of these studies included a single sham condition but two active TMS/rTMS conditions. Each of these comparisons is included as independent observations. Since the sham patients are contrasted with each active condition, the total number of subjects is artificially inflated. Similarly in studies that used a cross-over design, each phase of the study is presented as a separate comparison, again inflating the overall sample size. Finally, only two studies did not involve a sham comparison. Conca et al. (1966) compared a group assigned to TMS plus medication to a group treated with medications only. In one comparison, Kimbrell et al. (1999) compared fast LDLPFC rTMS (20 Hz) to slow LDLPFC rTMS (1 Hz). Since this study had two active conditions, its inclusion might be questionable. However, we present this comparison since the predominant hypothesis in the field would have been that the fast-frequency rTMS condition over the LDLPFC would be more effective.

Across the 23 comparisons in Table 3, the combined effect size (Cohen's d) was 0.67, indicating a moderate to large effect. With 432 individual cases, the point estimate for Cohen's d (unadjusted) was 0.79 [S.E. = 0.15, $t(22) = 5.38$, $p < 0.0001$]. Similarly, Hedges' adjusted g yielded a point estimate of 0.70 [S.E. = 0.13, $t(22) = 5.26$, $p <$

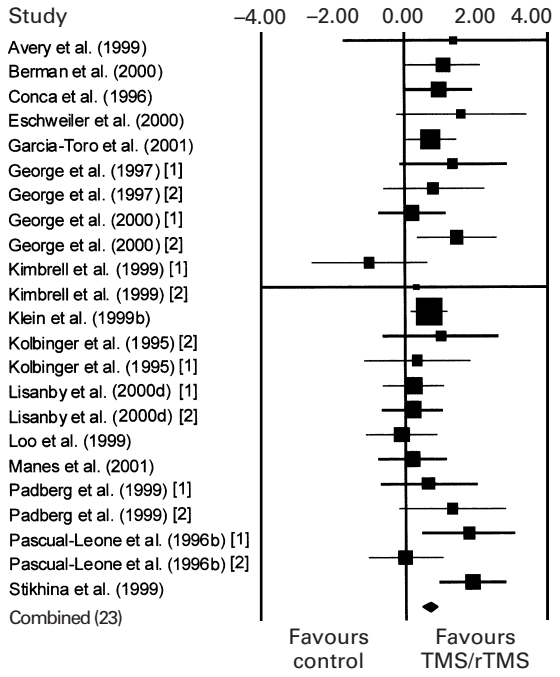

Figure 2. Effect size (d) and 95% confidence intervals for randomized, controlled studies of TMS and rTMS in the treatment of depression. The size of the boxes is proportional to the sample size. The overall combined effect size is indicated by a diamond. Figures within brackets following the study's authors refer to specific comparisons within a study.

0.0001]. As can be discerned in Figure 2, Cohen's d indicated that there was significant heterogeneity among studies in effect size [$Q(22) = 47.08$, $p = 0.001$]. In contrast, the detection of heterogeneity was only marginal with Hedges' g [$Q(22) = 33.21$, $p = 0.06$].

One of the studies in Table 3 had an especially large effect size and administered rTMS at an intensity that is unlikely to have biological effects (0.015 T) to patients characterized as having neurotic depression (Stikhina et al., 1999). Removing this study from the database did little in influencing the overall effects. The combined Cohen's d was reduced to 0.62, and the overall effects for Cohen's d and Hedges' g had p values < 0.0001. In contrast, we included in comparisons the condition used by Pascual-Leone et al. (1996b) with rTMS delivered over the RDLPFC and which yielded no effect. We included this comparison since at the time there was little grounds for hypothesizing a specific location for therapeutic action. In addition, the only comparison with a clearly negative effect size derived from the study by Kimbrell et al. (1999). Contrary to expectations of the field, using a cross-over design, they found that slow-frequency rTMS (1 Hz) over the LDLPFC had a superior outcome to rTMS (20 Hz) over the same location. This was the only comparison of active rTMS conditions listed in Tables 3 and 4. Were it deleted from the observations, the heterogeneity in effect size across studies would still be significant for Cohen's d [$Q(21) = 37.96$, $p = 0.01$], but not for Hedges' g [$Q(21) = 27.45$, $p = 0.16$].

Overall, this meta-analysis involving 23 comparisons indicates that slow and fast rTMS have statistically superior antidepressant properties compared to sham administration. We tested whether the effect sizes differed in studies using slow rTMS ($\leqslant 1$ Hz) or fast rTMS (> 1 Hz). As seen in Tables 3 and 4, five comparisons involved slow rTMS and 18 comparisons involved fast rTMS. The analysis of variance contrasting these groups of comparisons did not yield a significant between-class effect [$Q(1) = 0.18$, $p = 0.67$]. The point estimate for Hedges' g was somewhat higher for slow rTMS ($g = 0.68$, S.E. $= 0.17$, $z = 3.93$, $p = 0.0001$) than for fast rTMS ($g = 0.58$, S.E. $= 0.13$, $z = 4.37$, $p < 0.0001$). Using a parallel group design, George et al. (2000) obtained an effect size (d) of only 0.21 when comparing 20 Hz rTMS to a sham group and an effect size of 1.46 when comparing 5 Hz rTMS to the same sham group. These analyses suggest that higher frequency stimulation does not necessarily enhance the antidepressant properties of TMS. Since low-frequency stimulation has a lower risk of inducing seizures (Wassermann, 1998), and in the United States stimulation at frequencies $\leqslant 1$ Hz generally does not require investigational device protocol approval by the Federal Drug Administration (FDA), we may see more efforts concentrating on slow-frequency rTMS.

Despite the statistically impressive results in the meta-analysis of the controlled trials, on the whole, the magnitude of the therapeutic effects was of doubtful clinical significance. The average (unweighted) percentage change in HRSD scores in the active condition in the 23 comparisons was only 23.82% (S.D. = 24.90), while the sham or control condition resulted in a percentage improvement of 7.30% (S.D. = 25.12). Thus, the average difference in improvement between active and control conditions was only 16.25%. We excluded 3 questionable comparisons that may have biased these results: the Pascual-Leone et al. (1996b) use of rTMS over the RDLPFC, the Kimbrell et al. (1999) comparison of 20 Hz and 1 Hz rTMS/TMS over the LDLPFC, and the Stikhina et al. (1999) use of 0.015 T stimulation over the LDLPFC. These studies were excluded since Pascual-Leone et al. (1996b) was the only study to use fast-frequency rTMS over the RDLPFC, and the predominant hypothesis in the field is that such treatment should be ineffective. The Kimbrell et al. (1999) comparison involved two active forms of rTMS and the Stikhina et al. (1999) study, as indicated, used a stimulus intensity with doubtful biological effects. The average (unweighted) percentage improvement in the active conditions of the

remaining studies was 28.94% (S.D. = 23.19) and the percentage improvement with sham was 6.63% (S.D. = 25.56). While these exclusions enlarged the difference between active rTMS and sham (22.31%), it is still evident that the degree of therapeutic change, while consistently superior to sham, was modest with rTMS, and relatively few patients met standard criteria for response (e.g. 50% reduction in HRSD scores) or remission (e.g. final HRSD $\leqslant 8$).

To place these findings in context, we computed the percent improvement and effect sizes for the most potent forms of ECT we observed in our most recent study (Sackeim et al., 2000). High dosage (2.5 times seizure threshold) bilateral and high dosage (6 times seizure threshold) right unilateral ECT resulted in HRSD reductions of 71.63% (S.D. = 31.67) and 69.87% (S.D. = 32.90), respectively, corresponding to effect sizes of 2.26 and 2.12. The less effective forms of right unilateral ECT (1.5 times seizure threshold) and right unilateral ECT (2.5 times seizure threshold) resulted in considerably greater average improvement in HRSD scores than what has been common in rTMS studies. These two forms of treatment resulted in 49.15% (S.D. = 33.22) and 40.16% (S.D. = 37.54) improvement, respectively. Comparing the two most effective forms of ECT (high dosage bilateral and right unilateral) to the less effective treatments (low and moderate dosage right unilateral ECT) resulted in an effect size (Cohen's d) of 0.78 ($p = 0.0009$).

The modest therapeutic effects of rTMS in major depression may suggest that its primary role may be as an add-on or augmentation strategy. Virtually all studies in Tables 3 and 4 limited rTMS administration to either 5 or 10 sessions, corresponding to 1 or 2 wk. Antidepressant medications typically have a delayed onset of action (Hyman and Nestler, 1996; Nestler, 1998), and one can envisage a role for slow or fast rTMS to provide some level of symptomatic relief while patients await the full impact of antidepressant medications. To examine this possibility and the potential for concomitant antidepressant medications to either enhance or diminish rTMS effects we classified the 23 comparisons according to whether or not the sample was medication free. If the majority of patients (Table 4) were not receiving antidepressant medications, the comparison was classified as medication free. There was no between-group difference in effect size for studies conducted with patients receiving antidepressant medications compared to studies with patients medication free [$Q(1) = 0.21$, $p = 0.65$]. There was a somewhat greater effect size and less dispersion in 8 comparisons of medication free patients (Hedges' g point estimate = 0.71, S.E. = 0.12, $z = 5.92$, $p < 0.0001$) compared to the 15 comparisons of patients receiving medications (Hedges' g point estimate = 0.60, S.E. = 0.20, $z = 3.03$, $p = 0.003$). Thus, in general, it does not appear that concomitant antidepressant medication either enhances or detracts from rTMS therapeutic effects.

In all but one study in which patients were receiving concomitant antidepressant medications the regimens were heterogeneous, and this could mask potential interactions. After a substantial washout period, Lisanby et al. (2001d) placed 36 patients on sertraline (50 mg/d for 3 wk followed by 100 mg/d for 4 wk). As seen in Tables 3 and 4, patients were randomized to 10 sessions of sham, rTMS (1 Hz, RDLPFC) or rTMS (10 Hz, LDLPFC). The fast rTMS parameters (10 Hz, 110% MT, 8 s train duration, 20 trains) somewhat exceeded the suggested safety guidelines (Wasserman, 1998) constituting the most intensive form of rTMS used to date. The therapeutic results were disappointing, with effect sizes (d) at the end of the rTMS 2-wk period of only 0.24 for the fast rTMS comparison and 0.20 for the slow rTMS comparison (see Table 3 and Figure 2). In this study, patients who were classified as not being medication-resistant showed substantial improvement, regardless of randomized assignment, while medication-resistant patients showed little change. There was an indication that medication-resistant patients showed a small but statistically significant benefit in the 10 Hz rTMS LDLPFC condition.

The issue of medication resistance deserves greater attention. As seen in Table 4, the studies to date have either explicitly recruited patients who were established to be medication resistant (e.g. Berman et al., 2000) or the samples mostly comprised resistant patients. It has been repeatedly replicated that medication resistance is a negative predictor of response to ECT (Prudic et al., 1990, 1996; Sackeim et al., 2000), and it has been recently shown that degree of medication resistance (i.e. number of failed adequate antidepressant trials) is a strong predictor of poor outcome with vagus nerve stimulation (Sackeim et al., 2001b). It is not unexpected that when a new therapy is introduced, particularly a physical treatment, the first trials are in patients who have not benefited from traditional approaches. Indeed, the remarkably low rate of symptomatic improvement with sham rTMS seen across the 23 comparisons probably attests to the resistance of the samples that have been studied in failing to show a placebo effect despite the intensity and frequency of the intervention. It needs to be determined whether slow or fast rTMS has greater clinical potential when administered to patients earlier in the course of antidepressant treatment. Furthermore, using instruments like the Antidepressant Treatment History Form (Prudic et al., 1996; Sackeim, 2001; Sackeim et al., 1990), the relations between degree and specific forms of medication resistance and rTMS response need to be determined. For

example, there is evidence that failure to respond to adequate treatment with a selective serotonin reuptake inhibitor (SSRI) has little predictive value for ECT response, while failure to respond to adequate treatment with a tricyclic antidepressant augurs a lower response probability (Prudic et al., 1996).

TMS in the treatment of depression: comparisons to ECT

A small number of studies have randomly assigned depressed patients to treatment with rTMS or ECT. This work is summarized in Tables 5 and 6. Grunhaus et al. (2000) conducted an open, randomized study in which 20 patients received 4 wk of rTMS over the LDLPFC or a standard course of right unilateral (RUL) ECT. Patients who showed insufficient response to RUL ECT were switched to bilateral (BL) ECT. Overall, there was only a trend for a difference favouring ECT over rTMS in antidepressant effects on the HRSD. However, when the data were examined separately for patients with psychotic depression and nonpsychotic depression, there was a pronounced advantage of ECT in the psychotic subgroup ($p = 0.005$) and virtually identical improvement with rTMS and ECT among non-psychotic patients.

Using blinded raters, Pridmore et al. (2000) randomized 32 patients to rTMS over the LDLPFC or to RUL ECT at maximum device output (504 mC). The number of treatments was tailored to each patient, with no upper limit, and determined by the patient's treating psychiatrist. The average number of rTMS sessions was 12.2. In the 11 of 16 rTMS patients who achieved remission (HRSD < 8) the average number of sessions was 13.1 (S.D. $= 3.1$), while it was only 10.6 (S.D. $= 3.8$) in those who did not achieve remission. Overall, while changes in the HRSD favoured ECT over rTMS, this difference was not significant. On the other hand, the ECT group reported significantly greater improvement on the Beck Depression Inventory (BDI) and in visual analogue ratings. There was no difference between the groups in side-effect ratings. Unfortunately, Pridmore et al. (2000) did not report on the number of patients in the sample with psychotic depression, or analyze the data separately for this subgroup.

Grunahus and colleagues (Grunhaus L, Schreiber S, Dolberg OPD, Dannon P, unpublished observations) conducted a single-blind, randomized study in 40 non-psychotic patients assigned to rTMS or ECT. As in the previous study by this group, rTMS was administered over a fixed 4 wk, involving 20 sessions. The ECT group averaged 10.3 (S.D. $= 3.1$) treatments. Clinical outcome was virtually identical on HRSD ratings and the groups also did not differ in change on ancillary psychopathology measure, a sleep index, or Mini-Mental State scores. Grunhaus and colleagues concluded that among non-psychotic patients rTMS was as effective as ECT. Janicak completed a similar randomized study involving 25 patients and failed to find a difference in therapeutic effects of ECT and rTMS. Unfortunately, the details of this study are not yet available (Janicak P, personal communication: July 2001).

A meta-analysis of the three rTMS/ECT comparisons in Tables 5 and 6 yielded for these 112 cases a combined Cohen's d of 0.21 favouring ECT. The point estimate was 0.31 (S.E. $= 0.19$, $t = 1.62$, $p = 0.11$). For Hedges' g, the point estimate was 0.30 (S.E. $= 0.19$, $t = 1.56$, $p = 0.12$). Thus, although limited by three comparisons, there was not a statistically significant advantage for ECT over rTMS, nor was there significant heterogeneity in effect size (although limited by only 3 studies). Were the psychotic patients excluded from the original Grunhaus et al. (2000) study, the advantage for ECT would be further reduced.

The average percent improvement in HRSD scores in the rTMS conditions across the three rTMS/ECT comparisons was 47.13%. This was approximately double the degree of therapeutic improvement observed in the 23 comparisons of the controlled studies in Tables 3 and 4. The reasons for this greater therapeutic effect, which was also of much greater clinical significance, are unknown. However, two distinct possibilities should be considered. The rTMS/ECT comparisons provided considerably longer courses of rTMS, with 20 sessions in the studies by Grunhaus and colleagues (unpublished observations) and the number of treatments based on degree of clinical progress in the study by Pridmore et al. (2000). This raises the possibility that more extended treatment with rTMS has greater antidepressant properties. The other consideration is that the samples in these studies were selected for receiving ECT. ECT samples are unique in severity of depressive symptomatology, presentation of endogenous or melancholic features, and a high rate of psychotic depression. Sample characteristics may have predisposed to a more favourable rTMS response.

On the other hand, the average percentage improvement with ECT was only 54.47%. This is unusually low for this form of treatment. For example, in the recent report by Sackeim et al. (2000), high-dosage BL ECT (2.5 times threshold) averaged a 72.63% (S.D. $= 31.67$) improvement in HRSD scores immediately following treatment and high dosage RUL ECT (6 times threshold) averaged a 69.87% (S.D. $= 32.90$) improvement. Excluding patients with psychotic depression, these values were 75.66% (29.68) for high-dose BL ECT and 72.92% (S.D. $= 25.37$) for high-dose RUL ECT. Thus, this and many other ECT studies suggest that the degree of therapeutic

improvement observed with ECT in the rTMS/ECT comparisons was suboptimal. The reasons for this are unknown but suggest an underestimation of the therapeutic effects of ECT relative to prolonged courses of rTMS.

TMS in the treatment of depression: individual differences

At least two studies have suggested that patients with psychotic depression show reduced antidepressant effects with rTMS compared to non-psychotic patients with major depression (Figiel et al., 1998; Grunhaus et al., 2000). It is unknown whether, as with antidepressant medications, robust treatment with antipsychotic medications would enhance the response to rTMS in psychotically depressed patients (Parker et al., 1992; Spiker et al., 1985). It is also conceivable that optimal treatment of psychotic depression with rTMS may involve other sites that than the DLPFC.

Age also seems to be a factor associated with TMS response. In the Figiel et al. (1998) open study, 23% of patients over the age of 65 responded compared to 56% below this cut-off. Of those with late-onset major depression, only 11% responded. The mean age of responders in the Pridmore et al. (1999) study was 50 yr compared to 64 yr among non-responders, also a significant difference. Kozel (et al., 2000) examined the initial results of the study reported by George et al. (2000). They found that the distance between the coil and the DLPFC did not correlate significantly with response. However, they reported that the combination of older age and larger prefrontal distances was associated with poorer outcome. In essence, the implication was that prefrontal atrophy advances at a greater rate with ageing than distance between the coil and the motor cortex. This may result in under-dosing of older subjects when TMS parameters are based on a percentage of MT. George conducted an open trial in geriatric major depression (George MS, personal communication: November 2001). Using MRI to assess the extent to prefrontal atrophy, they dosed each patient ($n = 10$) in a manner adjusted for the coil/cortex distance and obtained a response rate of 50%.

There are indications that favourable response to rTMS is associated with favourable response to ECT. Epstein et al. (1988) reported that 8 of 10 patients with a history of response to ECT responded to rTMS. Eschweiler et al. (2000) treated rTMS responders who relapsed and rTMS non-responders with RUL ECT. Twelve of the 16 patients responded to ECT. All 4 ECT non-responders had been rTMS non-responders. On the other hand, there is no evidence that patients who fail to respond to ECT show substantial clinical benefit with rTMS. This may be like the case of vagus nerve stimulation, where ECT non-response is a negative predictive factor (Sackeim et al., 2001b).

Finally, Kimbrell et al. (1999) suggested that hypometabolism in the LDLPFC predicted superior response to fast frequency rTMS, while hypermetabolism was associated with superior response to slow frequency TMS. Somewhat in line with this perspective, Eschweiler et al. (2000) used task-related near-infrared spectroscopy to examine activation of the LDLPFC. Using 10 Hz rTMS, they found that absence of a task-related increase in total haemoglobin at the stimulation site, but not other locations, significantly predicted clinical response to active rTMS.

TMS in the treatment of depression: magnetic seizure therapy (MST)

A new development is the use of high-intensity rTMS to evoke seizures in a manner akin to ECT. The rationale for this approach rests on the observations that the anatomic positioning of ECT electrodes (electrode placement) and the electrical dosage of the ECT stimulus have a profound effect on the efficacy and cognitive side-effects of the procedure (McCall et al., 2000; Sackeim et al., 1987, 1993, 2000). This indicates that the intracerebral current paths of the electrical stimulus and current density within those paths are fundamental in determining behavioural effects. However, because of the high impedance of the skull and skull inhomogeneities, clinicians have limited controls over current paths and current density when using externally applied electrodes. In contrast, since the scalp and skull are transparent to the magnetic field produced by rTMS, focality and strength of stimulation are largely a function of stimulator output, coil geometry and orientation, and distance of the tissue from the coil. In other words, rTMS offers the possibility of greater control over the sites of seizure initiation and the current density within those sites (Sackeim et al., 1994).

Realizing this possibility has been a difficult engineering problem given the inefficiency in energy transfer from current in a magnetic coil to current in brain and the fact that general anaesthesia may raise seizure theshold. After building a custom stimulator with wider pulse width and higher sustained repetition rate, Lisanby et al. (2001b) were successful in consistently eliciting generalized seizures with rTMS in non-human primates. In May 2000, the first patient was treated with MST in Berne, Switzerland. Each of 4 rTMS sessions was successful in seizure elicitation and the patient showed clinical benefit before finishing the course with standard ECT treatments (Lisanby et al., 2001c).

Recently, we completed a study in which 10 patients with major depression received 2 treatments with MST

and 2 treatments with ECT (9 RUL an 1 BL), in randomized order (Lisanby S, Luber B, Schlaepfer T, Sackeim HA, unpublished observations). Seizure threshold was titrated at the first treatment with both MST and ECT and then dosed at the second treatment by a set amount above seizure threshold. For RUL ECT this was 6 times the initial threshold. For MST, the device was most often set at the maximal output since a value this high above threshold could not be obtained. The purpose of the study was to contrast the acute neuropsychological effects of MST relative to ECT and to investigate the utility of various coil placements and geometries. A round coil (9 cm) and a double-cone coil were effective in eliciting seizures in all patients. A more focal figure-of-eight coil was ineffective. In some patients, MST elicited seizures that were clearly non-generalized in motor expression, being restricted to a body part, highlighting the possibility of focal seizure induction. In terms of neuropsychological outcomes, MST was markedly superior in time to recovery of orientation and showed statistically superior effects on some measures of verbal memory and attention. Self-reported side-effects were also less with MST.

Future work will focus on identifying the MST parameters (coil placement, orientation, stimulation settings) that maximize the risk–benefit ratio. Once an optimal form of MST is identified, randomized comparison to ECT will take place.

Other psychiatric conditions

rTMS in the treatment of mania

An observed lateralization of mood with regards to the left or right prefrontal cortices (George et al., 1996b, Pascual-Leone et al., 1996a), together with the preliminary reports of rTMS efficacy in depression prompted the exploration of rTMS effects in mania. Grisaru et al. (1998c) reported greater improvement in manic symptomatology with 20 Hz rTMS over the RDLPFC when compared to 20 Hz rTMS over the LDLPFC. However, since high- frequency rTMS over the LDLPFC may induce manic symptomatology (Dolberg et al., 2001; Garcia-Toro, 1999; Nedjat and Folkerts, 1999), it is not clear whether the observed effect was the result of improvement with right 10 Hz or some worsening with left 10 Hz. Unfortunately, in another study, Grisaru was unable to replicate the original findings of a specific benefit for RDLPFC rTMS in acute mania (Grisaru N, personal communication: June 2001) . Erfurth et al. (2000) reported on a patient with euphoric mania who experienced marked improvement during monotherapy with right prefrontal rTMS.

rTMS in the treatment of OCD

Based on imaging data implicating overactivity of the prefrontal-basal ganglia circuits in the pathophysiology of OCD (e.g. Baxter, 1992), Greenberg et al. (1997) delivered 20 Hz rTMS to 12 OCD patients on a one-time basis on different days in a randomized fashion to the following areas: left and right PFC and the midoccipital cortex. Compulsive urges decreased significantly only after right lateral prefrontal stimulation. The effect lasted for 8 h. Although these exploratory observations are suggestive of the involvement of the right lateral prefrontal areas in the pathophysiology of OCD further studies should follow to examine the efficacy of rTMS in the treatment of OCD patients. Alonso et al. (2001) conducted a double-blind, sham-controlled study in patients with OCD. Ten patients were assigned to 18 session with TMS (110% MT, 1 Hz) over the RDLPFC and 8 patients received the same treatment at 20% MT. Low-frequency TMS over the RDLPFC did not differ from sham treatment or produce significant improvement in OCD symptoms. Thus, it would appear that slow frequency TMS over the RDLPFC may have limited value in the treatment of OCD, although low power may have obscured therapeutic effects in this study.

rTMS in the treatment of PTSD

Preliminary observations suggest efficacy of rTMS in the treatment of PTSD (Grisaru et al., 1998a; McCann et al., 1998). Grisaru et al. (1988a) treated 10 PTSD patients with one session of slow TMS, 30 pulses, 15 to each side of the motor cortex. TMS was found to be effective in lowering the core symptoms of PTSD: avoidance, anxiety, and somatization. Although general clinical improvement was found, the effect was mild and transient (Grisaru et al., 1998a). McCann et al. (1998) reported on two patients with a history of treatment-resistant depression and PTSD. Both patients failed to show benefit from treatment with LDLPFC rTMS (20 Hz) and latter received extended courses of slow frequency (1 Hz) RDLPFC TMS (80% MT). The first patient received 17 treatments, first at 3 times per week for the first 2 wk, and then 5 times weekly thereafter. The second patient received 30 sessions of RDLPFC TMS (1 Hz, 80% MT) with frequency of sessions varying from 3 to 5 times weekly. Both patients showed specific improvement in core symptoms of PTSD. PET scans immediately following the TMS course showed reductions in metabolism to age and gender matched control levels, with the reductions greatest over the RDLPFC. However, in both cases, PTSD symptoms returned to baseline levels within 1 month of TMS discontinuation.

rTMS in the treatment of schizophrenia

The reported hypofrontality in schizophrenia (e.g. Gur et al., 1985; Weinberger et al., 1986) and the encouraging preliminary results in depression prompted the initial trials of rTMS in schizophrenia. Geller et al. (1997) reported transient improvement in 2 of 10 schizophrenic patients with 30 stimuli at low frequency (0.03 Hz, 2 T) administered to the PFC bilaterally (15 stimuli to each side). Feinsod et al. (1998) administered, in open treatment, a course of 10 sessions over 2 wk of 1 Hz rTMS to the RDLPFC of 10 patients with schizophrenia. Seven patients reported amelioration of anxiety and restlessness, without improvement in core symptoms of schizophrenia. In contrast, Hoffman et al. (1999, 2000) reported significant reduction of auditory hallucinations in 12 patients with schizophrenia using a sham-controlled cross-over with 1 Hz rTMS (80% MT) administered to the left temporoparietal cortex. There has long been debate about whether auditory hallucinations reflect subvocal speech (e.g. release in Broca's area) or abnormal function in auditory reception areas (e.g. superior temporal gyrus). This work supports a role for abnormal auditory reception.

There are also case reports of improvement of symptoms in catatonic patients (Grisaru et al., 1998b; Koppi et al., 1996). Cohen et al. (1999) reported significant reduction in the PANSS negative symptom subscale scores, but only subtle clinical improvement, in 6 schizophrenic patients after 2 wk of 20 Hz rTMS to the PFC. Rollnik et al. (2000) reported a greater decrease on Brief Psychiatric Rating Scale (BPRS) ratings after active LDLPFC rTMS (20 Hz) when compared to sham rTMS in a 2-wk cross-over design in 12 patients with DSM-IV diagnosis of schizophrenia. Symptoms of psychosis improved significantly, without change in depressive symptomatology. In contrast, Klein et al. (1999a) reported no difference between sham intervention and slow right prefrontal rTMS in 31 schizophrenic patients in a randomized trial. Clearly, further controlled studies with standardized interventions (i.e. site and frequency of stimulation) are required in order to definitively establish the role of rTMS in the treatment of schizophrenia. The impact on auditory hallucinations, which appeared to have some enduring effect with left temporoparietal stimulation, appears particularly promising.

Safety

Numerous studies have confirmed the safety of TMS and rTMS (Chen et al., 1997b; Classen et al., 1995; Counter, 1993; Foerster et al., 1997; Gates et al., 1992; George et al., 1996b; Hufnagel et al., 1993; Jahanshahi et al., 1997; Michelucci et al., 1994; Pascual-Leone et al., 1993; Wassermann et al., 1996; Zyss and Witkowska, 1996; Zyss et al., 1995), and the absence of histopathological findings (Bridgers, 1991; Bridgers and Delaney, 1989; Masur et al., 1991). TMS was not associated with any clinically significant changes in hearing, cognitive performance, electroencephalogram, electrocardiogram, and hormone levels (prolactin, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone) (Hufnagel et al., 1993; Pascual-Leone et al., 1992a, 1993). Also, there were no histopathological findings in humans (Gates et al., 1992) and no effects on blood–brain barrier in rats (Ravnborg et al., 1990). The most significant risk of TMS is that of a seizure and is largely associated with administration of high-frequency rTMS rather than single- or paired-pulse TMS or slow-frequency TMS (Chen et al., 1997b; Classen et al., 1995; Homberg and Netz, 1989; Hufnagel and Elger, 1991; Pascual-Leone et al., 1993). Seven seizures associated with the administration of TMS have been documented through 1996, but none, to our knowledge, since (Wassermann, 1998). Standards of safety for the application of rTMS have been established (Chen et al., 1997b; Wassermann, 1998). In the face of the significant increase of use of TMS/rTMS since 1996, the lack of recent reports of TMS-induced seizures is probably a reflection of adherence to safety measures.

Adverse effects

TMS and rTMS are generally well tolerated. A small percentage of patients (10–30%) may experience discomfort due to scalp facial muscle twitching or headaches, but these usually respond to analgesics and rarely lead to termination of treatment (Klein et al., 1999b; Triggs et al., 1999; Wassermann, 1998). Mild tinnitus was also reported (Cohen et al., 1999). Manic symptomatology has been reported to emerge during high-frequency rTMS to the LDLPFC (Dolberg et al., 2001; Garcia-Toro, 1999; Nedjat and Folkerts, 1999).

Conclusions

There is little doubt that TMS and rTMS are powerful tools to investigate brain–behaviour relations, functional connectivity of neural circuits, and the excitability of motor cortex in psychopathology and with behavioural and pharmacological manipulations. The wide array of TMS approaches to the study of motor cortex excitability (MT threshold, input–output curves, paired-pulse paradigms, silent period assessment, post-exercise facilitation, etc.) have only been sparingly applied to studies of the pathophysiology of psychiatric conditions. This is par-

ticularly surprising since some paradigms, such as paired-pulse inhibition and facilitation are linked to the integrity of specific neurotransmitter systems, and at least in the case of schizophrenia, deficits in motor behaviour are well established. Similarly, despite the large number of studies exploring the therapeutic potential of slow and fast rTMS in the treatment of major depression, there has been little work using TMS paradigms to explore issues of pathophysiology. For example, it is a highly replicated finding that ECT progressively results in a profound increase in the threshold for seizures (Sackeim, 1999; Sackeim et al., 1983). It is unknown whether repeated rTMS in the treatment of depression results in similar inhibitory effects.

From the point of view of therapeutics, there should now be little doubt that slow and fast rTMS exert antidepressant properties. Our meta-analyses of the 9 open studies, the 23 controlled comparisons, and the 3 comparisons against ECT all suggest that rTMS has some immediate efficacy in reducing depressive symptomatology. In the open studies and the controlled comparisons, while the statistical effect sizes were large, the clinical significance of the therapeutic changes were modest. In contrast, the studies comparing rTMS and ECT, while suffering from suboptimal ECT response, showed more dramatic therapeutic effects of rTMS. Since these studies used longer periods of treatment than in the controlled comparisons against sham rTMS, it is conceivable that the therapeutic benefits of rTMS are cumulative and that the traditional 1- or 2-wk treatment protocol is insufficient. From a larger perspective, rTMS is characterized by a myriad of treatment-related parameters, and determining the optimal set for therapeutic purposes in any psychiatric condition will be an arduous task. Furthermore, few studies to date have reported on the durability or persistence of clinical gains once rTMS is terminated, so the duration of benefit is largely unknown. As described above, the evidence so far is not terribly encouraging, suggesting that rapid relapse is common. There has been no published attempt so far to use rTMS as a form of continuation or maintenance treatment, much like the growing use of continuation/maintenance ECT or to identify optimal continuation pharmacotherapy following response to rTMS (e.g. Sackeim et al., 2001a).

Regardless of utility in clinical application, the fact that slow and fast rTMS have antidepressant properties is of considerable theoretical importance. This work suggests that modulation of the functional activity of specific cortical sites results in at least some alleviation of depressive symptoms. There has yet to be analysis of whether the constellation of symptom change is homogeneous (e.g. mood, appetite, sleep, self-worth, etc.). Furthermore, virtually all work has concentrated on the use of fast frequency stimulation to the LDLPFC or slow-frequency stimulation to the RDLPFC. This approach hinges largely on a view we originally introduced (Sackeim et al., 1982), suggesting that depressed states were related to over activation of right prefrontal regions, while euphoric states were related to over-activation of left prefrontal regions. However, it is noteworthy that despite its critical theoretical importance no study has conducted the key 2×2 design, in which slow- and fast-frequency rTMS are each delivered to the left and right DLPFC. While Pascual-Leone et al. (1996) found fast-frequency RDLPFC rTMS ineffective in treating psychotic depression, this study is subject to a number of concerns regarding validity. In contrast, Kimbrell et al. (1999) found a greater effect size with slow-frequency stimulation over the LDLPFC than with fast-frequency rTMS, a direction of effect opposite to current hypotheses. In the treatment of major depression, there has clearly been a dogma in the field, emphasizing the therapeutic utility of fast-frequency rTMS to the LDLPFC and slow-frequency TMS to the RDLPFC. This perspective requires careful reassessment.

TMS and rTMS are nascent technologies. Undoubtedly, their use has much to teach us about the basic issues in the anatomic representation of psychological function, the functional connectivity of brain regions in health and disease, and the pathophysiology of psychiatric disorders. Whether this technology, which is highly labour intensive, will find a therapeutic role in psychiatry is uncertain. Much will depend on achieving both a larger clinically significant effect on psychopathology and one that can be sustained.

Acknowledgements

Supported in part by a Young Investigator Grant from the Stanley–Vada Foundation (T.B.) and a Distinguished Investigator Award from the National Alliance for Research on Schizophrenia and Depression (H.A.S.), and grant nos. K08 MH01577 (S.H.L.), R01 MH60884 (S.H.L.), R01 MH35636 (H.A.S.) from the National Institute of Mental Health.

References

Abarbanel JM, Lemberg T, Yaroslavski U, Grisaru N, Belmaker RH (1996). Electrophysiological responses to transcranial magnetic stimulation in depression and schizophrenia. *Biological Psychiatry 40*, 148–150.

Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchon JM, Capdevila A, Vallejo J (2001). Right prefrontal repetitive transcranial magnetic stimulation in

obsessive–compulsive disorder: a double-blind, placebo-controlled study. *American Journal of Psychiatry 158*, 1143–1145.

Anwyl R, Walshe J, Rowan M (1987). Electroconvulsive treatment reduces long-term potentiation in rat hippocampus. *Brain Research 435*, 377–379.

Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, Wilson L, Roy-Byrne P (1999). Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *Journal of Nervous and Mental Disorders 187*, 114–117.

Barker AT, Jalinous R, Freeston IL (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet 1*, 1106–1107.

Baxter Jr. LR (1992). Neuroimaging studies of obsessive compulsive disorder. *Psychiatric Clinics of North America 15*, 871–884.

Baxter Jr. LR, Phelps ME, Mazziotta JC, Schwartz JM, Gerner RH, Selin CE, Sumida RM (1985). Cerebral metabolic rates for glucose in mood disorders. Studies with positron emission tomography and fluorodeoxyglucose F18. *Archives of General Psychiatry 42*, 441–447.

Baxter Jr. LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry 46*, 243–250.

Belmaker RH, Fleischmann A (1995). Transcranial magnetic stimulation: a potential new frontier in psychiatry. *Biological Psychiatry 38*, 419–421.

Belmaker RH, Grisaru N (1998). Magnetic stimulation of the brain in animal depression models responsive to ECS. *Journal of ECT 14*, 194–205.

Ben-Shachar D, Belmaker RH, Grisaru N, Klein E (1997). Transcranial magnetic stimulation induces alterations in brain monoamines. *Journal of Neural Transmission 104*, 191–197.

Ben-Shachar D, Gazawi H, Riboyad-Levin J, Klein E (1999). Chronic repetitive transcranial magnetic stimulation alters beta-adrenergic and 5-HT2 receptor characteristics in rat brain. *Brain Research 816*, 78–83.

Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, Charney DS, Boutros NN (2000). A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry 47*, 332–337.

Bohning DE, Shastri A, McConnell KA, Nahas Z, Lorberbaum JP, Roberts DR, Teneback C, Vincent DJ, George MS (1999). A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. *Biological Psychiatry 45*, 385–394.

Bohning DE, Shastri A, Wassermann EM, Ziemann U, Lorberbaum JP, Nahas Z, Lomarev MP, George MS (2000). BOLD-f MRI response to single-pulse transcranial magnetic stimulation (TMS). *Journal of Magnetic Resonance Imaging 11*, 569–574.

Borenstein M, Rothstein H (1999). *Comprehensive Meta Analysis*. Englewood, NJ: Biostat, Inc.

Boroojerdi B, Phipps M, Kopylev L, Wharton CM, Cohen LG, Grafman J (2001). Enhancing analogic reasoning with rTMS over the left prefrontal cortex. *Neurology 56*, 526–528.

Boylan LS, Pullman SL, Lisanby SH, Spicknall KE, Sackeim HA (2001). Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease. *Clinical Neurophysiology 112*, 259–264.

Brandt SA, Ploner CJ, Meyer BU (1997). Repetitive transcranial magnetic stimulation. Possibilities, limits and safety aspects. *Der Nervenarzt 68*, 778–784.

Bridgers SL (1991). The safety of transcranial magnetic stimulation reconsidered: evidence regarding cognitive and other cerebral effects. *Electroencephalography and Clinical Neurophysiology 43* (Suppl.), 170–179.

Bridgers SL, Delaney RC (1989). Transcranial magnetic stimulation: an assessment of cognitive and other cerebral effects. *Neurology 39*, 417–419.

Catafau AM, Perez V, Gironell A, Martin JC, Kulisevsky J, Estorch M, Carrio I, Alvarez E (2001). SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. *Psychiatry Research 106*, 151–160.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997a). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology 48*, 1398–1403.

Chen R, Gerloff C, Classen J, Wassermann EM, Hallett M, Cohen LG (1997b). Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electroencephalography and Clinical Neurophysiology 105*, 415–421.

Classen J, Witte OW, Schlaug G, Seitz RJ, Holthausen H, Benecke R (1995). Epileptic seizures triggered directly by focal transcranial magnetic stimulation. *Electroencephalography and Clinical Neurophysiology 94*, 19–25.

Claus D, Foerster A, Schmitz JM, Bochannek T, Nouri S (1999). High-rate transcranial magnetic stimulation: influence on short-term-memory, heart rate and blood pressure changes. *Electroencephalography and Clinical Neurophysiology 50* (Suppl.), 408–412.

Cohen E, Bernardo M, Masana J, Arrufat FJ, Navarro V, Valls S, Boget T, Barrantes N, Catarineu S, Font M, Lomena FJ (1999). Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study. *Journal of Neurology, Neurosurgery and Psychiatry 67*, 129–130.

Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd edn). Hillsdale, NJ: Erlbaum.

Cohrs S, Tergau F, Riech S, Kastner S, Paulus W, Ziemann U, Ruther E, Hajak G (1998). High-frequency repetitive transcranial magnetic stimulation delays rapid eye movement sleep. *NeuroReport 9*, 3439–3443.

Conca A, Koppi S, Konig P, Swoboda E, Krecke N (1996). Transcranial magnetic stimulation: a novel antidepressive strategy? *Neuropsychobiology 34*, 204–207.

Costa Jr. PT, McCrae RR (2000). Overview: innovations in assessment using the revised NEO personality inventory. *Assessment 7*, 325–327.

Counter SA (1993). Neurobiological effects of extensive transcranial electromagnetic stimulation in an animal model. *Electroencephalography and Clinical Neurophysiology 89*, 341–348.

d'Arsonval A (1896). Dispositifs pour la mesure des courants alternatifs de toutes frequences. *Comptes Rendus de Société Biologique (Paris) 2*, 450–451.

Davey NJ, Puri BK, Lewis HS, Lewis SW, Ellaway PH (1997). Effects of antipsychotic medication on electromyographic responses to transcranial magnetic stimulation of the motor cortex in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry 63*, 468–473.

Davidson RJ (1995). Cerebral asymmetry, emoption, and affective style. In: Davidson RJ, Hugdahl K (Eds.), *Brain Asymmetry* (pp. 361–387). Cambridge, MA: MIT Press.

Dolberg OT, Schreiber S, Grunhaus L (2001). Transcranial magnetic stimulation-induced switch into mania: a report of two cases. *Biological Psychiatry 49*, 468–470.

Duman RS, Vaidya VA (1998). Molecular and cellular actions of chronic electroconvulsive seizures. *Journal of ECT 14*, 181–193.

Epstein CM, Figiel GS, McDonald WM, Amazon-Leece J, Figiel L (1998). Rapid rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. *Psychiatric Annals 28*, 36–39.

Erfurth A, Michael N, Mostert C, Arolt V (2000). Euphoric mania and rapid transcranial magnetic stimulation. *American Journal of Psychiatry 157*, 835–836.

Eschweiler GW, Plewnia C, Batra A, Bartels M (2000). Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *Canadian Journal of Psychiatry 45*, 845–846.

Feinsod M, Kreinin B, Chistyakov A, Klein E (1998). Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. *Depression and Anxiety 7*, 65–68.

Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, Glover S (1998). The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *Journal of Neuropsychiatry and Clinical Neuroscience 10*, 20–25.

Fleischmann A, Hirschmann S, Dolberg OT, Dannon PN, Grunhaus L (1999). Chronic treatment with repetitive transcranial magnetic stimulation inhibits seizure induction by electroconvulsive shock in rats. *Biological Psychiatry 45*, 759–763.

Fleischmann A, Prolov K, Abarbanel J, Belmaker RH (1995). The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. *Brain Research 699*, 130–132.

Fleischmann A, Sternheim A, Etgen AM, Li C, Grisaru N, Belmaker RH (1996). Transcranial magnetic stimulation downregulates beta-adrenoreceptors in rat cortex. *Journal of Neural Transmission 103*, 1361–1366.

Flitman SS, Grafman J, Wassermann EM, Cooper V, O'Grady J, Pascual-Leone A, Hallett M (1998). Linguistic processing during repetitive transcranial magnetic stimulation. *Neurology 50*, 175–181.

Foerster A, Schmitz JM, Nouri S, Claus D (1997). Safety of rapid-rate transcranial magnetic stimulation: heart rate and blood pressure changes. *Electroencephalography and Clinical Neurophysiology 104*, 207–212.

Fox P, Ingham R, George MS, Mayberg H, Ingham J, Roby J, Martin C, Jerabek P (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. *Brain Research and Molecular Brain Research 44*, 301–308.

Garcia-Toro M (1999). Acute manic symptomatology during repetitive transcranial magnetic stimulation in a patient with bipolar depression. *British Journal of Psychiatry 175*, 491.

Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, Mico J, Lafau O, Lafuente L (2001). Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *Journal of Affective Disorders 64*, 271–275.

Gates JR, Dhuna A, Pascual-Leone A (1992). Lack of pathologic changes in human temporal lobes after transcranial magnetic stimulation. *Epilepsia 33*, 504–508.

Geddes LA (1991). History of magnetic stimulation of the nervous system. *Journal of Clinical Neurophysiology 8*, 3–9.

Geller V, Grisaru N, Abarbanel JM, Lemberg T, Belmaker RH (1997). Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry 21*, 105–110.

George MS, Ketter TA, Post RM (1994). Prefrontal cortex dysfunction in clinical depression. *Depression 2*, 59–72.

George MS, Lisanby SH, Sackeim HA (1999). Transcranial magnetic stimulation: applications in neuropsychiatry. *Archives of General Psychiatry 56*, 300–311.

George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li XB, Arana GW, Risch SC, Ballenger JC (2000). A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry 48*, 962–970.

George MS, Wassermann EM (1994). Rapid-rate transcranial magnetic stimulation and ECT. *Convulsive Therapy 10*, 251–254.

George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M, Post RM (1997). Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in

patients with depression: a placebo-controlled crossover trial. *American Journal of Psychiatry 154*, 1752–1756.

George MS, Wassermann EM, Post RM (1996a). Transcranial magnetic stimulation: a neuropsychiatric tool for the 21st century. *Journal of Neuropsychiatry and Clinical Neuroscience 8*, 373–382.

George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, Hallett M, Post RM (1995). Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *NeuroReport 6*, 1853–1856.

George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, Hallett M, Post RM (1996b). Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *Journal of Neuropsychiatry and Clinical Neuroscience 8*, 172–180.

Gombos Z, Spiller A, Cottrell GA, Racine RJ, McIntyre Burnham W (1999). Mossy fiber sprouting induced by repeated electroconvulsive shock seizures. *Brain Research 844*, 28–33.

Grafman J, Pascual-Leone A, Alway D, Nichelli P, Gomez-Tortosa E, Hallett M (1994). Induction of a recall deficit by rapid-rate transcranial magnetic stimulation. *NeuroReport 5*, 1157–1160.

Grafman J, Wassermann E (1999). Transcranial magnetic stimulation can measure and modulate learning and memory. *Neuropsychologia 37*, 159–167.

Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, Altemus M, Wassermann EM, Post RM, Murphy DL (1997). Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive–compulsive disorder: a preliminary study. *American Journal of Psychiatry 154*, 867–869.

Greenberg BD, Ziemann U, Cora-Locatelli G, Harmon A, Murphy DL, Keel JC, Wassermann EM (2000). Altered cortical excitability in obsessive–compulsive disorder. *Neurology 54*, 142–147.

Grisaru N, Abaranel J, Belmalker RH (1995). Slow magnetic stimulation of motor cortex and frontal lobe in depression and schizophrenia. *Acta Neuropsychiatrica 7* (Suppl.), 10–12.

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

Grisaru N, Bruno R, Pridmore S (2001). Effect on emotion of healthy individuals of slow repetitive transcranial magnetic stimulation appled to the prefrontal cortex. *Journal of ECT 17*, 184–189.

Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH (1998b). Catatonia treated with transcranial magnetic stimulation. *American Journal of Psychiatry 155*, 1630.

Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH (1998c). Transcranial magnetic stimulation in mania: a controlled study. *American Journal of Psychiatry 155*, 1608–1610.

Grisaru N, Yarovslavsky U, Abarbanel J, Lamberg T, Belmaker RH (1994). Transcranial magnetic stimulation in depression and schizophrenia. *European Journal of Neuropsychopharmacology 4*, 287–288.

Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, Lefkifker E (2000). Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biological Psychiatry 47*, 314–324.

Gur R, Gur R, Skolnick B, Caroff S, Obrist W, Resnick S, Reivich M (1985). Brain functions in psychiatric disorders: III. Regional cerebral blood flow in unmedicated schizophrenics. *Archives of General Psychiatry 42*, 329–334.

Haag C, Padberg F, Moller HJ (1997). Transcranial magnetic stimulation. A diagnostic means from neurology as therapy in psychiatry? *Der Nervenarzt 68*, 274–278.

Hamano T, Kaji R, Fukuyama H, Sadato N, Kimura J (1993). Lack of prolonged cerebral blood flow change after transcranial magnetic stimulation. *Electroencephalography and Clinical Neurophysiology 89*, 207–210.

Hasey GM (1999). Transcranial magnetic stimulation: using a law of physics to treat psychopathology. *Journal of Psychiatry and Neuroscience 24*, 97–101.

Hasselblad V, Hedges LV (1995). Meta-analysis of screening and diagnostic tests. *Psychological Bulletin 117*, 167–178.

Hedges LV, Olkin I (1985). *Statistical Methods for Meta-Analysis*). London: Academic Press.

Herbst JH, Zonderman AB, McCrae RR, Costa Jr. PT (2000). Do the dimensions of the temperament and character inventory map a simple genetic architecture? Evidence from molecular genetics and factor analysis. *American Journal of Psychiatry 157*, 1285–1290.

Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C (2001). Transcranial magnetic stimulation in therapy studies: examination of the reliability of 'standard' coil positioning by neuronavigation. *Biological Psychiatry 50*, 58–61.

Hess CW, Mills KR, Murray NM, Schriefer TN (1987). Excitability of the human motor cortex is enhanced during REM sleep. *Neuroscience Letters 82*, 47–52.

Hickie I, Mason C, Parker G, Brodaty H (1996). Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. *British Journal of Psychiatry 169*, 68–74.

Hickie I, Parsonage B, Parker G (1990). Prediction of response to electroconvulsive therapy. Preliminary validation of a sign-based typology of depression. *British Journal of Psychiatry 157*, 65–71.

Hoffman RE, Boutros NN, Berman RM, Roessler E, Belger A, Krystal JH, Charney DS (1999). Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated 'voices'. *Biological Psychiatry 46*, 130–132.

Hoffman RE, Boutros NN, Hu S, Berman RM, Krystal JH, Charney DS (2000). Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. *Lancet 355*, 1073–1075.

Hoflich G, Kasper S, Hufnagel A, Ruhrmann S, Moller HJ (1993). Appication of transcranial magnetic stimulation in treatment of drug-resistant major depression – a report of two cases. *Human Psychopharmacology 8*, 361–365.

Homberg V, Netz J (1989). Generalised seizures induced by transcranial magnetic stimulation of motor cortex. *Lancet 2*, 1223.

Hufnagel A, Claus D, Brunhoelzl C, Sudhop T (1993). Short-term memory: no evidence of effect of rapid-repetitive transcranial magnetic stimulation in healthy individuals. *Journal of Neurology 240*, 373–376.

Hufnagel A, Elger CE (1991). Induction of seizures by transcranial magnetic stimulation in epileptic patients. *Journal of Neurology 238*, 109–110.

Hyman SE, Nestler EJ (1996). Initiation and adaptation: a paradigm for understanding psychotropic drug action. *American Journal of Psychiatry 153*, 151–162.

Izumi S, Takase M, Arita M, Masakado Y, Kimura A, Chino N (1997). Transcranial magnetic stimulation-induced changes in EEG and responses recorded from the scalp of healthy humans. *Electroencephalography and Clinical Neurophysiology 103*, 319–322.

Jahanshahi M, Ridding MC, Limousin P, Profice P, Fogel W, Dressler D, Fuller R, Brown RG, Brown P, Rothwell JC (1997). Rapid rate transcranial magnetic stimulation: a safety study. *Electroencephalography and Clinical Neurophysiology 105*, 422–429.

Janssen BA, Theiler R, Grob D, Dvorak J (1995). The role of motor evoked potentials in psychogenic paralysis. *Spine 20*, 608–611.

Kammer T, Beck S, Thielscher A, Laubis-Herrmann U, Topka H (2001). Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clinical Neurophysiology 112*, 250–258.

Kammer T, Spitzer M (1996). Triggered transcranial magnetic stimulation in high cognitive functions. *Fortschritte der Neurologie-Psychiatrie 64*, 205–211.

Kessels RP, d'Alfonso AA, Postma A, de Haan EH (2000). Spatial working memory performance after high-frequency repetitive transcranial magnetic stimulation of the left and right posterior parietal cortex in humans. *Neuroscience Letters 287*, 68–70.

Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM (1999). Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biological Psychiatry 46*, 1603–1613.

Kirkcaldie M, Pridmore S, Reid P (1997a). Bridging the skull: electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) in psychiatry. *Convulsive Therapy 13*, 83–91.

Kirkcaldie MT, Pridmore SA, Pascual-Leone A (1997b). Transcranial magnetic stimulation as therapy for depression and other disorders. *Australia and New Zealand Journal of Psychiatry 31*, 264–272.

Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M (1999a). Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. *Biological Psychiatry 46*, 1451–1454.

Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, Ben-Shachar D, Feinsod M (1999b). Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Archives of General Psychiatry 56*, 315–320.

Kolbinger HM, Hoflich G, Hufnagel A, Moller HJ, Kasper S (1995). Transcranial magnetic stimulation (TMS) in the treatment of major depression: a pilot study. *Human Psychopharmacology 10*, 305–310.

Koppi S, Conca A, Swoboda E, Konig P (1996). Transcranial magnetic stimulation in depressed patients: a new antidepressive therapeutic principle? Presentation of a pilot trial. *Wiener Medizinische Wochenschrift 146*, 49–54.

Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, Risch SC, George MS (2000). How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *Journal of Neuropsychiatry and Clinical Neuroscience 12*, 376–384.

Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA (2001a). Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry 49*, 460–463.

Lisanby SH, Luber B, Perera T, Sackeim HA (2000). Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology. *International Journal of Neuropsychopharmacology 3*, 259–273.

Lisanby SH, Luber B, Sackeim HA, Finck AD, Schroeder C (2001b). Deliberate seizure induction with repetitive transcranial magnetic stimulation in nonhuman primates. *Archives of General Psychiatry 58*, 199–200.

Lisanby SH, Pascual-Leone A, Sampson SM, Boylan LS, Burt T, Sackeim HA (2001d). Augmentation of sertraline antidepressant treatment with transcranial magnetic stimulation. *Biological Psychiatry 49*, 81S.

Lisanby SH, Sackeim HA (2000). Therapeutic brain interventions and the nature of emotion. In: Borod J (Eds.), *The Neuropsychology of Emotion* (pp. 456–491). New York: Oxford University Press.

Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA (2001c). Magnetic seizure therapy of major depression. *Archives of General Psychiatry 58*, 303–305.

Little JT, Kimbrell TA, Wassermann EM, Grafman J, Figueras S, Dunn RT, Danielson A, Repella J, Huggins T, George MS, Post RM (2000). Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry, Neuropsychology and Behavioural Neurology 13*, 119–124.

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

Loo CK, Taylor JL, Gandevia SC, McDarmont BN, Mitchell PB, Sachdev PS (2000). Transcranial magnetic stimulation

(TMS) in controlled treatment studies: are some 'sham' forms active? *Biological Psychiatry 47*, 325–331.

Malmivuo J, Plonskey R (1995). *Bioelectromagnetism: Prinicples and Applications of Bioelectric and Biomagnetic Fields*. New York: Oxford University Press.

Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG (2001). A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics 13*, 225–231.

Markwort S, Cordes P, Aldenhoff J (1997). Transcranial magnetic stimulation as an alternative to electroshock therapy in treatment resistant depressions: a literature review. *Fortschritte Neurologie-Psychiatrie 65*, 540–549.

Masur H, Ludolph AC, Hilker E, Hengst K, Knuth U, Rolf LH, Bals-Pratsch M (1991). Transcranial magnetic stimulation: influence on plasma levels of hormones of the anterior pituitary gland and of cortisol? *Functional Neurology 6*, 59–63.

McCall WV, Reboussin DM, Weiner RD, Sackeim HA (2000). Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Archives of General Psychiatry 57*, 438–444.

McCann UD, Kimbrell TA, Morgan CM, Anderson T, Geraci M, Benson BE, Wassermann EM, Willis MW, Post RM (1998). Repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Archives of General Psychiatry 55*, 276–279.

McConnell KA, Nahas Z, Shastri A, Lorberbaum JP, Kozel FA, Bohning DE, George MS (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biological Psychiatry 49*, 454–459.

Menkes DL, Bodnar P, Ballesteros RA, Swenson MR (1999). Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: a case-control pilot study of safety and efficacy. *Journal of Neurology, Neurosurgery and Psychiatry 67*, 113–115.

Meyer M, Osmand A, Campbell S, Logan G (1994). Focal cortical hypermetabolism during transcranial magnetic stimulation. *Muscle Nerve 17*, 1464–1465.

Michelucci R, Valzania F, Passarelli D, Santangelo M, Rizzi R, Buzzi AM, Tempestini A, Tassinari CA (1994). Rapid-rate transcranial magnetic stimulation and hemispheric language dominance: usefulness and safety in epilepsy. *Neurology 44*, 1697–1700.

Mosimann UP, Rihs TA, Engeler J, Fisch H, Schlaepfer TE (2000). Mood effects of repetitive transcranial magnetic stimulation of left prefrontal cortex in healthy volunteers. *Psychiatry Research 94*, 251–256.

Mull BR, Seyal M (2001). Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. *Clinical Neurophysiology 112*, 1672–1675.

Mullges W, Ferbert A, Buchner H (1991). Transcranial magnetic stimulation in psychogenic paralysis. *Der Nervenarzt 62*, 349–353.

Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H (1997). Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *Journal of Physiology (London) 498*, 817–823.

Nedjat S, Folkerts HW (1999). Induction of a reversible state of hypomania by rapid-rate transcranial magnetic stimulation over the left prefrontal lobe. *Journal of ECT 15*, 166–168.

Nemeroff CB (1996). Augmentation strategies in patients with refractory depression. *Depression and Anxiety 4*, 169–181.

Nestler EJ (1998). Antidepressant treatments in the 21st century. *Biological Psychiatry 44*, 526–533.

Oliviero A, Di Lazzaro V, Piazza O, Profice P, Pennisi MA, Della Corte F, Tonali P (1999). Cerebral blood flow and metabolic changes produced by repetitive magnetic brain stimulation. *Journal of Neurology 246*, 1164–1168.

Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, Hampel H, Moller HJ (1999). Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Research 88*, 163–171.

Parker G, Roy K, Hadzi-Pavlovic D, Pedic F (1992). Psychotic (delusional) depression: a meta-analysis of physical treatments. *Journal of Affective Disorders 24*, 17–24.

Pascual-Leone A, Bartres-Faz D, Keenan JP (1999). Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. *Philosophical Transactions of the Royal Society of London (B: Biological Sciences) 354*, 1229–1238.

Pascual-Leone A, Catala MD, Pascual-Leone Pascual A (1996a). Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. *Neurology 46*, 499–502.

Pascual-Leone A, Cohen LG, Shotland LI, Dang N, Pikus A, Wassermann EM, Brasil-Neto JP, Valls-Sole J, Hallett M (1992a). No evidence of hearing loss in humans due to transcranial magnetic stimulation. *Neurology 42*, 647–651.

Pascual-Leone A, Hallett M (1994). Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. *NeuroReport 5*, 2517–2520.

Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Sole J, Brasil-Neto JP, Wassermann EM, Cohen LG, Hallet M (1993). Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalography and Clinical Neurophysiology 89*, 120–130.

Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996b). Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet 348*, 233–237.

Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD (1998). Study and modulation of human

cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology 15*, 333–343.

Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallett M (1992b). Seizure induction and transcranial magnetic stimulation. *Lancet 339*, 997.

Paus T (1999). Imaging the brain before, during, and after transcranial magnetic stimulation. *Neuropsychologia 37*, 219–224.

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

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

Paus T, Wolforth M (1998). Transcranial magnetic stimulation during PET: reaching and verifying the target site. *Human Brain Mapping 6*, 399–402.

Perretti A, Grossi D, Fragassi N, Lanzillo B, Nolano M, Pisacreta AI, Caruso G, Santoro L (1996). Evaluation of the motor cortex by magnetic stimulation in patients with Alzheimer disease. *Journal of Neurological Science 135*, 31–37.

Post RM, Kimbrell TA, McCann U, Dunn RT, George MS, Weiss SR (1997). Are convulsions necessary for the antidepressive effect of electroconvulsive therapy: outcome of repeated transcranial magnetic stimulation. *Encephale 23* (Spec. no. 3), 27–35.

Post RM, Kimbrell TA, McCann UD, Dunn RT, Osuch EA, Speer AM, Weiss SR (1999). Repetitive transcranial magnetic stimulation as a neuropsychiatric tool: present status and future potential. *Journal of ECT 15*, 39–59.

Pridmore S (1999). Rapid transcranial magnetic stimulation and normalization of the dexamethasone suppression test. *Psychiatry and Clinical Neuroscience 53*, 33–37.

Pridmore S, Belmaker R (1999). Transcranial magnetic stimulation in the treatment of psychiatric disorders. *Psychiatry and Clinical Neuroscience 53*, 541–548.

Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M (2000). Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *International Journal of Neuropsychopharmacology 3*, 129–134.

Pridmore S, Rybak M, Turnier-Shea Y, Reid P, Bruno R, Couper D (1999). A naturalistic study of response in melancholia to transcranial magnetic stimulation (TMS). *German Journal of Psychiatry 2*, 13–21.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA (1996). Resistance to antidepressant medications and short-term clinical response to ECT. *American Journal of Psychiatry 153*, 985–992.

Prudic J, Sackeim HA, Devanand DP (1990). Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research 31*, 287–296.

Puri BK, Davey NJ, Ellaway PH, Lewis SW (1996). An investigation of motor function in schizophrenia using transcranial magnetic stimulation of the motor cortex. *British Journal of Psychiatry 169*, 690–695.

Puri BK, Lewis SW (1996). Transcranial magnetic stimulation in psychiatric research. *British Journal of Psychiatry 169*, 675–677.

Ravnborg M, Knudsen GM, Blinkenberg M (1990). No effect of pulsed magnetic stimulation on the blood–brain barrier in rats. *Neuroscience 38*, 277–280.

Reid PD, Pridmore S (1999). Dexamethasone suppression test reversal in rapid transcranial magnetic stimulation-treated depression. *Australia and New Zealand Journal of Psychiatry 33*, 274–247.

Reid PD, Shajahan PM, Glabus MF, Ebmeier KP (1998). Transcranial magnetic stimulation in depression. *British Journal of Psychiatry 173*, 449–452.

Robertson EM, Tormos JM, Maeda F, Pascual-Leone A (2001). The role of the dorsolateral prefrontal cortex during sequence learning is specific for spatial information. *Cerebral Cortex 11*, 628–635.

Rollnik JD, Huber TJ, Mogk H, Siggelkow S, Kropp S, Dengler R, Emrich HM, Schneider U (2000). High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients. *NeuroReport 11*, 4013–4015.

Sabatino M, Di Nuovo S, Sardo P, Abbate CS, La Grutta V (1996). Neuropsychology of selective attention and magnetic cortical stimulation. *International Journal of Psychophysiology 21*, 83–89.

Sackeim HA (1994). Magnetic stimulatuion therapy and ECT. *Convulsive Therapy 10*, 255–258.

Sackeim HA (1999). The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. *Journal of ECT 15*, 5–26.

Sackeim HA (2000). Repetitive transcranial magnetic stimulation: What are the next steps? *Biological Psychiatry 48*, 959–961.

Sackeim HA (2001). The definition and meaning of treatment-resistant depression. *Journal of Clinical Psychiatry 62* (Suppl. 16), 10–17.

Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S (1987). Effects of electrode placement on the efficacy of titrated, low-dose ECT. *American Journal of Psychiatry 144*, 1449–1455.

Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR (1983). Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. *Biological Psychiatry 18*, 1301–1310.

Sackeim HA, Greenberg MS, Weiman AL, Gur RC, Hungerbuhler JP, Geschwind N (1982). Hemispheric asymmetry in the expression of positive and negative emotions: neurologic evidence. *Archives of Neurology 39*, 210–218.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Amos JJ, Cooper

TB, Prudic J (2001a). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: A randomized, placebo-controlled trial. *Journal of the American Medical Association 285*, 1299–1307.

Sackeim HA, Long J, Luber B, Moeller JR, Prohovnik I, Devanand DP, Nobler MS (1994). Physical properties and quantification of the ECT stimulus: I. Basic principles. *Convulsive Therapy 10*, 93–123.

Sackeim HA, Prohovnik I (1993). Brain imaging studies in depressive disorders. In: Mann JJ, Kupfer D (Eds.), *Biology of Depressive Disorders* (pp. 205–258). New York: Plenum Press.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990). The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *Journal of Clinical Psychopharmacology 10*, 96–104.

Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *New England Journal of Medicine 328*, 839–846.

Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Archives of General Psychiatry 57*, 425–434.

Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson Jr. RK, Goodman RR (2001b). Vagus nerve stimulation (VNS™) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology 25*, 713–728.

Samii A, Wassermann EM, Ikoma K, Mercuri B, George MS, O'Fallon A, Dale JK, Straus SE, Hallett M (1996). Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression. *Neurology 47*, 1410–1414.

Shajahan PM, Glabus MF, Gooding PA, Shah PJ, Ebmeier KP (1999a). Reduced cortical excitability in depression. Impaired post-exercise motor facilitation with transcranial magnetic stimulation. *British Journal of Psychiatry 174*, 449–454.

Shajahan PM, Glabus MF, Jenkins JA, Ebmeier KP (1999b). Postexercise motor evoked potentials in depressed patients, recovered depressed patients, and controls. *Neurology 53*, 644–646.

Soares JC, Mann JJ (1997). The functional neuroanatomy of mood disorders. *Journal of Psychiatric Research 31*, 393–432.

Spiker DG, Weiss JC, Dealy RS, Griffin SJ, Hanin I, Neil JF, Perel JM, Rossi AJ, Soloff PH (1985). The pharmacological treatment of delusional depression. *American Journal of Psychiatry 142*, 430–436.

Stalder S, Rosler KM, Nirkko AC, Hess CW (1995). Magnetic stimulation of the human brain during phasic and tonic REM sleep: recordings from distal and proximal muscles. *Journal of Sleep Research 4*, 65–70.

Stern Y, Sackeim HA (In Press). The neuropsychiatry of memory and amnesia. In: Yudofsky SC, Hales RE (Eds.), *The American Psychiatric Press Textbook of Neuropsychiatry* (4th edn). Washington, DC: American Psychiatric Press.

Stewart CA, Reid IC (2000). Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. *Psychopharmacology 148*, 217–223.

Stikhina NI, Lyskov EB, Lomarev MP, Aleksanian ZA, Mikhailov VO, Medvedev SV (1999). Transcranial magnetic stimulation in neurotic depression. *Zhurnal Nevropatologii i Psikhiatrii im S.S. Korsakova 99*, 26–29.

Szuba MP, O'Reardon JP, Rai AS, Snyder-Kastenberg J, Amsterdam JD, Gettes DR, Wassermann E, Evans DL (2001). Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biological Psychiatry 50*, 22–27.

Teneback CC, Nahas Z, Speer AM, Molloy M, Stallings LE, Spicer KM, Risch SC, George MS (1999). Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *Journal of Neuropsychiatry and Clinical Neuroscience 11*, 426–435.

Tormos JM, Canete C, Tarazona F, Catala MD, Pascual-Leone Pascual A, Pascual-Leone A (1997). Lateralized effects of self-induced sadness and happiness on corticospinal excitability. *Neurology 49*, 487–491.

Tormos JM, Catala MD, Pascual-Leone A (1999). Transcranial magnetic stimulation. *Review of Neurology 29*, 165–171.

Triggs WJ, McCoy KJ, Greer R, Rossi F, Bowers D, Kortenkamp S, Nadeau SE, Heilman KM, Goodman WK (1999). Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biological Psychiatry 45*, 1440–1446.

Ucles P, Lorente S, Rosa F (1996). Neurophysiological methods testing the psychoneural basis of attention deficit hyperactivity disorder. *Children's Nervous System 12*, 215–217.

Wang H, Wang X, Scheich H (1996). LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. *NeuroReport 7*, 521–525.

Wang H, Wang X, Wetzel W, Scheich H (1999). Rapid-rate transcranial magnetic stimulation in auditory cortex induces LTP and LTD and impairs discrimination learning of frequency-modulated tones. *Electroencephalography and Clinical Neurophysiology* (Suppl. 51), 361–367.

Wassermann EM (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, 5–7 June, 1996. *Electroencephalography and Clinical Neurophysiology 108*, 1–16.

Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, Hallett M (1996). Use and safety of a new repetitive transcranial magnetic stimulator. *Electroencephalography and Clinical Neurophysiology 101*, 412–417.

Wassermann EM, Greenberg BD, Nguyen MB, Murphy DL (2001). Motor cortex excitability correlates with an anxiety-related personality trait. *Biological Psychiatry 50*, 377–382.

Wassermann EM, Wedegaertner FR, Ziemann U, George MS, Chen R (1998). Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. *Neuroscience Letters 250*, 141–144.

Weinberger D, Berman K, Zec R (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: II. Regional cerebral blood flow evidence. *Archives of General Psychiatry 43*, 114–124.

Zheng XM (2000). Regional cerebral blood flow changes in drug-resistant depressed patients following treatment with transcranial magnetic stimulation: a statistical parametric mapping analysis. *Psychiatry Research 100*, 75–80.

Ziemann U, Bruns D, Paulus W (1996a). Enhancement of human motor cortex inhibition by the dopamine receptor agonist pergolide: evidence from transcranial magnetic stimulation. *Neuroscience Letters 208*, 187–90.

Ziemann U, Chen R, Cohen LG, Hallett M (1998). Dextromethorphan decreases the excitability of the human motor cortex. *Neurology 51*, 1320–1324.

Ziemann U, Lonnecker S, Paulus W (1995). Inhibition of human motor cortex by ethanol. A transcranial magnetic stimulation study. *Brain 118*, 1437–1446.

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996b). Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Annals of Neurology 40*, 367–378.

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996c). The effect of lorazepam on the motor cortical excitability in man. *Experimental Brain Research 109*, 127–135.

Ziemann U, Paulus W, Rothenberger A (1997a). Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. *American Journal of Psychiatry 154*, 1277–1284.

Ziemann U, Tergau F, Bruns D, Baudewig J, Paulus W (1997b). Changes in human motor cortex excitability induced by dopaminergic and anti-dopaminergic drugs. *Electroencephalography and Clinical Neurophysiology 105*, 430–437.

Zyss T (1992). Will electroconvulsive therapy induce seizures: magnetic brain stimulation as hypothesis of a new psychiatric therapy. *Psychiatria Polska 26*, 531–541.

Zyss T, Gorka Z, Kowalska M, Vetulani J (1996). Behavioral and biochemical effects of magnetic brain stimulation and electroshock in rats. *Psychiatria Polska 30*, 593–610.

Zyss T, Gorka Z, Kowalska M, Vetulani J (1997). Preliminary comparison of behavioral and biochemical effects of chronic transcranial magnetic stimulation and electroconvulsive shock in the rat. *Biological Psychiatry 42*, 920–924.

Zyss T, Krawczyk A (1996). Magnetic brain stimulation in treatment of depression: the search for effective parameters of stimulation. *Psychiatria Polska 30*, 611–628.

Zyss T, Mamczarz J, Roman A, Vetulani J (1999). Comparison of effectiveness of two schedules of rapid transcranial magnetic stimulation on enhancement of responsiveness to apomorphine. *Polish Journal of Pharmacology and Pharmacy 51*, 363–366.

Zyss T, Witkowska B (1996). Transcranial magnetic stimulation neurophysiological and biochemical response in man. *Neurologia i Neurochirugia Polska 30*, 399–408.

Zyss T, Witkowska B, Jarosz J (1995). Repetitive transcranial magnetic stimulation EEG, serum prolactin and cortisol studies in humans. *Psychiatria Polska 29*, 513–527.