"Getting physical": the management of neuropsychiatric disorders using novel physical treatments

Gin S Malhi[1,2]
Colleen Loo[1,2]
Catherine M Cahill[1,2]
Jim Lagopoulos[1,2,4]
Philip Mitchell[1,2]
Perminder Sachdev[1,3]

[1]School of Psychiatry, University of New South Wales, Australia; [2]Mood Disorders Unit, Black Dog Institute, Australia; [3]Neuropsychiatric Institute, Prince of Wales Hospital, Australia; [4]Department of Neurology, Westmead Hospital, Australia

Objective: To summarize and review the utility of physical interventions in the treatment of psychiatric disorders.

Methods: A systematic review of the literature pertaining to novel physical interventions, namely, transcranial magnetic stimulation, deep brain stimulation, vagus nerve stimulation, and neurosurgery, was conducted using MEDLINE, EMBASE, and PSYCHLIT. Bibliographies of papers were scrutinized for further relevant references along with literature known to the authors.

Results: Currently available physical interventions worldwide are reviewed with respect to efficacy, applications, and putative indications. Physical interventions have experienced a resurgence of interest for both the investigation of brain function and the treatment of neuropsychiatric disorders. The widespread availability of neuroimaging technology has advanced our understanding of brain function and allowed closer examination of the effects of physical treatments. Clinically, transcranial magnetic stimulation seems likely to have a role in the management of depression, and its use in other neuropsychiatric disorders appears promising. Following on from its success in the management of intractable epilepsy, vagus nerve stimulation is undergoing evaluation in the treatment of depression with some success in refractory cases. Deep brain stimulation has improved mood in patients with Parkinson's disease and may also relieve symptoms of obsessive-compulsive disorder. Neurosurgery has re-invented itself by way of increased technical sophistication, and although further assessment of its efficacy and clinical utility is still needed, its widespread practice reflects its increasing acceptance as a viable treatment of last resort.

Conclusion: It is clear that physical treatments are here to stay and "getting physical" offers a useful addition to the neuropsychiatrist's therapeutic armamentarium. However, like all new treatments these interventions need to remain under rigorous scientific scrutiny to determine accurately their immediate and long-term effects.

Keywords: physical treatments, psychosurgery, transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation, neuropsychiatry

Introduction

The development of psychopharmacological treatments for psychiatric disorders has made physical interventions less popular, evidenced by the marked decline in neurosurgery since its hey-day in the 1960s. Many psychiatric patients are resistant to medications or are unable to tolerate their side-effects, and therefore novel treatments for neuropsychiatric disorders are necessary. In the last decade, several new physical treatments have been introduced that hold the potential to join the mainstream of psychiatric therapy. In this paper we review the efficacy of transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS) and the current status of neurosurgery which, although not new, continues to be

Correspondence: Gin S Malhi
Mayne Clinical Research Imaging Centre, Prince of Wales Medical Research Institute, Barker St, Randwick NSW 2031, Australia
Tel +61 2 9382 3719
Fax +61 2 9382 8208
Email g.malhi@unsw.edu.au

novel among neuropsychiatric treatments. Light therapy was excluded from this review as much of the literature pertaining to it is linked with seasonal affective disorder and it does not generally come under the rubric of "physical treatments" in neuropsychiatry.

Method

The literature was reviewed selectively by entering the search terms "transcranial magnetic stimulation", "vagus nerve stimulation", "deep brain stimulation", "psychosurgery", and "neurosurgery" into MEDLINE, EMBASE, and PSYCHLIT. To identify more-specific articles the names of some of the surgical procedures, eg, "stereotactic subcaudate tractotomy", "capsulotomy", "limbic leucotomy", and "cingulotomy", were entered. As few randomized controlled trials have been possible or indeed attempted using VNS, DBS, and neurosurgery, the use of strict criteria such as inclusion of placebo or blinding status was not possible and studies were hence included based on their clinical salience. We also included industry-sponsored trials as although these include an interest on the part of the sponsor, they have withstood quality control and audit by bodies such as the FDA and often have attracted the largest numbers of participants.

Transcranial magnetic stimulation (TMS)

TMS is performed by placing an electromagnetic coil on the scalp through which large currents are pulsed to generate rapidly fluctuating magnetic fields. These cross the scalp unimpeded and generate eddy currents in the underlying brain cortex that depolarise neurons and produce an associated effect (Roth et al 1991) (see Figure 1a). The neural response is contingent upon a number of variables, such as the site of application, the stimulation parameters, and the use of single or multiple stimuli (Cohen et al 1990). The application of repeated TMS pulses to a particular site is termed repetitive TMS (rTMS) and the application at frequencies above 1Hz is referred to as fast-frequency repetitive TMS (FF-rTMS). The latter has been most investigated in neuropsychiatric treatment studies.

TMS in neuropsychiatric disorders

The rapid and widespread implementation of TMS over the last 20 years has generated considerable debate about the effects and implications of using this noninvasive method of brain stimulation.

Depression

In preclinical studies with rats TMS shows an effect similar to that produced by antidepressants and electroconvulsive shock (Ben-Shachar et al 1997; Lisanby and Belmaker 2000; Keck et al 2001; Levkovitz and Ng 2001). There have also been findings that support it having an antidepressant action in humans, including reports that it delays the onset of rapid eye movement (REM) sleep in healthy subjects (Cohrs et al 1998) and normalizes the dexamethasone suppression test in depressed patients (Pridmore 1999).

Guided by neuroimaging studies, the prefrontal cortex was proposed as a suitable target for antidepressant rTMS (George et al 1995), and initial studies of focal rTMS of the left prefrontal cortex (PFC) seemed encouraging (Pascual-Leone et al 1996). Comparison across studies has been difficult because of differences in patient populations, study design, duration, and rTMS parameters. A summary of sham-controlled treatment trials of rTMS is shown in Table 1.

There have been several meta-analyses of these placebo-controlled trials of rTMS for major depression. The Cochrane Collaboration (Martin et al 2003) concluded that two weeks of high-frequency rTMS to the left dorsolateral prefrontal cortex led to significant improvement on the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), but not on a self-rating scale such as Beck (Beck 1961). This improvement was not sustained at 2-week follow-up. The authors concluded that the published evidence for an antidepressant effect of rTMS was weak. Burt et al (2002) conducted an independent meta-analysis of treatment studies, which included controlled and uncontrolled, blind, and open study designs. Analysis of effects in uncontrolled studies found a consistent but modest treatment effect (37% mean reduction in HDRS) and for controlled studies the magnitude of change was even smaller (27% mean reduction in HDRS for TMS group, compared with 7% reduction for sham treatment). In summary, meta-analyses show that statistical evidence for the efficacy of rTMS is fairly robust but that clinical outcomes are modest. An important caveat, though, is that most of the trials to date have only compared rTMS to a sham control over a 2-week period, whereas evidence from trials allowing longer treatment periods, either in an open extension (eg, Loo et al 1999) or within the controlled phase (Rumi et al 2005), suggests further improvement occurs with increasing duration of rTMS.

A number of studies randomized depressed subjects to receive electroconvulsive therapy (ECT) or 4 weeks of rTMS. These reported a clear advantage (Grunhaus et al 2000)

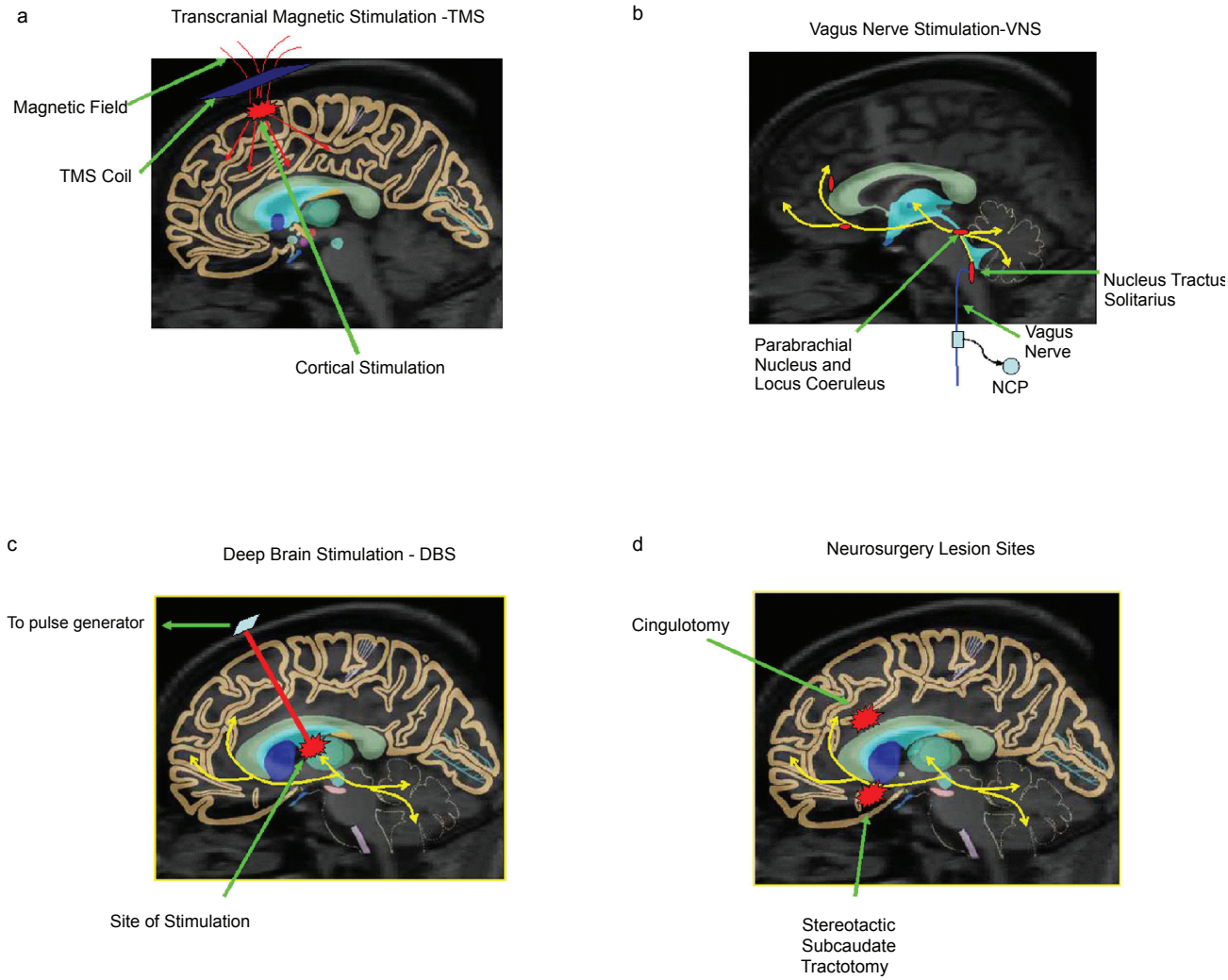

Figure 1 Illustration of brain regions affected by the physical treatments transcranial magnetic stimulation (a), vagus nerve stimulation (b), deep brain stimulation (c), and neurosurgery (d).
Abbreviations: NCP, neurocybernetic prosthesis.

or emerging trends (Pridmore et al 2000; Janicak et al 2002) in favour of ECT, though one study found no difference (Grunhaus et al 2003). Of interest, the results of Grunhaus et al (2000) suggested that rTMS may be equally effective as ECT for treating nonpsychotic depression, but had little efficacy in psychotic depression.

Investigators in the field concur that there still remains a need for large multi-center trials with longer sham-controlled periods and greater scientific rigor including appropriate and documented randomization and assessment as well as increased monitoring of both the patient and the therapeutic characteristics that modulate treatment outcome (Holtzheimer et al 2004).

Another experimental application of TMS has been magnetic seizure therapy (MST), the use of rTMS at high stimulus frequency and intensity to deliberately induce a generalized seizure under anesthesia for the treatment of depression (Morales et al 2004). MST stimulation is more focal than that of ECT, thus leading to the expectation of fewer cognitive side effects. So far, preliminary trials in nonhuman primates and human subjects have confirmed this expectation, while case reports have found that MST led to significant improvement in two medication-resistant depressed subjects (Morales et al 2004).

Bipolar disorder

There have been a number of case reports of the induction of mania in depressed subjects receiving rTMS treatment (Garcia-Toro 1999; Dolberg et al 2001; Sakkas et al 2003; Su 2005; Hausmann et al 2004b). Grisaru et al (1998a)

Table 1 TMS/sham controlled studies

Study	N	Design/RTMS treatment	Mean % change HDRS[4]	Number of responders[5]
Pascual-Leone et al 1996	17	Multiple crossover: L and R DLPFC (active/sham), vertex (active) 10 Hz[1], 5 days[2]	L DLPFC active: 48%, Other: 4%–12%	L DLPFC active: 4 Other: 0
George et al 1997a	12	Crossover: L DLPFC (active/sham), 20 Hz, 10 days	Active: 16% Sham: 13%↑	Active: 1 Sham: 0
Loo et al 1999	18	Parallel: L DLPFC (active/sham), 10 Hz, 10 days	Active: 23% Sham: 25%	Active: 0 Sham: 1
Padberg et al 1999	18	Parallel: L DLPFC (active) 10 Hz/0.3 Hz, (sham) 10 Hz, 5 days	10 Hz: 6% 0.3 Hz: 19% Sham: 6% ↑	All: 0
Klein et al 1999	70 dep	Parallel: R DLPFC (active/sham), 1 Hz, 10 days	Active: 47% Sham: 22%	Active: 17/35 Sham: 8/32
Berman et al 2000	20	Parallel: L DLPFC (active/sham), 20 Hz, 10 days	Active: 39% Sham: 0.5%	Active: 1 Sham: 0
Eschweiler et al 2000	12	Crossover: L DLPFC (active/sham), 10 Hz, 5 days	Active: 22% Sham: 7%↑	?[6]
George et al 2000a	30	Parallel: L DLPFC (active) 20 Hz/5 Hz, (sham) 20 Hz/5 Hz, 10 days	20 Hz: 26% 5 Hz: 48% Sham: 21%	20 Hz: 3 5 Hz: 6 Sham: 0
Garcia-Toro et al 2001	28	Parallel: L DLPFC (active / sham), 20 Hz, 10 days	Active: 38% Sham: 34%	Active: 4 Sham: 3
Lisanby et al 2001	36	Parallel: L DLPFC (active) 10 Hz, R DLPFC (sham) 1 Hz	L DLPFC: 21% R DLPFC: 20% Sham: 13%	?
Manes et al 2001	20	Parallel: L DLPFC (active/ sham), 20 Hz, 5 days	Active: 37% Sham: 32%	Active: 3 Sham: 3
Dolberg et al 2002	20	Parallel, 10 days	Active: 29% Sham: 17%	?
Padberg et al 2002	30	Parallel: L DLPFC (active) 100% MT[3], 90% MT, (sham) 10 Hz, 10 days	100%: 30% 90%: 15% Sham: 7%	100%: 3 90%: 2 Sham: 0
Loo et al 2003	19	Parallel: Bilateral prefrontal (active/sham), 15 Hz, 15 days	Active: 24% Sham: 21%	Active: 2 Sham: 1
Nahas et al 2003	23	Parallel: L DLPFC (active/sham), 5 Hz, 10 days	Active: 25% Sham: 25%	Active: 4 Sham: 4
Hoppner et al 2003	30	Parallel: L DLPFC (active) 20 Hz, R 1 Hz, (sham) L 20 Hz, 10 days	L 20 Hz: 17% R 1 Hz: 10.5% Sham: 23%	L 20 Hz: 5 R 1 Hz: 3 Sham: 5
Fitzgerald et al 2003	60	Parallel: L DLPFC (active) 10 Hz, R DLPFC 1 Hz, (sham) L 10 Hz/ R 1 Hz, 10 days	MADRSL 10 Hz: 13.5% R 1 Hz: 15% Sham: 0.76%	L 10 Hz: 8 R 1 Hz: 7 Sham: 2
Jorge et al 2004	20	Parallel: L DLPFC (active/ sham) 10 Hz, 10 days	Active: 38% Sham: 13%	Active: 3 Sham: 0
Kauffmann et al 2004	12	Parallel: R DLPFC (active/ sham) 1 Hz, 10 days	Active: 48% Sham: 30%	Active: 4 Sham: 2
Holtzheimer et al 2004	15	Parallel: L DLPFC (active/sham) 10 Hz, 10 days	Active: 32% Sham: 28%	Active: 2 Sham: 1
Mosimann et al 2004	24	Parallel: L DLPFC (active/ sham) 20 Hz, 10 days	Active: 20% Sham: 17%	Active: 4 Sham: 0
Hausmann et al 2004	41	Parallel: L DLPFC (active) 20 Hz, L DLPFC 20 Hz + R DLPFC 1 Hz, (sham) L 20 Hz + R 1 Hz, 10 days	Active (both groups): 30.6% Sham: 24.8%	?
Koerselman et al 2004	55	Parallel: L DLPFC (active/ sham), 20 Hz,10 days	Active: 18.5% Sham: 15.4%	?
Rumi et al 2005	46	Parallel: L DLPFC (active/sham) 5 Hz, 20 days	Active: 57% Sham: 35%	Active: 21 Sham: 11

[1] Hz, frequency of TMS pulses.
[2] days, duration of TMS treatment in sham-controlled period.
[3] % MT, % of subject's resting MT.
[4] Decreases in HDRS (Hamilton 1960) scores except where otherwise indicated.
[5] Defined as ≥ 50% decrease in HDRS from baseline.
[6] information not available.
Abbreviations: L DLPFC, left dorsolateral prefrontal cortex; MADRS, Montgomery Asberg Depression Rating Scale (Montgomery and Asberg 1979); R DLPFC, right dorsolateral prefrontal cortex; TMS, transcranial magnetic stimulation; MT, motor threshold.

published the first trial of rTMS for the treatment of acute mania, randomizing patients to receive high-frequency rTMS to the left or right prefrontal cortices. Right prefrontal stimulation appeared to have an anti-manic effect with 71% mean improvement on the Young Mania Rating Scale (Young et al 1978), whereas left prefrontal stimulation was associated with 29% mean improvement. Taken together with the results of depression trials demonstrating efficacy for high-frequency left prefrontal rTMS, these findings suggest that rTMS to the left and right prefrontal cortices respectively may have opposing effects. In further open studies, Saba et al (2002) and Michael and Erfurth (2004) also reported that rTMS may be a useful add-on treatment to medication in acute mania. However, the only sham-controlled study of rTMS in mania, which used the exact same rTMS parameters as in the study by Grisaru et al (1998a), failed to find any advantage for right prefrontal rTMS over sham (Kapstan et al 2003).

Schizophrenia

Left prefrontal high-frequency rTMS and right prefrontal low-frequency rTMS have also been trialled as treatments in patients with schizophrenia (Cohen et al 1999; Klein et al 1999; Rollnik et al 2000; Hajak et al 2004; Holi et al 2004). Results have shown variable degrees of improvement in positive and negative symptoms and in mood. The inconsistent findings of the sham-controlled studies (Klein et al 1999; Rollnik et al 2000; Hajak et al 2004; Holi et al 2004) can perhaps be partly explained by the effect of interaction in that daily attendance required by the rTMS treatment protocol may have accounted for some of the changes observed, particularly any reduction in negative symptoms.

Some sham-controlled studies have reported that slow TMS over the left auditory cortex can reduce auditory hallucinations (Hoffman et al 2000, 2003; Poulet et al 2005). Others have failed to find any significant effects (McIntosh et al 2004; Schonfeldt-Lecuona et al 2004) despite the use of individual fMRI to specifically identify and target the cortical sites for inner speech production, thought to be involved in the production of hallucinations. Some of the inconsistencies in findings may also be explained by a lack of consensus for rating of auditory hallucinations.

Other psychiatric disorders

There have been preliminary reports examining the use of rTMS in the treatment of other psychiatric disorders such as obsessive-compulsive disorder (OCD) (Sachdev et al 2001a; Alonso et al 2001), post traumatic stress disorder (Grisaru et al 1998; McCann et al 1998a; Cohen et al 2004), and Tourette's syndrome (Chae et al 2004). There have also been reports of high-frequency rTMS exacerbating anxiety and panic (Greenberg et al 1997) and low-frequency rTMS alleviating panic disorder (Zwanzger et al 2002). The role of rTMS in these disorders is at present unclear.

Neurological disorders

TMS has been investigated particularly in patients with Parkinson's disease and epilepsy. In Parkinson's disease, rTMS has been administered in an attempt to treat bradykinesia and improve motor control. During movement, simultaneous stimulation of the motor cortex has been reported to be of no benefit (Ghabra et al 1999) and stimulation of the supplementary motor area has been shown to worsen fine movements (Cunnington et al 1996). Other studies stimulating the PFC have noted modest benefits (Sommer et al 1998; Shinamoto et al 1999; Siebner et al 1999), some researchers suggesting that rTMS can diminish bradykinesia and enhance motor speed (Sommer et al 1998; Siebner et al 1999).

Interestingly, the application of TMS is associated with a measurable risk of seizure induction and yet, paradoxically, it has been found to be relatively safe in patients with epilepsy (Tassinari et al 1990). Indeed, it may in fact be an effective means of reducing seizure activity (Tegaru et al 1999; Menkes and Gruenthal 2000; Werhahn et al 2000), although further research is needed.

Investigational applications of TMS

In cognitive neuroscience TMS has proven to be a versatile and valuable investigational tool, and has been used to examine cortical excitability and various aspects of brain cognition. It has been applied to the motor cortex in humans to examine motor evoked potentials (MEP) and motor threshold (MT). MT is the stimulus intensity required to elicit MEP and in any given individual is relatively constant with interhemispheric differences, but is subject to modulation by drugs and disease.

Paired pulse TMS (ppTMS)

Paired pulse TMS involves the application of a pair of stimuli separated by a variable inter-stimulus interval. The first stimulus is subthreshold whereas the second is above the threshold. Varying the inter-stimulus interval allows modulation of the overall response to the paired stimuli such that response can be facilitated or inhibited. Facilitation can usually be achieved with an inter-stimulus interval

of 10–20 msec, and on either side of this (shorter or longer), inhibition is more likely. Neurochemically, inhibition and facilitation are mediated by gamma-amino butyric acid (GABA) and glutamate respectively.

When a TMS pulse elicits a MEP against a background of voluntary muscle contraction, the background activity is suppressed for a period after the MEP. This "silent period" is considered another measure of inhibitory cortical activity (Pascual-Leone et al 2002a).

Psychiatric disorders

The above TMS testing paradigms have been used to investigate abnormalities in cortical inhibitory and facilitatory processes in the motor cortex of patients with psychiatric disorders (Maeda and Pascual-Leone 2003). In schizophrenia, abnormalities have been reported in the MEP response to single pulse TMS (Abarbanel et al 1996; Puri et al 1996), and in silent period measurements and response to paired pulse stimulation (Daskalakis et al 2001; Fitzgerald et al 2001), suggesting a reduction in cortical inhibitory processes. However, these investigations were mostly done in medicated patients, and alterations in motor cortical functioning in the presence of antipsychotic medication have been demonstrated elsewhere (Ziemann et al 1997; Pascual-Leone et al 2002b).

Several studies have reported increased cortical inhibition (Steele et al 2000) or reduced post-exercise cortical facilitation in depressed subjects (Samii et al 1996; Shajahan et al 1999), though others have reported that the latter findings appeared to be nonspecific, occurring also in patients with mania and schizophrenia (Chroni et al 2002). There are also preliminary reports of abnormalities in motor cortical functioning in OCD (Greenberg et al 2000), and Tourette's syndrome (Ziemann et al 1997).

Cognition

TMS is increasingly being used in neuropsychological investigations (eg, Li et al 2004). During TMS or rTMS, functioning of the stimulated cortical area can be temporarily disrupted, creating in effect a "virtual lesion". This technique can then be applied to examine the cortical sites involved in a particular function and the critical time periods of their involvement (Pascual-Leone et al 1999). For example, rTMS can be used to noninvasively identify the lateralization of verbal functions (Epstein 1998). Studies of the frontal and prefrontal cortex have examined aspects of memory and word generation (Grafman et al 1994; Jahanshahi et al 1998). For example, Devlin et al (2005) have recently demonstrated that TMS-induced interference in the left inferior prefrontal cortex has an effect on semantic but not perceptual processing. TMS can also enhance neuropsychological functioning when administered to specific cortical areas with precise timing, eg, picture naming (Topper et al 1998).

Clearly, this innovative field of research has expanded tremendously with the introduction of TMS as an investigative tool and is an area of research that is likely to yield many new insights into the functioning of the normal and diseased brain.

Overall, TMS remains a useful tool for the investigation of abnormal physiological processes in psychiatric disorders. Further research in larger samples of unmedicated subjects is needed before definitive conclusions can be made.

Adverse effects

TMS has few adverse effects as it is relatively noninvasive. The risks that are associated with its use are determined largely by the number, intensity, and frequency of stimuli applied. Occasionally, rTMS results in a headache that may last several hours. Some subjects complain of scalp discomfort during TMS, attributable to the associated stimulation of muscles and nerves near the coil. Low frequency TMS and ppTMS are unlikely to produce seizures, or have any lasting effects on cognition, but rTMS, by increasing cortical excitability, can precipitate seizures even in healthy subjects, though the risk is very low (Wassermann 1998).

It is important to note that TMS can cause a temporary shift in auditory threshold and to protect patients from this during stimulation a set of precautionary earplugs should be worn (Wassermann 1998).

Vagus nerve stimulation (VNS)

The vagus nerve or the Xth cranial nerve is a mixed nerve, composed predominantly of sensory afferents carrying information from the thorax, abdomen, head, and neck to the brain. Cell bodies of these vagus-sensory afferents lie predominantly in the nodose ganglion and project information primarily to the nucleus tractus solitarius (NTS) as well as the area postrema, the spinal trigeminal nucleus, the medullary reticular formation, the dorsal nucleus of the vagus, and the nucleus ambiguous (Henry 2002). Information is conveyed via these direct projections and by an autonomic feedback loop to the rest of the brain and ascending projections to the forebrain which travel via the parabrachial nucleus and the locus coeruleus. These structures have direct connections with the forebrain, thalamus, hypothalamus, amygdala, and

stria terminalis – regions that are important in the modulation of mood (George et al 1997b; Van Bockstade et al 1999). Vagus nerve projections attend brain regions that are thought to be involved in several neuropsychiatric disorders presenting the potential for VNS to have several important clinical roles in addition to its use in treating epilepsy and depression.

In humans, VNS involves stimulation of the left cervical vagus nerve using a commercial device – the Neuro-Cybernetic Prosthesis (NCP) System (Schacter and Saper 1998). This device comprises a bipolar pulse generator, electrodes, and a programming wand. The generator is implanted in the left chest wall below the clavicle and delivers electrical signals via a bipolar lead to an electrode that is wrapped around the vagus nerve in the neck (see Figure 1b). Implantation usually takes less than an hour and can be conducted under general or local anesthesia (Amar et al 1998). On-line modification and data retrieval are possible as a proprietary instrument is used to program the pulse generator. The latter can be stopped briefly using a hand held magnet but stimulus interruption does not interfere with preprogrammed stimulation which automatically resumes when the magnet is displaced (George et al 2000b).

VNS reduces the excitability of neurons involved in the propagation of seizure activity (Zagon and Kemeny 2000); however, its exact mechanisms of action remain unknown though it is thought to produce slow hyperpolarization. EEG and neuroimaging data, using single photon emission computed tomography, implicate the thalamus (Ring et al 2000; Vonck et al 2000), inhibition of which may prevent the onset or propagation of seizures (Van Laere et al 2000).

Efficacy

To date, the main use of VNS has been to reduce seizure frequency in both adults (Ben-Menachem et al 1994; Handforth et al 1998; Morrow et al 2000; Wakai and Kotagal 2001) and children (Patwardhan et al 2000; Wakai and Katagal 2001) with treatment-resistant epilepsy. Improvements gained appear to be sustained and may continue with time (Salinsky et al 1995; DeGiorgio et al 2000).

Two studies have shown an improvement in mood in epileptic patients receiving VNS compared with controls (Harden et al 1999; Hoppe et al 2001) and such observations have led researchers to hypothesize that it may be effective in treating mood disorders (Harden et al 1999; Elger et al 2000). The fact that it increases central noradrenergic and serotonergic neurotransmission would be in keeping with such a hypothesis (Krahl et al 1998; Jobe et al 1999), and in common with other effective antidepressant therapies it alters limbic system blood flow, involving in particular the cingulate (Henry et al 1999).

Open studies to examine the effects of VNS on mood have been conducted in treatment-resistant depressed patients (Rush et al 2000; Sackeim et al 2001). In a multicenter study, 30 depressed patients (n = 21; nonpsychotic treatment-resistant major depression, n = 4; bipolar, and n = 5 bipolar II) underwent 10 weeks of VNS after which 40% of patients reported having a significant reduction in mood-scale scores (Ham-D and MADRS). These findings were sustained during long-term follow-up (Rush et al 2000). Further preliminary studies (Kosel and Schlaepfer 2003) also suggest that VNS has antidepressant properties; however, there is a need for larger controlled trials and at least one is currently underway (Schlaepfer and Kosel 2004). Several recently published studies provide preliminary support for VNS having an antidepressant role. Firstly, in a multicenter trial Rush et al (2005a) compared the effects of 10 weeks' active as opposed to sham VNS in 222 participants with treatment-resistant depression. They found VNS was linked with greater symptom reduction across measures but the finding did not reach significance and hence could not be considered definitive evidence of its efficacy. This group subsequently published further results of a one-year open trial involving patients who had completed the initial acute phase (Rush et al 2005b). The results from 205 participants in this study revealed statistically significant reduction in depressive symptoms and despite the lack of a control group and nonmasking of ratings, these data seem to support further investigation of VNS as an antidepressant. Finally, George et al (2005) compared the results from the one-year open trial with the results from a comparable treatment-as-usual (TAU) group. The primary analysis in this study yielded a significant difference between the groups favoring VNS plus TAU over TAU alone. The addition of VNS to TAU resulting in improved response supports its role as an antidepressant, although this still requires further investigation.

VNS was initially approved in the US by the FDA for the treatment of epilepsy in 1997 and just recently (July 2005) the VNS therapy system has been approved to treat depressed patients of 18 years and over who have not had a response to four or more trials of an antidepressant (Cyberonics website 2005). It has also been approved for use in the treatment of depression in the EU and Canada. It would be useful to extend VNS trials to include depressed patients other than those who are treatment resistant, in order

to examine its differential efficacy across depressive subtypes and also its effects on cognition (Schacter 2004).

Adverse effects

The adverse effects of VNS are, firstly, those associated with the procedure of implantation and, secondly, those that occur as a consequence of stimulation. Surgical adverse effects include pain, coughing, left-vocal cord paralysis, hoarseness, nausea, and very occasionally infection. Most patients describe these as a moderate inconvenience and the effects are usually transient (Schachter and Saper 1998). Of note, during implantation, there have been no deaths and no reports of serious adverse events such as the alteration of cardiac or pulmonary function. However, transient asystole has occurred in a small number of patients when the stimulator is first activated during in-theatre testing. The most significant stimulation-related adverse effects are those of dyspnea and voice-alteration (Charous et al 2001), which can be reversed by application of the hand-held magnet and prevented by lowering the stimulation current (Schachter and Sapel 1998).

Deep brain stimulation (DBS)

In the management of Parkinson's disease (PD) and other movement disorders DBS is an important treatment that appears to have an additional antidepressant effect without causing any global cognitive deterioration (Funkiewiez et al 2004). In PD, neural degeneration and transmitter deficiencies lead to neural dysfunction and abnormal activity in motor system relays such as the thalamus, the internal segment of the globus pallidus (GPi) (Miller et al 1987), and the subthalamic nucleus (STN) (Wichmann et al 1994), with the last emerging as the most popular target for treatment interventions (Breit et al 2004).

Using implanted quadripolar electrodes connected to a battery-powered pulse-generating device (see Figure 1), DBS delivers an electrical current, the strength of which can be adjusted by varying electrode selection and polarity and by altering frequency, amplitude and pulse-width. In the treatment of PD, parameters that are typically used include a voltage of more than 3 V with a pulsewidth of 60–90 μsec and a frequency of 150–185 Hz (Lozano 2001).

The mechanism of action of DBS, like other physical treatments, is unknown but both clinical and experimental evidence indicate that the frequency of stimulation affects clinical outcome. Breit et al (2004) outline the main hypotheses that account for the benficial effects of high frequency stimulation as follows: the effect is due to depolarization blocking neuronal transmission through inactivation of voltage-dependent ion channels; the jamming of information imposes an efferent stimulation-driven high frequency pattern; stimulation of inhibitory afferents results in synaptic inhibition to the target nucleus; and stimulation induces neurotransmitter depletion, and hence causes synaptic depression. This explanation is corroborated to some extent by animal models of PD in which there is increased basal spontaneous activity in the STN that drives GPi nucleus inhibitory outflow. The outflow in turn inhibits motor systems within the thalamus, brainstem, and cortex and results in the akinesia and bradykinesia of PD (DeLong and Wichmann 2001). Hence the rationale for surgical intervention is to interrupt the excessive inhibition from these nuclei (Lang et al 1999). Electrical stimulation achieves this by producing neuronal inactivation either by direct disruption of neuronal activity or by increasing GABA-mediated inhibitory neurotransmission. Interestingly, the afferents that impinge upon neurones in the GPi nucleus and STN are rich in GABA (see Figure 1c).

Indications for DBS in PD include advanced idiopathic illness with motor complications, tremor, and related disability. With GPi or STN DBS the symptoms of PD can be improved by up to 80% and in many cases the use of concurrent medications can be significantly reduced if not stopped altogether (Limousin et al 1998; Volkmann et al 1998). Vim thalamus DBS has a greater specificity of action and is effective in alleviating the tremor of PD in up to 80% of patients; however, unlike DBS applied to the GPi and STN, it fails to produce significant functional improvement and has few additional benefits (Schuurman et al 2000) such as alleviating motor fluctuations, bradykinesia, gait disturbances, and drug-induced dyskinesias. Not surprisingly, GPi and STN DBS are being increasingly favored and there is now almost no indication for Vim thalamus DBS as these treatments are far superior in effect. The disadvantage of this trend is that speech and cognition are less responsive and some of the problems that patients face can in fact be exacerbated by surgery (Limousin et al 1998).

Efficacy

As a treatment DBS has the advantage of being precise and reversible (Greenberg and Rezai 2003), a clear advance in comparison to neurosurgery for intractable psychiatric disorders (Rees Cosgrove 2004; Kopell et al 2004). Furthermore, the strength of stimulation can be controlled allowing treatment to be adjusted according to individual

needs, which has made it an increasingly popular choice for the treatment of refractory PD.

DBS has also been found to be beneficial in two of three cases of treatment refractory OCD described by Gabriels et al (2003). Aouizerate et al (2004) describe DBS of the ventral caudate nucleus as effective in improving functioning and achieving remission in a patient with intractable severe OCD and concomitant major depression. Lonzano and Hamani (2004) report an increase in the number of applications for DBS, indicating recognition of its potential for treating neuropsychiatric disorders as well as its continued importance in the treatment of movement disorders.

Adverse effects

Predictably, the adverse effects associated with DBS are largely the consequence of surgery as opposed to stimulation. One of the most common side-effects is that of transient confusion; More serious side-effects can also occur although the likelihood is less than 2%. Stimulation is also associated with speech disturbance, paraesthesiae, eye movement difficulties, and motor contractions. Complications can also arise because of device failure; however, this is easily remedied by replacement of the necessary components.

Neurosurgery

Psychosurgery has been "practised" since antiquity involving trephination thought to release "evil spirits". At the beginning of the twentieth century neurosurgery experienced a resurgence of interest; however, the development of psychotropic medications largely eliminated the need for standard prefrontal leucotomy (Freeman and Watts 1942), which was used to "treat" schizophrenia and affective psychoses (Tooth and Newton 1961*)*. However, neurosurgery for mental disorders has survived in modified form and in many parts of the world remains a treatment option for neuropsychiatric illnesses where all other options have been exhausted.

Modern-day neurosurgical procedures, although more refined and sophisticated, continue to target the limbic system and its connections, particularly frontal lobe circuits that involve striatal structures such as the thalamus and caudate (Cummings 1993). Currently, four neurosurgical procedures are performed worldwide namely: cingulotomy, stereotactic subcaudate tractotomy (SST), anterior capsulotomy (AC), and limbic leucotomy (LL) (Malhi et al 1997), with the last in essence combining the lesions of the first two (Kelly et al 1973) (see Figure 1d). The indications, ablative techniques, lesion sites, and targets of these procedures are summarized in Table 2.

It is noteworthy that all three neurosurgical lesions interrupt the interconnecting pathways of the limbic system and the prefrontal cortex, in particular the amygdalofugal pathways and those of the limbic loop, explaining perhaps the overlapping effects of these procedures.

Efficacy

Psychosurgery for psychiatric disorders is almost always considered a treatment of last resort and as a consequence psychiatric patients that undergo surgical procedures are by definition treatment refractory. Nevertheless, in countries where these procedures are available, strict regulations govern the selection and consent of patients to ensure that all reasonable alternatives have been adequately explained (Clinical resource audit group 1996).

In the treatment of OCD, psychosurgery has been reasonably effective with significant improvement in 40%–60% of cases undergoing anterior capsulotomy (Mindus and Nyman 1991; Mindus and Jenike 1992; Rasmussen et al 2000). In comparison, SST has generally been less helpful in OCD, with improvement occurring in only a third of patients (Hodgkiss et al 1994); however, it is effective in mood disorders, with more than a third of patients achieving a good outcome (Hodgkiss et al 1994; Malizia 1994; Poynton et al 1995; Malhi and Bartlett 2000). Recently, the mechanism of action of SST in depression has been investigated (Dalgleish et al 2004), with improvement thought to occur by way of an acquired insensitivity to negative information. This interesting but provocative suggestion warrants further investigation.

In addition to its use in OCD, capsulotomy has also been used to treat refractory social phobia, generalized anxiety disorder, and panic disorder. Long term it appears to produce a notable reduction in anxiety, with 67% of subjects showing significant response (Ruck et al 2003); however, concerns have been raised as to whether the procedure causes frontal lobe dysfunction, which may be masked by seeming improvement.

In contrast to capsulotomy and SST, cingulotomy introduced by Fulton and refined by Ballantine et al (1997) (Mashour et al 2005) has been used almost exclusively to treat OCD with reasonable success in approximately one third of patients (Jennike et al 1991), and because of the conservative nature of the procedure many patients benefit from a second operation to extend the original lesion. However, worsening of obsessionality has also

Table 2 Neurosurgical procedures used in the treatment of neuropsychiatric disorders

Neurosurgical procedure	Indications	Ablative technique	Lesion	Target
Anterior capsulotomy	OCD and anxiety disorders	Gammacapsuolomy (gamma knife focuses 200+ beams of cobalt^{60} gamma radiation upon a designated point)	Anterior limb of internal capsule (between head of caudate nucleus and putamen)	Neuronal tracts connecting thalamus and orbito-frontal cortex
SST	Affective disorders (UP/BP) Anxiety Disorders OCD	Radiofrequency electrocoagulation supplanted yttrium in 1997	White matter beneath and just anterior to the head of the caudate nucleus	Fibres connecting prefrontal cortex and dorsomedial nucleus of thalamus
Cingulotomy	OCD (primarily) and affective/ anxiety disorders	Radiofrequency thermocoagulation	Cingulum (1 cm in width extending 2 cm dorsally from the corpus callosum)	Thalamofrontal neuronal loops

After Knight 1965; Strom-Olsen and Carlisle 1971; Bingley et al 1973; Newcombe 1975; Goktepe et al 1975; Bartlett et al 1977; Alexander et al 1986; Ballantine et al 1987; Meyerson and Mindus 1988; Alexander et al 1990; Jennicke et al 1991; Mindus 1993; Devinsky et al 1993; Ebert and Ebmeier 1996; Marino Junior and Cosgrove 1997; Osview and Frim 1997; Malhi and Barlett 1998.

Abbreviations: BP, bipolar; OCD, obsessive-compulsive disorder; SST, stereotactic subcaudate tractotomy; UP, unipolar.

been described, with one study reporting pre-operative obsessive traits predisposing epileptic patients to develop OCD (Kulaksizoglu et al 2004).

Limbic leucotomy has been less widely used than the other procedures but has been utilized to treat a broad range of symptoms with modest success (treatment response of 36%–50%) in patients with major depression and OCD (Montoya et al 2002).

Adverse effects

All surgery confers some degree of risk and this is particularly true of neurosurgery in as the operation involves structural reorganization of cortical matter. The most common complaints following SST are confusion, a transient lack of sphincter control, and lethargy, with the latter persisting beyond one week in 12% of patients (Malhi et al 1997). These are similar to the adverse effects associated with AC except that no deaths have been reported and documented seizures have been rare. Similarly, cingulotomy has not resulted in any reported deaths, and reports of seizures are scarce; however, it has caused two cases of hemiplegia (Ballantine et al 1987; Marino Junior and Cosgrove 1997).

Despite the relative safety of these procedures, concerns remain about the effects of neurosurgical procedures on personality and behaviour (Happe et al 2001) and there is some evidence to suggest that frontal lobe deficits such as disinihibition, apathy, and cognitive inflexibility have occurred following cingulotomy (Irle et al 1998; Ruck et al 2003). Cumming et al (1995) also found no differences between post-surgical patients and controls on tests of memory and global ability; however, there were deficits present in formation and shifting of set. Bejerot (2003) makes the point that many patients are asked to self-report on symptoms post-operatively and that the validity of information gathered in this context is questionable, especially if patients have compromised frontal lobe function.

Discussion

Limited knowledge of the neuropsychiatric disorders themselves, as well as the mechanisms underpinning physical treatments, continues to hamper growth in this field that is further constrained by a tendency for polarization of opinions in relation to its evidence base and ethics. Thus far, TMS is the only physical treatment that has acquired a firm footing, with studies demonstrating its efficacy in the treatment of depression. Equally valuable is its application into research where it has been used to create "virtual lesions". Its relative noninvasiveness and acceptance by patients have made it a popular therapy.

More invasive treatments such as DBS and VNS offer greater control than neurosurgery by allowing stimulation to be titrated to achieve an optimal response. In some cases the specificity of these interventions makes them preferable to pharmacotherapy which, although more widely acceptable, is relatively blunt as regards site of action and timing of effect. With respect to the latter, DBS produces effects over a matter of milliseconds, in tune with the electrophysiology of the brain. It is therefore potentially capable of mimicking normal physiological function and its use in the management of PD has paved the way for wider application. Initial studies of its efficacy in the treatment of refractory psychiatric illnesses are encouraging. Similarly, the application of VNS has expanded beyond its role as an "anticonvulsant" to studies examining its

antidepressant properties. A recent study indicated 15.5% of patients with treatment-resistant depression achieved sustained remission compared with 4.6% of the participants receiving treatment as usual (George et al 2005). Recently, it has been approved as an antidepressant treatment in the EU and Canada, and this opens up the possibility of its application in a range of psychiatric illnesses including pain syndromes, addictions, and eating disorders.

Somewhat surprisingly neurosurgery has regained popularity as an effective treatment for refractory psychiatric disorders, even though it is still considered only following the failure of traditional methods. Part of the reason for this is its apparent success in a patient population that has a very low rate of placebo response. However, psychosurgical research has been plagued by the lack of standardized nosology and the inherent referral bias, as patients undergoing such procedures are clearly not representative of the respective phenotypes to which they belong. Clearly, the fact that few procedures are performed and they are necessarily invasive limits the prospects of sham-controlled prospective studies. Improvements in technology and surgical techniques with increasing sophistication of instrumentation will likely make such studies possible in the future. However, in the interim research along the lines of Dagliesh et al (2004) has shed light on the specific cognitive processes altered by such procedures and is likely to inspire greater clinical confidence.

Conclusion

In the past decade physical interventions have once again captured the imagination of neuroscientists and clinicians alike. However, in comparison with pharmacological treatments they remain under-researched due to a range of political, economic, and sociological factors. It is also difficult to compare efficacy rates of pharmacologically treated patients with those who receive physical interventions as the characteristics of the two groups vary substantially in terms of resistance, duration of illness, and prior treatment. Despite this, these treatments provide novel insights into the neurobiology of these neuropsychiatric disorders and interventions such as TMS are beginning to establish themselves as viable therapeutic options. However, if history is not to repeat itself, the field has to be cautious in its predictions and claims. Key advances in neuroimaging, for instance, have ensured much better localization and monitoring of the effects of these interventions but the longer-term effects have yet to be determined. In reality, each of the physical treatments described requires much further clinical investigation. Fortunately, this is at last a possibility and many researchers have taken up the challenge. It is hoped that in the coming decade some of these interventions in their modified forms will become more widely accepted as mainstream treatments and benefit the many patients with intractable neuropsychiatric disorders.

References

Abarbanel JM, Lemberg T, Yaroslavski U. 1996. Electrophysiological responses to transcranial magnetic stimulation in depression and schizophrenia. *Biol Psychol*, 40:148–50.

Alexander GE. DeLong MR. Strick PL. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*, 93:57–81.

Alexander GE, Crutcher MD, DeLong MR. 1990. Basal ganglia-thalamocortical circuits; parallel substrates for motor, occulomotor, 'prefrontal' and 'limbic' functions. *Prog Brain Res*, 85:119–46.

Alonso P, Pujol J, Cardoner N. 2001. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*, 158:1143–5.

Amar AP. Heck CN. Levy ML, et al. 1998. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: Rationale, technique, and outcome. *Neurosurgery*, 43: 1265–80.

Aouizerate B, Cuny E, Martin-Guehl C, et al. 2004. Deep brain stimulation of the ventral caudate nucleus in the treatment of OCD and major depression. *J Neurosurg*, 101:682–6.

Ballantine HT, Bouckoms AJ, Thomas EK, et al. 1987. Treatment of psychiatric illness by sterotactic cingulotomy. *Biol Psychiatry*, 22: 807–19.

Bartlett JR, Bridges PK, Sweet WH, et al. 1977. Neurosurgical treatment in psychiatry, pain and epilepsy. Baltimore: University Park Press

Beck AT, Ward CH, Mendelson M, et al. 1961. An inventory for measuring depression. *Arch Gen Psychiatry*, 4 561–71.

Ben-Menachem E. Manon-Espaillat R, Ristanovic R, et al. 1994. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. *Epilepsia*, 35:616–26.

Ben-Shachar D, Belmaker RH, Grisaru N, et al. 1997. Transcranial magnetic stimulation induces alterations in brain monoamines. *J Neural Transm*, 104:191–7.

Berjerot S. 2003. Psychosurgery for obsessive compulsive disorder-concerns reamin. *Acta Psychiatr Scand*, 107:241–3.

Berman R, Narasimhan M, Sanacora G, et al. 2000. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry*, 47:332–7.

Bingley T, Leksell T, Meyerson BA, et al. 1973. Stereotactic anterior capsulotomy in anxiety and compulsive states. In Laitenen LV, Livingstone KE (eds). Surgical approaches in psychiatry. Lancaster: Medical and Technical Publishing Co. p 159–64.

Breit S, Schulz JB, Benabid AL. 2004. Deep brain stimulation. *Cell Tissue Res*, 318:275–88.

Burt T, Lisanby SH, Sackeim HA. 2002. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*, 5:73–103.

Chae JH, Nahas Z, Wassermann E, et al. 2004. A pilot safety study of repetitive transcranial magnetic stimulation (rTMS) in Tourette's syndrome. *Cogn Behav Neurol*, 17:109–17.

Charous SJ, Kempster G, Manders E, et al. 2001. The effect of vagal nerve stimulation on voice. *Laryngoscope*, 111:2028–31.

Chroni E, Lekka NP, Tsoussis I, et al. 2002. Effect of exercise on motor evoked potentials elicited by transcranial magnetic stimulation in psychiatric patients. *J Clin Neurophysiol*, 19:240–4.

Clinical resource audit group (CRAG). 1996. Neurosurgery for mental disorders. Scotland: HMSO.

Cohrs S, Tergau F, Riech S, et al. 1998. High-frequency repetitive transcranial magnetic stimulation delays rapid eye movement sleep. *Neuroreport*, 9:343–9.

Cohen E, Bernardo M, Masana J.1999. Repetitive transcranial magnetic stimulation in the treatment of chroic negative schizophrenia: a pilot study. *J Neurol Neurosurg Pyschiatry*, 67:129–30.

Cohen H, Kaplan Z, Kotler M, et al. 2004. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in post-traumatic stress disorder: A double blind, placebo controlled study. *Am J Psychol*, 161:515–24.

Cohen LG, Roth BJ, Nilsson J, et al. 1990. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. *Electroencephalogr Clin Neurophysiol*, 75:350–7.

Cumming S, Hay P, Lee T, et al. 1995. Neuropsychological outcome from psychosurgery for obsessive –compulsive disorder. *Aust N Z J Psychiatry*, 29:293–8.

Cummings JL. 1993. Frontal-subcortical circuits and human beahviour. *Arch Neurol*, 50:873–80.

Cunnington R, Iansek R, Thickbroom GW. 1996. Effects of magnetic stimulation over supplementary motor area on movement in Parkinson's disease. *Brain*, 119:815–22.

Cyberonics website. 2005. Accessed 9 September 2005. URL: http://www.cyberonics.com.

Dalgleish T, Yiend J, Bramham J, et al. 2004. Neuropsychological processing associated with recovery from depression after stereo tactic subcaudte tractotomy. *Am J Psychiatry*, 161:1913–6.

Daskalakis ZJ, Kapur S, Christensen BK, et al. 2001. Direct demonstration of cortical inhibition in schizophrenia using TMS. *Schizophr Res*, 49s:200–1.

Degiorgio CM, Schachter SC, Handforth A, et al. 2000. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia*, 41:1195–200.

DeLong MR. Wichmann T. 2001. Deep brain stimulation for Parkinson's disease. *Ann Neurol*, 49:142–3.

Devinsky O, Luciano D, Vogt BA, et al. 1993. Neurobiology of cingulate cortex and limbic thalamus. Boston: Birkhauser.

Devlin JT, Rushworth MF, Matthews PM. 2005. Category-related activation for written words in the posterior fusiform is task specific. *Neuropsychologica*, 43:69–74.

Dolberg OT, Dannon PN, Schreiber S, et al. 2002. Magnetic motor threshold and response to TMS in major depressive disorder. *Acta Psychiatr Scand*, 106:220–3.

Dolberg O, Schreiberg S, Grunhaus L. 2001. Transcranial magnetic stimulation-induced switch into mania: a report of two cases. *Biol Psychiatry*, 49:468–70.

Ebert D, Ebmeier KP. 1996. The role of the cingulated gyrus in depression: from functional anatomy to neurochemistry. *Biol Psychiatry*, 39:1044–50.

Elger G. Hoppe C. Falkai P, et al. 2000. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res*, 42:203–10.

Eschweiler G, Wegerer C, Schlotter W, et al. 2000. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Res*, 99:161–72.

Fitzgerald PB, Brown TL, Daskalakis ZJ, et al. 2002. A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. *Psychiatry Res*, 114:11–22.

Fitzgerald PB, Brown TL, Marston NA et al. 2003. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*, 60:1002–8.

Freeman W, Watts JW. 1942. Psychosurgery. Springfield: Charles C Thomas.

Funkiewiez A, Ardouin C, Caputo E, et al. 2004. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 75:834–9.

Gabriels L, Cosyns P, Nuttlin B. et al. 2003. Deep brain stimulation for treatment refractory obsessive compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr Scand*, 107:275–82.

Garcia-Toro M. 1999. Acute manic symptomatology during repetitive transcranial magnetic stimulation in a patient with bipolar depression. *Br J Psychiatry*, 175:491.

Garcia-Toro M, Mayol A, Arnillas H, 2001. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *J Affect Disord*, 64:271–5.

George MS, Wassermann EM, Williams W, et al. 1995. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport*, 6:1853–6.

George MS, Wassermann EM, Williams W, et al. 1997. Mood improvements following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression. A placebo-controlled crossover trial. *Am J Psychol*, 154:1752–1756.

George M, Nahas Z, Molloy MA, et al. 2000a. controlled trial of daily left prefrontal cortex TMS for treating depression. *Biol Psychiatry*, 48:962–70.

George MS, Nahas Z, Bohning DE, et al. 2000b. Vagus nerve stimulation: A new form of therapeutic brain stimulation. *CNS Spectr*, 5:43–52.

George MS, Rush AJ, Marangell LB, et al. 2005. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*, 58:364–73.

Ghabra MB, Hallett M, Wassermann EM. 1999. Simultaneous repetitive transcranial magnetic stimulation does not speed fine movement in PD. *Neurology*, 52:768–70.

Goktepe EO, Young LB, Bridges PK. 1975. A further review of the results of stereoactic subcaudate tractotomy. *Br J Psychiatry*, 126:270–80.

Grafman J, Pasual-Leone A, Alway D, et al. 1994. Induction of a recall deficit by rapid-rate transcranial magnetic stimulation. *Neuroreport*, 5:2517–20.

Greenberg BD, George MS, Martin JD, et al. 1997. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry*, 154:867–9.

Greenberg BD, Rezai AR. 2003. Mechanisms and the current state of deep brain stimulation in neuropsychiatry. *CNS Spectr*, 8:522–6.

Greenberg BD, Ziemann U, Cora-Locatelli G, et al. 2000. Altered cortical excitability in obsessive compulsive disorder. *Neurology*, 54:142–7.

Grisaru N, Amir M, Cohen H, et al. 1998a. Effect of transcranial magetic stimulation in posttraumatic stress disorder: a preliminary study. *Biol Psychiatry*, 44:52–5.

Grisaru N, Chudakov B, Yaroslavsky Y, et al. 1998b. TMS in mania. A controlled study. *Am J Psychiatry*, 155:1608–10.

Grunhaus L, Dannon P, Schreiber S, et al. 2000. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry*, 47:314–24.

Grunhaus L, Shcriber S, Dolberg O, et al. 2003. A randomised controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry*, 53:324–31.

Hajak G, Marienhagen J, Langguth B, et al. 2004. High-frequency repetitive transcranial magnetic stimulation in schizophrenia: a combined treatment and neuroimaging study. *Psychol Med*, 34:1157–63.

Hamilton M. 1960. A rating scale for depression. *J Neurol Neurosurg Psychiatry*, 23:56–62.

Handforth A, DeGiorgio CM, Schachter SC, et al. 1998. Vagus nerve stimulation theapy for partial-onset seizures: A randomized active control trial. *Neurology*, 51:48–55.

Happe F, Malhi GS, Checkley S. 2001. Acquire mind-blindness following frontal lobe surgery? A single case study of impaired 'theory of mind'. *Neuropsychologia*, 39:83–90.

Harden CL, Pulver MC, Nikolov B, et al. 1999. Effect of vagus nerve stimulation on mood in adult epilepsy patients. *Neurolog*y, 52(Suppl 2):A238–P03122.

Hausmann A, Kemmler G, Walpoth M, et al. 2004b. No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add on" trial. *J Neurol Neurosurg Psychiatry*, 75:320–2.

Hausmann A, Kramer-Reinstadler K, Lechner-Schoner T, et al. 2004b. Can bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) induce mania? A case report. *J Clin Psychiatry*, 65:1575–6.

Henry TR, Votaw JR, Pennell PB, et al. 1999. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology*, 52:1166–73.

Henry TR. 2002. Therapeutic mechanisms of vagus nerve stimulation. *Neurology*, 59(Suppl 4):S3–14.

Hodgkiss AD, Malizia AL, Bartlett JR, Bridges PK. 1994, Outcome after the physiological operation of stereotactic subcaudate tractotomy. *J Neuropsychiatr*, 7:230–4.

Hoffman RE, Boutros NN, Hu S, et al. 2000. Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. *Lancet*, 355:1073–5.

Hoffman RE, Hawkins KA, Gueorguieva R, et al. 2003. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Arch Gen Psychiatry*, 60:49–56.

Holi MM, Eronen M, Toivonen K, et al. 2004. Left prefrontal repetitive transcranial magnetic stimulation in schizophrenia. *Schizophr Bull*, 30:429–34.

Holtzheimer PE, Avery D, Schlaepfer TE. 2004. Antidepressant effects of repetitive transcranial magnetic stimulation. *Br J Psychiatry*, 184:541–2.

Hoppe C, Helmstaedter C, Scherrmann J, et al. 2001. Self reported mood changes following 6 months of vagus nerve stimulation in epilepsy pateitns. *Epilepsy Behav*, 2:335–42.

Hoppner J, Schulz M, Irmisch G, et al. 2003. Antidepressant efficacy of two different rTMS procedures. High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. *Eur Arch Psychiatry Clin Neurosci*, 253:103–9.

Irle E, Exner C, Thielen K, et al. 1998. Obsessive-compulsive disorder and ventromedial frontal lesions: clinical and neuropsychological findings. *Am J Psychiatry*, 155:255–63.

Jahanshahi M, Profice P, Brown RG, et al. 1998. The effects of transcranial magnetic stimulation over the dorsolateral prefrontal cortex on suppression of habitual counting during random number generation. *Brain*, 121:1533–44.

Janicak PG, Dowd SM, Martis B, et al. 2002. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry*, 51:659–67.

Jennike MA, Baer L, Ballantine HT et al. 1991. Cingulatomy for refractory obsessive-compulsive disorder. A long-term follow-up of 33 patients. *Arch Gen Psychiatry*, 48:548–52.

Jobe PC. Dailey JW. Wernicke JF. 1999. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Crit Rev Neurobiol*, 13:317–56.

Jorge RE, Robinson RG, Tateno A, et al. 2004. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry*, 55:398–405.

Kaptsan A, Yaroslavsky Y, Applebaum J, et al. 2003. Right prefrontal TMS versus sham treatment of mania: a controlled study. *Bipolar Disord*, 5:36–9.

Kauffmann CD, Cheema MA, Miller BE. 2004. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depress Anxiety*, 19:59–62.

Keck M, Welt T, Post A, et al. 2001. Neuroendocrine and behavioural effects of repetitive transcranial magnetic stimulation in a psychopathological animal model are suggestive of antidepressant-like effects. *Neuropsychopharmacology*, 24:337–49.

Kelly D, Richardson A, Mitchell-Heggs NA. 1973. Sterotactic limbic tractotomy: neuropsychological aspects and operative technique. *Br J Psychiatry*, 123:133–40.

Klein E, Kreinin I, Chistyakov A, et al. 1999. Therapeutic efficiency of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double blind controlled trial. *Arch Gen Pyschiatry*, 56:315–20.

Knight G. 1965. Sterotactic tractotomy in the surgical treatment of mental illness. *J Neurol Neurosurg Psychiatry*, 28:304–10.

Koerselman F, Laman DM, van Duijn H, et al. 2004. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *J Clin Psychiatry*, 65:1323–8.

Kopell BH, Greenberg B, Rezai AR. 2004. Deep brain stimulation for psychiatric disorders. *J Clin Neurophysiol*, 21:51–67.

Kosel M, Schapefler TE. 2003. Beyond the treatment of epilepsy: New applications of vagus nerve stimulation in Psychiatry. *CNS Spect*, 8:515–521.

Krahl SE, Clark KB, Smith DC, et al. 1998. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia*, 39:709–14.

Kulaksizoglu IB, Bebek N, Baykan B, et al. 2004. Obsessive compulsive disorder after epilepsy surgery. *Epilepsy Behav*, 5:113–18.

Lang AE, Lozano AM, Montgomery E, et al. 1997. Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med*, 337:1036–42.

Lang AE. Duff J. Saint-Cyr JA. Trepanier L, et al. 1999. Posteroventral medial pallidotomy in Parkinson's disease. *J Neurol*, S246:II28–II41.

Levkovitz Y, Ng M. 2001. Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. *Neuropsychopharmacology*, 24:608–16.

Li X, Nahas Z, Perry Anderson RN, et al. 2004. Can left frontal rTMS be used as a maintenance treatment for bipolar depression? *Depress Anxiety*, 20:98–100.

Limousin P, Krack P, Pollak P. 1998. Electrical stimulation of the subthalamic nucleus in advance Parkinson's disease. *N Engl J Med*, 339:1105–11.

Lisanby S, Belmaker R. 2000. Animal models of the mechanisms of action of repetitive transcranial magnetic simulation (RTMS): comparisons with electroconvulsive shock (ECS). *Depress Anxiety*, 12:178–87.

Lisanby H, Pascual-Leone A, Sampson S, et al. 2001. Augmentation of sertraline antidepressant treatment with transcranial magnetic stimulation. *Biol Psychiatry*, 49:81S.

Loo C, Mitchell P, Croker V. et al. 2003. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychol Med*, 33:33–40.

Loo C, Mitchell P, Sachdev P, et al. 1999. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry*, 156:946–8.

Lozano AM. 2001. Deep brain stimulation for Parkinson's disease. *Parkinsonism Relat Disord*, 7:199–203.

Lozano AM, Hamani C. 2004. The future of deep brain stimulation. *J Clin Neurophysiol*, 21:68–9.

McCann UD, Kimbrell TA, Morgan CM. 1998. Repetitive transcranial magentic stimulation for posttraumatic stress disorder. *Arch Gen Psychiatry*, 55:276–8.

McIntosh AM, Semple D, Tasker K, et al. 2004. Transcranial magnetic stimulation for auditory hallucinations in schizophrenia. *Psychiatry Res*, 127:9–17.

Maeda F, Pascual-Leone A. 2003. Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders. *Psychopharmacology*, 168:359–76.

Malhi GS, Bartlett JR. 1998. A new lesion for the psychosurgical operation of stereotactic subcaudate tractotomy (SST). *Br J Neurosurg*, 12:335.

Malhi GS, Bartlett JR. 2000. Depression: A role for neurosurgery? *Br J Neurosurg*, 14:415–23.

Malhi GS, Bridges PK, Malizia AL. 1997. Neurosurgery for mental disorders (NMD): a clinical worldwide perspective: past, present and future. *Int J Psychiatr Clin Pract*, 1:119–29.

Malizia AL. 1994. Stereotactic subcaudate tractotomy in the management of severe psychiatric disorders. In Sensky T et al (eds). Psychiatry in Europe, directions and developments. London: Gaskell. p 85–94.

Manes F, Jorge R, Morcuende M, et al. 2001. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *Int Psychogeriatr*, 13:225–31.

Marino Junior R, Cosgrove GR. 1997. Neurosurgical treatment of neuropsychiatric illness. *Psychiatr Clin N Am*, 20:933–43.

Martin, JLR, Barabanoj MJ, Scalaepfler TE, et al. 2003. Repetitive transcranial magnetic stimulation for the treatment of depression: Systematic review and meta-analysis. *Br J Psychiatry*, 182:480–91.

Mashour GA, Walker EE, Martuza RL. 2005. Psychosurgery: past, present and future. *Brain Res Brain Res Rev*, 48:409–19.

Menkes DL, Gruenthal M. 2000. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. *Epilepsia*, 41:240–2.

Meyerson BA, Mindus P. 1988. The role of the anterior interior capsulotomy in psychiatric surgery. In Lundsford LD (ed). Modern stereotactic neurosurgery. Boston: Martinus.

Michael N, Erfurth A. 2004. Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. *J Affect Disord*, 78:253–7.

Miller R. 1987. The time course of neuroleptic therapy for psychosis: role of learning processes and implications for concepts of psychotic illness. *Psychopharmacol*, 92:405–15.

Mindus P. 1993. Present-day indications for capsulotomy. *Acta Neurochir*, 58(Suppl): 29–33.

Mindus P. Jenike MA. 1992. Neurosurgical treatment of malignant obsessive compulsive disorder. *Psychiatr Clin North Am*, 15:921–38.

Mindus P. Nyman H. 1991. Normalization of personality characteristics in patients with incapacitating anxiety disorders after capsulotomy. *Acta Psychiatr Scand*, 83:283–91.

Montgomery SA. Asberg M. 1979. A new depression scale designed to be sensitive to change. *Br J Psychiatry*, 134:382–9.

Montoya A, Weiss AP, Price BH et al. 2002. MRI guided stereotactic limbic leucotomy for treatment of intractable psychiatric disease. *Neurosurgery*, 50:1043–9.

Morales O, Sackeim H, Berman R, et al. 2004. Magnetic seizure therapy: development of a novel intervention for treatment resistant depression. *Clinical Neuroscience Research*, 4:59–70.

Morrow JI, Bingham E, Craig JJ, et al. 2000. Vagal nerve stimulation in patients with refractory epilepsy. Effect on seizure frequency, severity and quality of life. *Seizure*, 9:442–5.

Mosimann UP, Schmitt W, Greenberg BD, et al. 2004. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Res*, 126:123–33.

Nahas Z, Kozel FA, Li X, et al. 2003. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord*, 5:40–7.

Newcombe R. 1975. The lesion in stereotactic subcaudate tractotomy. *Br J Psychiatry*,126:478–81.

Osview F, Frim DM. 1997. Neurosurgery for psychiatric disorders. *J Neurol Neurosurg Psychiatry*, 63:701–5.

Padberg F, Zwanzger P, Keck ME, et al. 2002. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology*, 27:638–45.

Padberg F, Zwanzger P, Thoma H, et al. 1999. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res*, 88:163–71.

Pascual-Leone A, Davey NJ, Rothwell J, et al. 2002a. Handbook of transcranial magnetic stimulation. London: Arnold.

Pascual-Leone A, Manoach DS, Birnbaum R, et al. 2002b. Motor cortical excitability in schizophrenia. *Biol Psychiatry*, 52:24–31.

Pascual-Leone A, Rubio B, Pallardo F et al. 1996. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet*, 348:233–7.

Pascual-Leone A, Bartres-Faz D, Keenan JP. 1999. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. *Philos Trans R Soc Lond B Biol Sci*, 354: 1229–38.

Patwardhan RV, Stong B, Bebin EM, et al. 2000. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. *Neurosurgery*, 47:1353–8.

Poulet E, Brunelin J, Bediou B, et al. 2005. Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. *Biol Psychiatry*, 57:188–91.

Poynton AM, Kartsounis LD, Bridges PK. 1995. A prospective clinical study of stereotactic subcaudate tractotomy. *Psychol Med*, 25:763–70.

Pridmore S. 1999. Rapid transcranial magnetic stimulation (rTMS) and normalization of the dexamethasone suppression test (DST). *Psychiatry Clin Neurosci*, 53:33–7.

Pridmore S, Bruno R, Turnier-Shea Y, et al. 2000. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol*, 3:129–34.

Puri BK, Davey NJ, Ellaway PH. et al. 1996. An investigation of motor function in schizophrenia using transcranial magnetic stimulation of the motor cortex. *Br J Psychiatry*, 169:690–5.

Rasmussen S, Greenberg B, Mindus P, et al. 2000. Neurosurgical approaches to intractable obsessive-compulsive disorder. *CNS Spect*, 5:23–34.

Rees Cosgrove G. 2004. Deep brain stimulation and psychosurgery. *J Neurosurg*, 101:574–6.

Ring HA, White S, Costa DC, et al. 2000. A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy. *Seizure*, 9:380–4.

Roth BJ, Cohen LG, Hallett M. 1991. The electrical field induced during magnetic stimulation, magnetic motor stimulation. In Lecy WJ, Cracco RQ, Barker AT, et al (eds). Basic principles and clinical experience (EEG Suppl 43). Amsterdam: Elsevier. p 268–78.

Rollnik JD, Huber TJ, Mogk H, et al. 2000. High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients. *Neuroreport*, 11:4013–15.

Ruck C, Andreewitch S, Flyckt K, et al. 2003. Capsulotomy for treatment refractory anxiety disorders: long term follow up of 26 patients. *Am J Psychiatry*, 160:513–21.

Rumi DO, Gattaz WF, Rigonatti SP, et al. 2005. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry*, 57:162–6.

Rush AJ, George MS, Sackeim HA, et al. 2000. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry*, 47:276–86.

Rush AJ, Marangell LB, Sackeim HA, et al. 2005a. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*, 58:347–54.

Rush AJ, Sackeim HA, Marangell LB et al. 2005b. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*, 58:355–63.

Saba G, Rocamora JF, Kalalou K, et al. 2002. Catatonia and transcranial magnetic stimulation. *Am J Psychiatry*, 159:1794.

Sachdev P, McBride R, Loo C, et al. 2001a. Right vs. left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. *J Clin Psychiatry*, 62:981–4.

Sakkas P, Mihalopoulou P, Mourtzouhou P, et al. 2003. Induction of mania by rTMS: report of two cases. *Eur Psychiatry*, 18:196–8.

Salinsky MC, George R, Sonnen A, et al. 1995. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology*, 45:224–30.

Samii A, Wassermann EM, Ikoma K, et al. 1996. Decreased postexercise faciliatation of motor evoked potentials in patients with chronic fatigue syndrome or depression. *Neurology*, 47:1410–14.

Schachter SC, Saper CB. 1998. Vagus nerve stimulation. *Epilepsia*, 39:677–86.

Schachter SC. 2004. Vagus nerve stimulation:mood and cognitive effects. *Epilepsy Behav*, 5:S56–9.

Schlaepfer T, Kosel M. 2004. Novel physical treatments for major depression, transcranial magenetic stimulation and magnetic seizure therapy. *Curr Opin Psychiatry*, 17:15–20.

Schuurman PR, Bosch DA, Bossuyt PMM, et al. 2000. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med*, 342:461–8.

Schonfeldt-Lecuona C, Gron G, Walter H, et al. 2004. Stereotaxic rTMS for the treatment of auditory hallucinations in schizophrenia. *Neuroreport*, 15:1669–73.

Shajahan PM, Glabus MF, Gooding PA, et al. 1999. Reduced cortical excitability in depression. Impaired postexercise motor facilitation with transcranial magnetic stimulation. *Br J Psychiatry*, 174:449–54.

Shimamoto H, Morimitsu H, Sugita S, et al. 1999. Therapeutic effect of repetitive transcranial megnatic stimulation in Parkinson's disease. *Rinsho Shinkeigaku*, 39:1264–7.

Siebner HR, Mentschel C, Auer C, et al. 1999. Repetitive transcranial megnetic stimulation has a benficial effect on bradykinesia in Parkinson's disease. *Neuroreport*, 10:589–94.

Sommer M, Kamm T, Tergau F. 1998. Beneficial effects of repetitive transcranial megnetic stimulation (rTMS) on fine motor control in Parkinson's disease. *Mov Disord*, 13(Suppl 2):298.

Strom-Olsen R, Carlisle S.1971. Bifrontal sterotactic tractotomy: a follow-up of its effects on 210 patients. *Br J Psychiatry*, 118:141–54.

Steele JD, Glabus MF, Shajahan PM, et al. 2000. Increased cortical inhibition in depression: a prolonged silent period with transcranial magnetic stimulation (TMS). *Psychol Med*, 30 565–70.

Su TP, Huang CC, Wei IH. 2005. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *J Clin Psychiatry*, 66:930–7.

Tassinari CA, Michelucci R, Forti A.1990. Transcranial magnetic stimulation in epileptic patients: usefulness and safety. *Neurology*, 40:1132–3.

Tooth, GC, Newton MP. 1961. Leucotomy in England and Wales 1942-1954. Reports on Public Health and Medical Subjects. London: HMSO.

Topper R, Mottaghy FM, Brugmann M, et al. 1998. Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. *Exp Brain Res*, 121:371–8.

Van Bockstaele EJ, Peoples J, Valentino RJ. 1999. Anatomic basis for differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. *Biol Psychiatry*, 46:1352–63.

Van Laere K, Vonck K, Boon P, et al. 2000. Vagus nerve stimulation in refractory epilepsy: SPECT activation study. *J Nucl Med*, 41:1145–54.

Volkmann J, Sturm V, Freund H-J. 1998. High-frequency deep brain stimulation for the treatment of movement disorders. *Aktuelle Neurologie*, 25:288–96.

Vonck K, Boon P, Van Laere K, et al. 2000. Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. *Epilepsia*, 41:601–9.

Wakai S. Kotagal P. 2001. Vagus nerve stimulation for children and adolescents with intractable epilepsies. *Pediatr Int*, 43:61–5.

Wasserman EM. 1998. Risk and safety of repetitive transcranial magnetic stimulation. Report and suggested guidelines from the International Workshop in the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7. *Electroencephofr Clin Neurophysiol*, 108:1–16.

Werhahn KJ, Lieber J, Classen J, et al. 2000. Motor excitability in patients with focal epilepsy. *Epilepsy Res*, 41:179–89.

Wichmann T, Bergman H, DeLong MR. 1994. The primate subthalamic nucleus. III. Changes in motor behaviour and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. *J Neurophysiol*, 72:521–30.

Young RC, Biggs, JT, Ziegler VE, et al. 1978. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*, 133:429–35.

Zagon A. Kemeny AA. 2000. Slow hyperpolarization in cortical neurons: A possible mechanism behind vagus nerve simulation therapy for refractory epilepsy? *Epilepsia*, 41:1382–9.

Zald DH, Kim SW. 1996. Anatomy and function of the orbital frontal cortex, II: function and relevance to obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*, 82:49–61.

Ziemann U, Winter M, Reimers CD, et al. 1997. Impaired motor cortex inhibition in patients with amyotrophic lateral sclerosis. Evidence from paired transcranial magnetic stimulation. *Neurology*, 49:1292–8.

Zwanzger P, Minov C, Ella R, et al. 2002. Transcranial magnetic stimulation for panic. *Am J Psychiatry*, 159:315–6.