# Technology Insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS

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## SUMMARY

**In neurology, as in all branches of medicine, symptoms of disease and the resulting burden of illness and disability are not simply the consequence of the injury, inflammation or dysfunction of a given organ; they also reflect the consequences of the nervous system's attempt to adapt to the insult. This plastic response includes compensatory changes that prove adaptive for the individual, as well as changes that contribute to functional disability and are, therefore, maladaptive. In this context, brain stimulation techniques tailored to modulate individual plastic changes associated with neurological diseases might enhance clinical benefits and minimize adverse effects. In this Review, we discuss the use of two noninvasive brain stimulation techniques—repetitive transcranial magnetic stimulation and transcranial direct current stimulation—to modulate activity in the targeted cortex or in a dysfunctional network, to restore an adaptive equilibrium in a disrupted network for best behavioral outcome, and to suppress plastic changes for functional advantage. We review randomized controlled studies, in focal epilepsy, Parkinson's disease, recovery from stroke, and chronic pain, to illustrate these principles, and we present evidence for the clinical effects of these two techniques.**

**KEYWORDS epilepsy, noninvasive brain stimulation, pain, Parkinson's disease, stroke**

### REVIEW CRITERIA

PubMed was searched for articles published from January 1985 to December 2006, including electronic early release publications. Search terms included "transcranial magnetic stimulation", "transcranial direct current stimulation" and "brain polarization", with "stroke", "epilepsy", "pain" or "Parkinson's disease". The abstracts of retrieved citations were reviewed and prioritized by relevant content. Full articles were obtained and references were checked for additional material when appropriate. We included randomized, double-blind, sham-controlled therapeutic trials with results published in English.

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**Received** 12 February 2007 **Accepted** 13 April 2007

www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0530

## INTRODUCTION

Neurological disorders are not simply the direct result of an initial insult, but also represent the consequences of dynamic, plastic changes in distributed neural networks as the entire nervous system attempts to adapt. This plastic response includes compensatory changes that prove adaptive for the individual, as well as changes that contribute to functional disability and are consequently maladaptive. With this in mind, an ideal therapy should be tailored to the individual and based on detailed knowledge of the pathophysiology of the specific patient's condition, underlying disease, and degree of disability. Such a therapy should selectively target the specific nervous system dysfunction, be associated with minimal or no adverse effects, take into account the patient's cultural and psychological attitudes, be highly effective, and be financially and practically feasible for use in clinical practice.

Despite major advances over the past few decades, current neurological treatments, especially pharmacologic treatments, have significant limitations, such as nonspecific effects, insufficient tailoring to the individual, and moderate to severe adverse effects. Other treatments, such as physical or behavioral therapy, depend to a large extent on the expertise of the therapist and the patient's cooperation. Also, the mechanisms of action of current treatments are not sufficiently well known, so deleterious effects could be inadvertently induced. Brain stimulation techniques have the theoretical appeal of being able to specifically and selectively enhance adaptive patterns of activity, suppress maladaptive patterns of activity, and restore equilibrium in imbalanced neural networks—particularly if they are guided by neuroimaging and neurophysiologic measures of a patient's pathophysiology and of the impact of stimulation on the patient's brain. Deep brain stimulation and cortical stimulation by implanted epidural or subdural electrodes have become established therapies for certain indications, such as pain and Parkinson's disease (PD),[1,2] and are being

explored for other conditions, such as stroke and epilepsy.

Other approaches, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), are appealing because of their noninvasive characters. Evidence of efficacy, necessary for these techniques to be used in clinical practice, is currently insufficient, but a growing number of proof-of-principle and pilot studies have revealed that rTMS and tDCS are associated with only mild adverse effects, and might offer clinical benefits in neurology.

In this Review, we focus on noninvasive brain stimulation in four main areas of neurology: pain, hand motor deficits after stroke, PD, and focal epilepsy. We provide a comprehensive overview of the underlying principles, and present examples illustrating the potential of noninvasive brain stimulation in neurological therapeutics.

## HISTORICAL NOTES AND BASIC MECHANISMS OF ACTION

The concept of using noninvasive electrical stimulation to treat neurological disease dates back at least as far as the earliest documentation of the practice of medicine. *De Compositionibus Medicamentorum,* by Scribonius Largus, a detailed collection of drug compounds and recipes used by physicians around AD 47–48, includes reference to the use of electrical currents to treat headaches and pain through the application of electric torpedo fish to the affected regions or through placement of painful extremities into a pool of water containing torpedo fish. The resulting electric shocks presumably stunned the peripheral skin receptors, or affected spinal or brain structures, inducing numbness and an associated transient period of pain relief. This might be considered a very early use of transcutaneous electrical nerve stimulation for therapeutic purposes.

In the 1960s, researchers began systematic investigation of noninvasive brain stimulation with the use of weak direct currents applied directly to the exposed cortices of animals. They demonstrated controllable effects on the spontaneous activities and evoked responses of neurons.[3,4] In recent years, it has become apparent that tDCS can influence cortical activity in humans in a manner similar to that seen in these pioneering experiments.[5,6] During tDCS, low-amplitude direct currents are applied via scalp electrodes, and these currents penetrate the skull to enter the brain. Although there is substantial shunting of current in the scalp, two recent modeling studies have shown that sufficient current penetrates the brain to modify neuronal transmembrane potentials, thereby influencing the levels of excitability and modulating the firing rates of individual neurons.[7,8] When tDCS is applied for a sufficient duration, cortical function can remain altered beyond the stimulation period.[9]

Electromagnetic brain stimulation was first investigated in the late 19$^{th}$ century.[10] It was not until the mid-1980s, however, that Barker and colleagues introduced transcranial magnetic stimulation (TMS),[11] having solved the technical challenges involved in bridging the scalp and skull with a magnetic field pulse of sufficient strength and rapid enough change over time. TMS is a neurostimulatory and neuromodulatory application, whereas tDCS is a purely neuromodulatory intervention. TMS uses the principle of electromagnetic induction to focus induced currents in the brain.[12] Single pulses of current can be of sufficient magnitude to depolarize neurons transiently, but when these currents are applied repetitively—an approach known as rTMS—they can modulate cortical excitability, decreasing or increasing it depending on the parameters of stimulation, beyond the duration of the train of stimulation.[13]

## CHRONIC PAIN

### Rationale

Although the mechanisms underlying chronic pain are still unclear, recent evidence indicates that it is associated with maladaptive plastic changes in the CNS and PNS.[14] At the peripheral level, neurogenic inflammation leads to changes in the physiology of the peripheral receptors, a process referred to as sensitization.[15] At the central level, various areas, including thalamic nuclei and limbic and cortical regions (such as the parietal, sensorimotor and insular regions), are believed to contribute to a state of central overactivation.[16–18] In this scenario, treatments aiming to modulate specific involved structures in the CNS might be advantageous. Studies that used deep brain stimulation[19,20] and epidural motor cortex stimulation[21,22] have indicated the potential therapeutic utility of noninvasive motor cortex stimulation. Upregulation of motor cortex excitability might modulate pain perception through indirect effects via neural networks on pain-modulating areas, such as thalamic nuclei (Figure 1). Neuroimaging research has

shown that stimulation of the motor cortex with epidural electrodes changes activity in thalamic and subthalamic nuclei.[21,23,24]

### Clinical experience

To date, results of 14 randomized, sham-controlled, clinical trials evaluating the effects of rTMS (12 studies) and tDCS (2 studies) for the treatment of chronic pain have been published (see Supplementary Table 1 online).[14] Overall, rTMS seems to be effective, with mean pain relief in the range of 20–45%.[25–27] The outcome of rTMS is somewhat heterogeneous, however, as negative results have been reported.[28] These negative results might have been related to the study design (i.e. evaluation of rTMS as a predictor of the effects of epidural stimulation).[28] Although only two studies have evaluated the effects of tDCS on chronic pain, they have shown even greater efficacy, with mean pain relief up to 58%.[29,30]

### Outstanding questions

Many issues require further study. First, a systematic exploration of the efficacy of stimulation of other, nonsensorimotor, cortical targets should be conducted. For example, stimulation of the prefrontal cortex seems to modify pain sensation,[31] and might hold therapeutic promise. Second, the timing of the brain stimulation might be critical, in that early stimulation, during the development of the pain syndrome, might prevent the development of maladaptive plastic changes that sustain chronic pain. Third, the interaction of brain stimulation with concurrent opioids or other analgesic medications needs to be carefully evaluated. Last, brain stimulation might be useful to control acute pain by suppressing secondary processes of pain amplification and might even offer a novel approach to anesthesia as shown in a recent study.[32]

## HAND MOTOR FUNCTION AFTER STROKE

### Rationale

After stroke, there are multifocal, bihemispheric changes in brain activity (Figure 2), some of which, rather than being functionally advantageous, might be maladaptive and impair recovery.[33,34] A number of lines of evidence converge on the conclusion that activation of the motor cortex is of paramount importance to motor recovery. Anatomically, this region is the main contributor of fibers to the pyramidal tract,[35] which is crucial for generating rapid, distal or fractionated movements.[36] Greater stroke-related injury to the

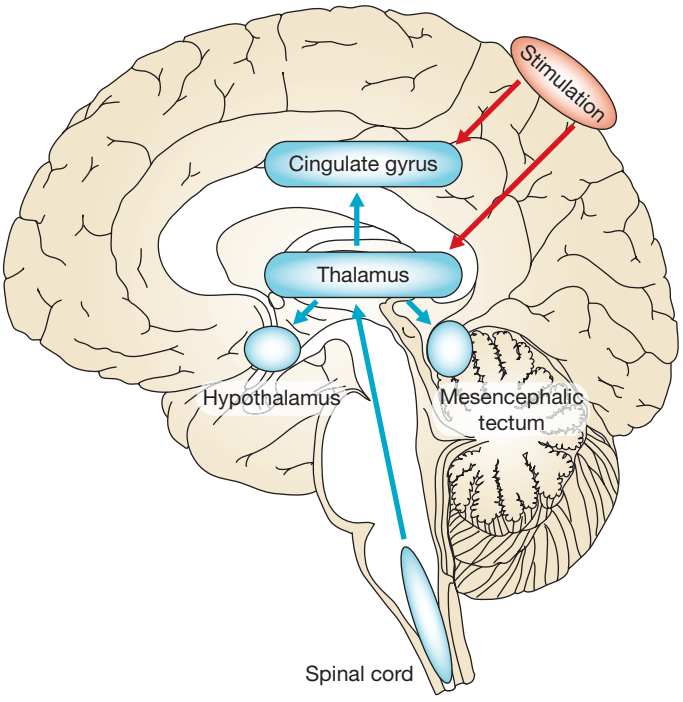


**Figure 1** Noninvasive brain stimulation in chronic pain. The diagram shows the neural structures associated with chronic pain. Modulation of the primary motor cortex with excitability-enhancing high-frequency repetitive transcranial magnetic stimulation or anodal transcranial direct current stimulation (area in red) induces distant changes that might modulate the pain neural network, thereby alleviating chronic pain.

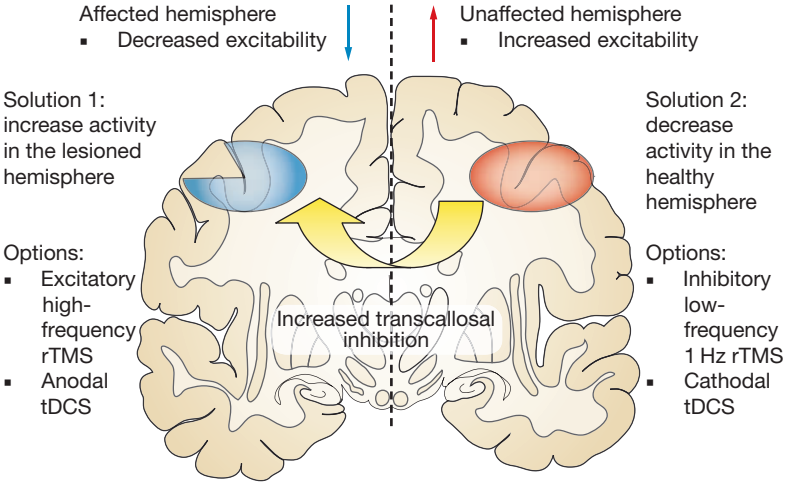


**Figure 2** Noninvasive brain stimulation in stroke. After a stroke, there is increased activity in the unaffected hemisphere (red area) and decreased activity in the affected hemisphere (blue area) as a result of increased transcallosal inhibition (yellow arrow) from the unaffected to the affected hemisphere. In this type of case, enhancing the excitability of the affected hemisphere (with high-frequency rTMS or anodal tDCS) or suppressing the unaffected hemisphere (with low-frequency rTMS or cathodal tDCS) can promote recovery of motor function. Note, however, that specific brain regions might need to be targeted, and that the effects of stimulation might differ between patients and brain areas depending on the nature and site of the initial insult. Abbreviations: rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

cortical area housing the hand motor map correlates more strongly with poorer motor outcome than does total infarct volume.[37] Reduced sensorimotor cortex activation volume during finger movement is associated with poorer outcome,[38] whereas an enlargement of the primary motor cortex area for the hand, as defined by TMS,[39,40] correlates with better motor outcome. Studies in animals[41] and humans[42] have described a shift in sensorimotor cortex activation from bilateral to stroke-affected hemisphere in association with poststroke recovery, particularly in patients with subcortical stroke.[43] Much interest has, therefore, focused on changes in interhemispheric interactions following stroke.[44] After a stroke affecting the motor cortex, cortical excitability is decreased in the affected primary motor cortex relative to the unaffected motor cortex.[45] This phenomenon might result from a shift in interhemispheric interactions, with increased transcallosal inhibition from the unaffected to the affected motor cortex.[46] Similar shifts in interhemispheric interactions have been postulated for parietal cortices in strokes that lead to a neglect syndrome.[47]

The behavioral impact of the modulation of interhemispheric competition has been demonstrated in normal subjects. For example, slow rTMS, which in most subjects suppresses excitability in the targeted cortical region,[48] can improve motor performance with the ipsilateral hand by releasing interhemispheric inhibition in the unstimulated hemisphere.[49] A similar study in which healthy subjects received 1 Hz rTMS of the primary motor cortex did not show a change in pinch force or reaction time in the ipsilateral hand, although it did show a significant increase in excitability in the contralateral motor cortex.[50] The lack of motor function improvement in this study might be attributable to a ceiling effect for these two tasks in healthy subjects. Slow rTMS of one parietal cortex has been shown to improve ipsilateral attention by enhancing excitability in the unstimulated parietal cortex.[51]

In the setting of a stroke, desirable effects might be induced by either suppressing activity in the undamaged hemisphere or increasing activity in the perilesional cortex of the damaged hemisphere in order to promote restoration of activity across bihemispheric neural networks and guidance towards more-adaptive plasticity.[52,53] This matter is still controversial, as one study has shown that stimulation of the unaffected premotor cortex slowed reaction time in the affected ipsilateral hand in comparison with healthy subjects (although only single pulse TMS was used and the effects were measured online).[54] In addition, Lotze *et al.* showed that stimulation of the dorsal premotor cortex, primary motor cortex and superior parietal lobe resulted in a significant worsening of motor function in stroke patients.[55] It should be noted, however, that the patients in this study had already made a good recovery.

## Clinical experience

We will focus specifically on hand motor deficits after strokes affecting the motor cortex or the corticospinal tract. Promising results have also been reported, however, in the cases of neglect[56] and aphasia,[57,58] with noninvasive brain stimulation targeting frontoparietal or language regions, respectively.

We found eight published studies that met our inclusion criteria and evaluated the effect of noninvasive brain stimulation for promoting recovery of hand motor function after a stroke (see Supplementary Table 2 online). The strategy in each case was either to increase excitability in the affected hemisphere or to decrease excitability in the unaffected hemisphere. All of these studies showed a significant improvement in motor function when active stimulation was compared with sham stimulation. In addition, some of these studies showed that motor function improvement was associated with a change in neurophysiologic parameters. For instance, in three studies, motor function improvement was associated with an increase in cortical excitability in the affected hemisphere.[59–61] Studies in which several sessions of noninvasive brain stimulation were administered showed that the effects could last for several weeks.[59,62]

## Outstanding questions

It is important to note that, in most of these studies, effects were indexed as movement speed or strength change, so it is still not clear whether the observed improvements represent a quality of life change. Furthermore, because the methodology of these studies has been heterogeneous, and the sample sizes have been small, it is difficult to draw strong conclusions about ideal patients for noninvasive brain stimulation. Interestingly, even stroke patients with severe motor deficits seem to improve after appropriate stimulation of the lesioned or healthy primary

motor cortex.[63,64] Similar preliminary findings suggest promise of rTMS in patients with severe global aphasia.[65]

Importantly, the studies to date have examined the effects of noninvasive brain stimulation without coupling it with any specific behavioral, physical or occupational therapy. This is probably a suboptimal approach. Maximum behavioral gains with treatments that aim to modify cortical plasticity are found when such treatments are coupled with relevant behavioral experience.[66,67] Plautz *et al.* showed that monkeys submitted to subthreshold electrical stimulation combined with rehabilitative training had significant improvements in motor performance that could not be achieved by training or stimulation alone.[68] In addition, a recent study showed that intensive rehabilitation therapy combined with the use of an invasive epidural electrode was associated with a significant improvement in motor function when compared with rehabilitation alone.[69] For this reason, occupational therapy of the upper extremity should accompany rTMS or tDCS in future studies. A particularly appealing approach might be to use constraint-induced therapy or peripheral sensory stimulation in combination with noninvasive brain stimulation, as both of these strategies can increase excitability in the lesioned motor cortex (possibly via synaptic strengthening) and decrease it in the contralateral healthy hemisphere. Critically, the question of when stimulation should begin following the stroke requires careful consideration. Although there is evidence that decreasing local activity in the lesioned area immediately after stroke might be beneficial,[70] it is unclear whether excessively early modulation of interhemispheric interaction might worsen clinical outcomes.

## PARKINSON'S DISEASE

### Rationale

The effects of noninvasive brain stimulation are not limited to the directly targeted brain region, but spread trans-synaptically to distant cortical and subcortical structures depending on the strength of the anatomical connections, and probably on the level of activity across the specific neural networks. This spread has been elegantly demonstrated in animal studies,[71] as well as in studies combining noninvasive brain stimulation with various neuroimaging methods in humans.[72]

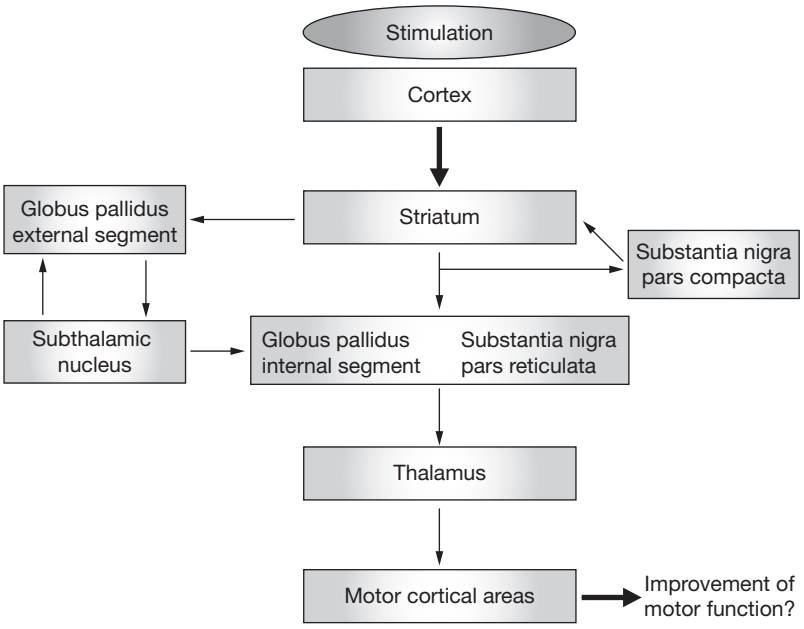


**Figure 3** Noninvasive brain stimulation in Parkinson's disease. The diagram shows the basal ganglia dysfunction model associated with Parkinson's disease. Modulation of the primary motor cortex is associated with a modulation of the basal ganglia structures that might result in an improvement in motor function.

Several studies have indicated that patients with PD also have cortical dysfunction.[73] Targeting the specific areas in the cortical convexity that can be reached by noninvasive brain stimulation could affect the cortical dysfunction in PD directly, or could modify activity in the basal ganglia networks that are dysfunctional in PD through glutamatergic corticostriatal and corticosubthalamic projections (Figure 3). Indeed, Strafella *et al.* have shown that rTMS applied to the prefrontal cortex resulted in dopamine release in the head of the striatum, as measured by raclopride PET,[74] and Chen and collaborators have shown that modulation of activity in the internal pallidus or subthalamic nucleus resulted in changes in motor cortex activity.[75] Thus, the cortical targets of noninvasive brain stimulation might be conceptualized as 'entry ports' for modulation of activity in specific bihemispheric, corticosubcortical neural networks.

### Clinical experience

Fourteen randomized clinical trials have been published in which rTMS or tDCS was used with therapeutic intent in PD (see Supplementary Table 3 online). In 2005, a meta-analysis of

the studies published up to that date showed that the pooled effect size across these studies significantly favored the active stimulation as compared with sham stimulation (effect size of 0.62).[76] Significant variation in the results and parameters of stimulation was, however, observed across the studies. For instance, Okabe *et al.*[77] found no significant motor benefits of rTMS of the primary motor cortex in their study of 81 patients, although the parameters that they used—0.2 Hz stimulation with a circular coil once per week for 8 weeks—might have been suboptimal. A recent study by Miranda *et al.*, which was not included in this meta-analysis, reported that patients who received 25 Hz rTMS for eight sessions over the course of 4 weeks showed a gradual improvement in walking and complex hand movement tasks, and that the benefits lasted for at least 1 month after treatment ended.[8]

### Outstanding questions

Overall, the motor effects of noninvasive brain stimulation in PD are very variable. Indeed, replication of early encouraging findings[78] has proved to be difficult.[79] Variability in the clinical picture between patients, the progressive nature of the disease and the confounding effects of medications all call for cautious assessment of the findings. On the other hand, noninvasive brain stimulation might be a valuable adjunct in the treatment of patients with PD, targeting cognitive and mood symptoms of the disease, which often greatly affect a patient's quality of life, and which are inadequately treated by dopaminergic medications in doses optimized for motor function. The preliminary reports of such an approach are encouraging,[80–82] but more work is certainly needed.

## FOCAL EPILEPSY

### Rationale

Extensive studies of animals and limited work in humans has shown that epileptogenesis involves an increase in excitatory synaptic strength in a manner similar to long-term potentiation,[83] and that seizure foci are characterized by a pathological reduction of inhibitory (γ-aminobutyric acid [GABA]-releasing) terminals and an increase in excitatory (glutamatergic) terminals.[84] Appropriately applied, noninvasive brain stimulation (e.g. slow [≤1 Hz] rTMS or cathodal tDCS) can promote intracortical inhibition (Figure 4). In many ways, the effects resemble long-term depression.[85,86] Consequently, directly targeting a seizure focus with parameters of stimulation that induce long-term-depression-like phenomena might reverse (or at least counteract) the hyperexcitable state of the epileptic focus. If this proves to be the case, noninvasive brain stimulation might provide an attractive alternative for treatment of patients with medication-resistant focal epilepsies, particularly those who are either unable to have surgery (i.e. the epileptic focus is in the eloquent cortex) or do not wish to have surgery. Suppression of epileptic activity by rTMS has indeed been shown,[87] lending support to this approach.

Noninvasive brain stimulation might also help to interrupt ongoing seizure activity, for example in the setting of epilepsia partialis continua or even in status epilepticus.[88] Such concepts have been discussed, but have not to date been sufficiently explored in experiments.

### Clinical experience

Only three randomized sham-controlled studies of noninvasive brain stimulation in focal epilepsy have so far been published (see Supplementary Table 4 online), and the results are unsatisfactory as most of the studies showed only a trend for seizure reduction, although they did reveal a marked reduction in the occurrence of epileptiform discharges. Theodore *et al.*[89] found only a trend towards seizure reduction after active rTMS, whereas Fregni *et al.*[90] found a significant seizure reduction after active rTMS. These differences might be attributable to patient selection (Theodore *et al.* included patients whose epileptic foci were in deep mesial structures, and might, therefore, be unlikely to be affected by rTMS) and parameters of stimulation.

### Outstanding questions

The investigation of noninvasive brain stimulation for epilepsy treatment is still in its infancy. Future neuroimaging-guided studies exploring such treatment might help to identify cortical areas with dysfunctional activity. Indeed, the optimal site of stimulation is a crucial issue that requires further research. For patients with focal lesions and epileptogenic activity, the first logical approach would be to target the dysfunctional brain area directly. For patients with discordant lesion location and epileptiform focus, as indexed by electroencephalogram (EEG), we speculate that the functional focus should be targeted. Clinical trials are needed, however, to

address this question. Patients with multifocal epileptic activity, and those with primary generalized epilepsy, might not be suitable candidates for noninvasive brain stimulation, although one could consider targeting a bihemispheric central area, such as the vertex, using a large circular coil.[91] A recent open-label study showed a trend for seizure reduction after rTMS treatment in patients with multiple epileptogenic foci.[92]

An interesting observation worthy of further investigation is that in some patients the beneficial antiepileptic effect of rTMS continued even after the end of the treatment.[91] Such an effect might indicate that plastic changes have been induced by rTMS. At the very least, noninvasive brain stimulation might provide a valuable screening and guidance tool for the implantation of epidural or subdural electrodes for cortical stimulation.

In parallel with trials of rTMS protocols for the treatment of epilepsy, new technological developments have occurred, rendering EEG recording online to TMS feasible. The continuous monitoring of EEG signals during rTMS in epilepsy research is of interest in several regards. Real-time EEG monitoring might allow immediate discontinuation of an rTMS trial in the event that EEG abnormalities are induced by TMS.[93] In addition, the ability to assess the immediate impact of TMS on epileptic discharges provides new possibilities for epilepsy research that go beyond the use of EEG to document the long-term effects of rTMS treatment.[88,90,92,94,95] More information on the mechanisms through which rTMS interferes with the generation of epileptic activity is undoubtedly needed to further develop rTMS into an effective, alternative, treatment strategy for pharmacoresistant epilepsy. Finally, online EEG recording might enable the development of a system of EEG-guided TMS in which the pulses of TMS could be precisely coordinated with the epileptic spike for maximal efficacy and for prevention of seizure progression. It is unclear, however, whether EEG resolution would be adequate for such a system.

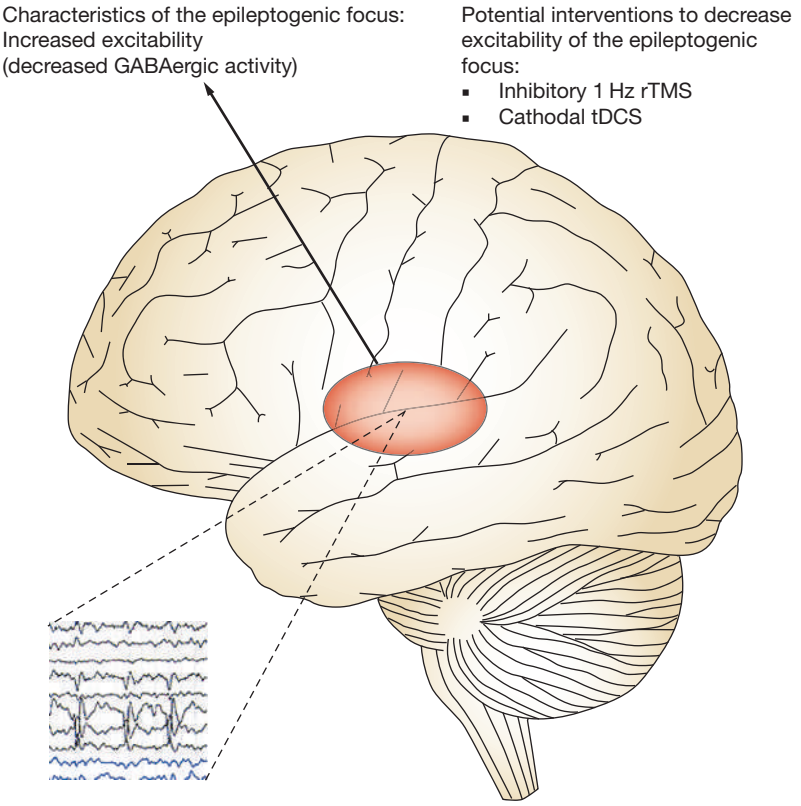


**Figure 4** Noninvasive brain stimulation in focal epilepsy. Diagram showing that suppression of the epileptogenic focus with excitability-diminishing low-frequency rTMS or cathodal tDCS might decrease local excitability, thereby decreasing epileptiform discharges and reducing seizures. Abbreviations: GABA, γ-aminobutyric acid; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

## EFFECTS OF SHAM STIMULATION AND STIMULATION PARAMETERS

An important issue in the design of randomized, sham-controlled clinical trials of noninvasive brain stimulation is the use of appropriate sham stimulation conditions that provide a reliable blinding of patients and investigators. There is an important difference between tDCS and rTMS in this regard. Whereas tDCS provides a reliable sham condition, as demonstrated by a recent study,[96] sham stimulation for rTMS is more challenging. In tDCS there are minimal or no scalp sensations with stimulation (and subjects tend to get habituated to it after a few seconds of stimulation). By contrast, rTMS induces a strong scalp sensation, along with facial and scalp muscle twitches, and is associated with a loud click. Although sham TMS coils produce a similar sound artifact, they do not induce the same scalp sensations or muscle twitches. Patients in randomized trials, therefore, need to be naive to rTMS, so rTMS studies should not have a crossover design. The matter of placebo effect is especially important in some conditions, such as pain and PD.[97,98] A recent meta-analysis of the rTMS studies in PD, however, showed that the effect size of placebo in rTMS trials was only 0.1 (95% CI

–0.16 to 0.35).[76] Alternative methods of brain stimulation to provide suitable control conditions have been proposed. In a large PD study, Okabe *et al.* developed a sham coil that also delivered electrical stimulation to the skin.[77] Similarly, Rossi *et al.* have developed a new method of sham stimulation, known as real electromagnetic placebo or REMP, in which a fake coil (made of wood) with the same shape as a real TMS coil is attached to the real coil. This fake coil has two functions: to block the magnetic field from the real coil, and to house a bipolar electrical stimulator in contact with the scalp. This device is more likely to be judged as real stimulation by naive TMS subjects.[99]

Other important considerations are the parameters of stimulation (i.e. number of stimulation sessions, frequency, intensity and site of stimulation). Repeated sessions, with cumulative effect, seem to be superior to a single session, and are needed to induce a sustained effect. Indeed, although some studies have shown a relatively long-lasting effect (of 2 weeks), this period is short if the goal is to induce a clinically meaningful result. Maintenance treatments or other patterns of stimulation that might induce longer-lasting modulation of cortical excitability should be explored. One possibility is to increase the total number of sessions, as in a recent study of major depression, in which up to 30 sessions of rTMS were administered.[100] Novel patterns of stimulation, for example primed 1 Hz stimulation[101] or theta burst stimulation,[102] might offer advantages as they seem to induce longer-lasting long-term-depression-like phenomena. Careful consideration of cortical targets seems to be critical, and this might need to be individualized for each patient and underlying pathology. Finally, the use of special coil designs that allow deeper penetration into the brain[103] might enable more-reliable targeting of the insula or the cingulate cortex.

In summary, there is a complex range of parameters that need to be explored in order to optimize the clinical effects of rTMS. At this stage, it is difficult to make predictions regarding the efficacy of this approach as the number of available studies is not sufficient. Clinical trials should explore this question further. Individualizing stimulation parameters by carefully considering the underlying pathophysiology and informing the stimulation settings by online physiologic and neuroimaging measures might prove to be critical.

## CONCLUSIONS

There is mounting evidence for the efficacy of noninvasive brain stimulation in various neurological conditions. Experience in various clinical trials illustrates different fundamental uses of TMS in neurological disorders: modulation of activity in the targeted cortex (focal epilepsy); modulation of activity in a dysfunctional corticosubcortical network (PD); restoration of adaptive equilibrium in a disrupted network, guiding plasticity for best behavioral outcome (stroke); and suppression of plastic changes for functional advantage (pain). To date, findings are encouraging, but sham-controlled clinical trial evidence is still insufficient to allow endorsement of widespread use of these techniques, despite the great margin of safety if appropriate guidelines and precautions are followed.

**Supplementary information** in the form of tables summarizing the studies discussed in this Review is available on the *Nature Clinical Practice Neurology* website.

## KEY POINTS

- The clinical consequences of brain insults include compensatory plastic changes that can be either adaptive or maladaptive
- An ideal therapy should be tailored to the individual, promote compensatory plastic changes, inhibit maladaptive plastic changes, be associated with minimal or no adverse effects, be highly effective, and be financially and practically feasible
- An advantage of brain stimulation is that it can be focal and targeted to the underlying pathophysiology of the patient
- Two techniques of noninvasive brain stimulation—repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)—are powerful tools for brain modulation
- A growing number of proof-of-principle and pilot studies have revealed that rTMS and tDCS are associated with mild adverse effects and can induce clinical benefits; however, the evidence for efficacy is currently insufficient
- Initial studies have shown that noninvasive brain stimulation can be used to modulate activity in the targeted cortex (focal epilepsy); modulate activity in a dysfunctional corticosubcortical network (Parkinson's disease); restore adaptive equilibrium in a disrupted network (stroke); or suppress plastic changes for functional advantage (pain)

**References**

1 Coffey RJ (2001) Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review. *Pain Med* **2:** 183–192
2 Moro E and Lang AE (2006) Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. *Expert Rev Neurother* **6:** 1695–1705
3 Bindman LJ *et al.* (1964) The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J Physiol* **172:** 369–382
4 Purpura DP and McMurtry JG (1965) Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol* **28:** 166–185
5 Nitsche MA *et al.* (2003) Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. *Suppl Clin Neurophysiol* **56:** 255–276
6 Priori A (2003) Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clin Neurophysiol* **114:** 589–595
7 Wagner T *et al.* (2007) Transcranial direct current stimulation: a computer-based human model study. *Neuroimage* **35:** 1113–1124
8 Miranda PC *et al.* (2006) Modeling the current distribution during transcranial direct current stimulation. *Clin Neurophysiol* **117:** 1623–1629
9 Nitsche MA and Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* **57:** 1899–1901
10 Walsh V *et al.* (2005) *Transcranial Magnetic Stimulation: A Neurochronometrics of Mind.* Cambridge, MA: MIT Press
11 Barker AT *et al.* (1985) Non-invasive magnetic stimulation of human motor cortex. *Lancet* **1:** 1106–1107
12 Hallett M (2000) Transcranial magnetic stimulation and the human brain. *Nature* **406:** 147–150
13 Pascual-Leone A *et al.* (1999) Transcranial magnetic stimulation and neuroplasticity. *Neuropsychologia* **37:** 207–217
14 Fregni F *et al.* (2007) Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurol* **6:** 188–191
15 Patrizi F *et al.* (2006) Novel therapeutic approaches to the treatment of chronic abdominal visceral pain. *ScientificWorldJournal* **6:** 472–490
16 Craig AD (2003) Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* **26:** 1–30
17 Drossman DA (1996) Chronic functional abdominal pain. *Am J Gastroenterol* **91:** 2270–2281
18 Ringel Y and Drossman DA (1999) From gut to brain and back—a new perspective into functional gastrointestinal disorders. *J Psychosom Res* **47:** 205–210
19 Mundinger F and Salomao JF (1980) Deep brain stimulation in mesencephalic lemniscus medialis for chronic pain. *Acta Neurochir Suppl (Wien)* **30:** 245–258
20 Ray CD and Burton CV (1980) Deep brain stimulation for severe, chronic pain. *Acta Neurochir Suppl (Wien)* **30:** 289–293
21 García-Larrea L *et al.* (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* **83:** 259–273
22 Tsubokawa T *et al.* (1993) Chronic motor cortex stimulation in patients with thalamic pain. *J Neurosurg* **78:** 393–401
23 Peyron R *et al.* (1995) Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. *Pain* **62:** 275–286
24 García-Larrea L *et al.* (1997) Positron emission tomography during motor cortex stimulation for pain control. *Stereotact Funct Neurosurg* **68:** 141–148
25 Lefaucheur JP *et al.* (2004) Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatry* **75:** 612–616
26 Pleger B *et al.* (2004) Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* **356:** 87–90
27 Khedr EM *et al.* (2005) Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatry* **76:** 833–838
28 André-Obadia N *et al.* (2006) Transcranial magnetic stimulation for pain control: double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin Neurophysiol* **117:** 1536–1544
29 Fregni F *et al.* (2006) A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* **122:** 197–209
30 Fregni F *et al.* (2006) A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum* **54:** 3988–3998.
31 Graff-Guerrero A *et al.* (2005) Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. *Brain Res Cogn Brain Res* **25:** 153–160
32 Borckardt JJ *et al.* (2006) Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology* **105:** 557–562
33 Ward NS *et al.* (2003) Neural correlates of outcome after stroke: a cross-sectional fMRI study. *Brain* **126:** 1430–1448
34 Ward NS *et al.* (2003) Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain* **126:** 2476–2496
35 Galea MP and Darian-Smith I (1994) Multiple corticospinal neuron populations in the macaque monkey are specified by their unique cortical origins, spinal terminations, and connections. *Cereb Cortex* **4:** 166–194
36 Brinkman J and Kuypers HG (1973) Cerebral control of contralateral and ipsilateral arm, hand and finger movements in the split-brain rhesus monkey. *Brain* **96:** 653–674
37 Crafton KR *et al.* (2003) Improved understanding of cortical injury by incorporating measures of functional anatomy. *Brain* **126:** 1650–1659
38 Zemke AC *et al.* (2003) Motor cortex organization after stroke is related to side of stroke and level of recovery. *Stroke* **34:** e23–e28
39 Traversa R *et al.* (1997) Mapping of motor cortical reorganization after stroke: a brain stimulation study with focal magnetic pulses. *Stroke* **28:** 110–117
40 Cicinelli P *et al.* (1997) Post-stroke reorganization of brain motor output to the hand: a 2–4 month follow-up with focal magnetic transcranial stimulation. *Electroencephalogr Clin Neurophysiol* **105:** 438–450
41 Dijkhuizen RM *et al.* (2003) Correlation between brain reorganization, ischemic damage, and neurologic status after transient focal cerebral ischemia in rats: a functional magnetic resonance imaging study. *J Neurosci* **23:** 510–517

42 Marshall RS *et al.* (2000) Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke* **31:** 656–661
43 Feydy A *et al.* (2002) Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation. *Stroke* **33:** 1610–1617
44 Theoret H *et al.* (2003) Exploring paradoxical functional facilitation with TMS. *Suppl Clin Neurophysiol* **56:** 211–219
45 Shimizu T *et al.* (2002) Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. *Brain* **125:** 1896–1907
46 Murase N *et al.* (2004) Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* **55:** 400–409
47 Kinsbourne M (1977) Hemi-neglect and hemisphere rivalry. *Adv Neurol* **18:** 41–49
48 Maeda F *et al.* (2002) Inter- and intra-individual variability of paired-pulse curves with transcranial magnetic stimulation (TMS). *Clin Neurophysiol* **113:** 376–382
49 Kobayashi M *et al.* (2004) Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology* **62:** 91–98
50 Schambra HM *et al.* (2003) Modulation of excitability of human motor cortex (M1) by 1 Hz transcranial magnetic stimulation of the contralateral M1. *Clin Neurophysiol* **114:** 130–133
51 Hilgetag CC *et al.* (2001) Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat Neurosci* **4:** 953–957
52 Fregni F and Pascual-Leone A (2006) Hand motor recovery after stroke: tuning the orchestra to improve hand motor function. *Cogn Behav Neurol* **19:** 21–33
53 Hummel FC and Cohen LG (2006) Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol* **5:** 708–712
54 Johansen-Berg H *et al.* (2002) The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci USA* **99:** 14518–14523
55 Lotze M *et al.* (2006) The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. *J Neurosci* **26:** 6096–6102
56 Oliveri M *et al.* (1999) Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. *Brain* **122:** 1731–1739
57 Martin PI *et al.* (2004) Transcranial magnetic stimulation as a complementary treatment for aphasia. *Semin Speech Lang* **25:** 181–191
58 Naeser MA *et al.* (2005) Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. *Brain Lang* **93:** 95–105
59 Fregni F *et al.* (2006) A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke* **37:** 2115–2122
60 Kim YH *et al.* (2006) Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke* **37:** 1471–1476
61 Hummel F *et al.* (2005) Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* **128:** 490–499
62 Khedr EM *et al.* (2005) Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology* **65:** 466–468
63 Hummel FC *et al.* (2006) Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neurosci* **7:** 73
64 Boggio PS *et al.* (2006) Hand function improvement with low-frequency repetitive transcranial magnetic stimulation of the unaffected hemisphere in a severe case of stroke. *Am J Phys Med Rehabil* **85:** 927–930
65 Naeser MA *et al.* (2005) Improved naming after TMS treatments in a chronic, global aphasia patient—case report. *Neurocase* **11:** 182–193
66 Feeney DM *et al.* (1982) Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science* **217:** 855–857
67 Gladstone DJ and Black SE (2000) Enhancing recovery after stroke with noradrenergic pharmacotherapy: a new frontier? *Can J Neurol Sci* **27:** 97–105
68 Plautz EJ *et al.* (2003) Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurol Res* **25:** 801–810
69 Brown JA *et al.* (2006) Motor cortex stimulation for the enhancement of recovery from stroke: a prospective, multicenter safety study. *Neurosurgery* **58:** 464–473
70 Sick TJ *et al.* (1999) Mild hypothermia improves recovery of cortical extracellular potassium ion activity and excitability after middle cerebral artery occlusion in the rat. *Stroke* **30:** 2416–2421
71 Valero-Cabre A and Pascual-Leone A (2005) Impact of TMS on the primary motor cortex and associated spinal systems. *IEEE Eng Med Biol Mag* **24:** 29–35
72 van Eimeren T and Siebner HR (2006) An update on functional neuroimaging of parkinsonism and dystonia. *Curr Opin Neurol* **19:** 412–419
73 Lefaucheur JP (2006) Repetitive transcranial magnetic stimulation (rTMS): insights into the treatment of Parkinson's disease by cortical stimulation. *Neurophysiol Clin* **36:** 125–133
74 Strafella AP *et al.* (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci* **21:** RC157
75 Cunic D *et al.* (2002) Effects of subthalamic nucleus stimulation on motor cortex excitability in Parkinson's disease. *Neurology* **58:** 1665–1672
76 Fregni F *et al.* (2005) Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. *J Neurol Neurosurg Psychiatry* **76:** 1614–1623
77 Okabe S *et al.* (2003) 0.2 Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. *Mov Disord* **18:** 382–388
78 Pascual-Leone A *et al.* (1994) Akinesia in Parkinson's disease. I: shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. *Neurology* **44:** 884–891
79 Ghabra MB *et al.* (1999) Simultaneous repetitive transcranial magnetic stimulation does not speed fine movement in PD. *Neurology* **52:** 768–770
80 Fregni F *et al.* (2006) Effects of antidepressant treatment with rTMS and fluoxetine on brain perfusion in PD. *Neurology* **66:** 1629–1637
81 Boggio PS *et al.* (2005) Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. *Mov Disord* **20:** 1178–1184
82 Boggio PS *et al.* (2006) Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol Sci* **249:** 31–38
83 Johnston MV (1996) Developmental aspects of epileptogenesis. *Epilepsia* **37 (Suppl 1):** S2–S9
84 Lowenstein DH (1996) Recent advances related to basic mechanisms of epileptogenesis. *Epilepsy Res Suppl* **11:** 45–60

85 Chen R *et al.* (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* **48:** 1398–1403
86 Nitsche MA *et al.* (2005) Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol* **568:** 291–303
87 Dhuna A *et al.* (1991) Transcranial magnetic stimulation in patients with epilepsy. *Neurology* **41:** 1067–1071
88 Misawa S *et al.* (2005) Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia. *J Neurol Sci* **234:** 37–39
89 Theodore WH *et al.* (2002) Transcranial magnetic stimulation for the treatment of seizures: a controlled study. *Neurology* **59:** 560–562
90 Fregni F *et al.* (2006) A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Ann Neurol* **60:** 447–455
91 Pascual-Leone A *et al.* (2002) *Handbook of Transcranial Magnetic Stimulation*. London: Arnold Press
92 Joo EY *et al.* (2007) Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. *Clin Neurophysiol* **118:** 702–708
93 Kanno M *et al.* (2001) Monitoring an electroencephalogram for the safe application of therapeutic repetitive transcranial magnetic stimulation. *J Neurol Neurosurg Psychiatry* **71:** 559–560
94 Menkes DL and Gruenthal M (2000) Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. *Epilepsia* **41:** 240–242
95 Fregni F *et al.* (2005) Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study. *Stereotact Funct Neurosurg* **83:** 57–62
96 Gandiga PC *et al.* (2006) Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* **117:** 845–850
97 Strafella AP *et al.* (2006) Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. *Neuroimage* **31:** 1666–1672
98 Fregni F *et al.* (2006) Immediate placebo effect in Parkinson's disease—is the subjective relief accompanied by objective improvement? *Eur Neurol* **56:** 222–229
99 Rossi S *et al.* (2007) A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). *Clin Neurophysiol* **118:** 709–716
100 Fitzgerald PB *et al.* (2006) A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* **163:** 88–94
101 Iyer MB *et al.* (2003) Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *J Neurosci* **23:** 10867–10872
102 Huang YZ *et al.* (2005) Theta burst stimulation of the human motor cortex. *Neuron* **45:** 201–206
103 Roth Y *et al.* (2007) Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *J Clin Neurophysiol* **24:** 31–38

**Acknowledgments**
This work was partially supported by grants from the NIH (K24 RR018875, RO1-DC05672, RO1-NS 47754, RO1-NS 20068, R01-EB 005047, RO1-NS47754, RO3-DK071851).

**Competing interests**
A Pascual-Leone has declared associations with the following company: Northstar Neuroscience. See the article online for full details of the relationship. F Fregni declared he has no competing interests.