

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 19th 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

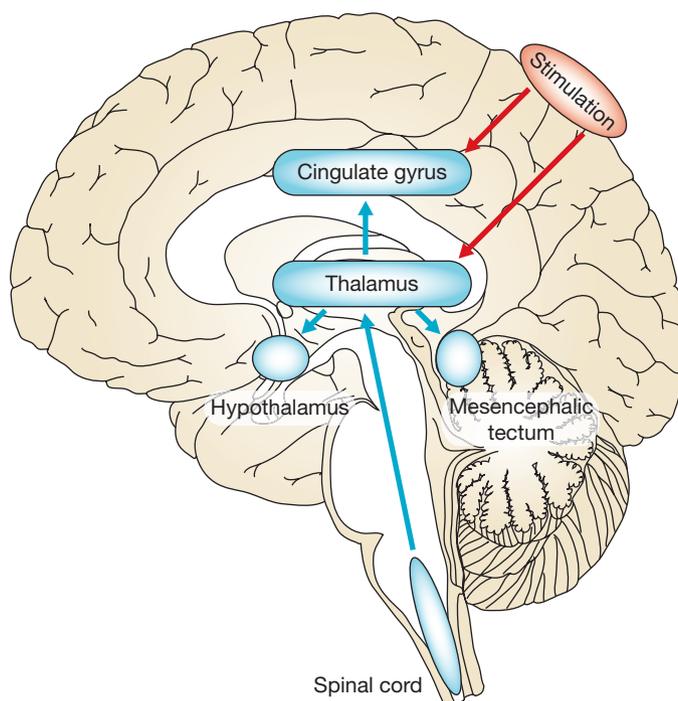


Figure 1 Noninvasive brain stimulation in chronic pain. The diagram shows the neural structures associated with chronic pain. Modulation of the primary motor cortex with excitability-enhancing high-frequency repetitive transcranial magnetic stimulation or anodal transcranial direct current stimulation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

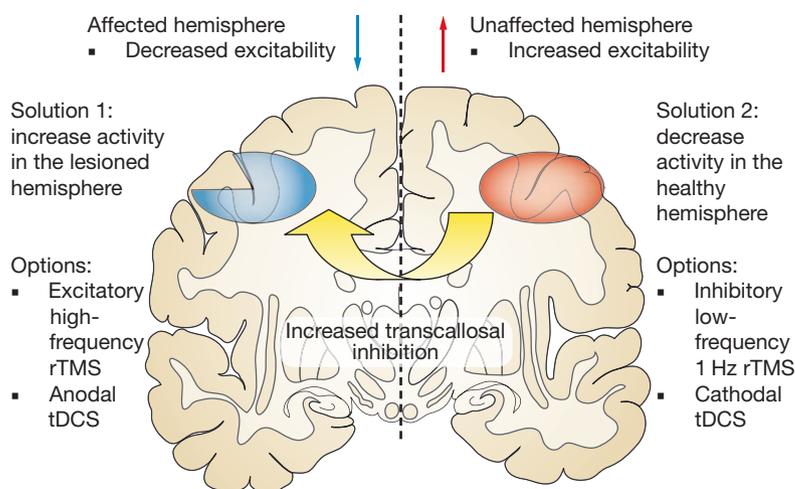


Figure 2 Noninvasive brain stimulation in stroke. After a stroke, there is increased activity in the unaffected hemisphere (red area) and decreased activity in the affected hemisphere (blue area) as a result of increased transcallosal inhibition (yellow arrow) from the unaffected to the affected hemisphere. 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 animals⁴¹ and humans⁴² 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 neglect⁵⁶ 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

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 findings⁷⁸ 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 epilepsy 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.

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

Characteristics of the epileptogenic focus:
Increased excitability
(decreased GABAergic activity)

Potential interventions to decrease excitability of the epileptogenic focus:

- Inhibitory 1 Hz rTMS
- Cathodal tDCS

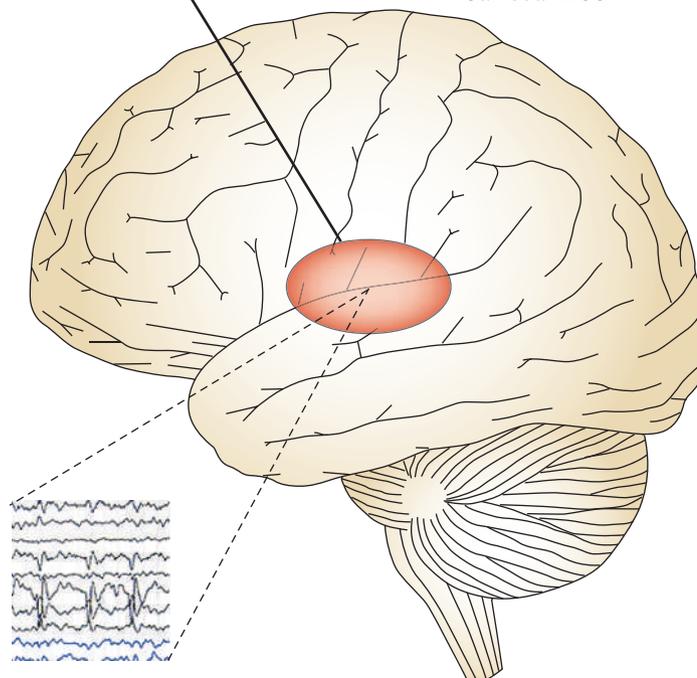


Figure 4 Noninvasive brain stimulation in focal epilepsy. Diagram showing that suppression of the epileptogenic focus with excitability-diminishing low-frequency rTMS or cathodal tDCS might decrease local excitability, thereby decreasing epileptiform discharges and reducing seizures. Abbreviations: GABA,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

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 stimulation¹⁰¹ 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 brain¹⁰³ 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 cortico-subcortical 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)

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Acknowledgments

This work was partially supported by grants from the NIH (K24 RR018875, RO1-DC05672, RO1-NS47754, RO1-NS20068, RO1-EB005047, 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.