J Rehabil Med 2009; 41: 305–311

EDUCATIONAL REVIEW

UPDATES ON THE USE OF NON-INVASIVE BRAIN STIMULATION IN PHYSICAL AND REHABILITATION MEDICINE*

Julie A. Williams, MA[1], Marta Imamura, MD, PhD[2] and Felipe Fregni, MD, PhD[1]

From the [1]Department of Neurology, Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA and [2]Department of Orthopaedics and Traumatology, Division of Physical Medicine and Rehabilitation, University of São Paulo School of Medicine, São Paulo, Brazil

Brain stimulation for the treatment of neuropsychiatric diseases has been used for more than 50 years. Although its development has been slow, current advances in the techniques of brain stimulation have improved its clinical efficacy. The use of non-invasive brain stimulation has significant advantages, such as not involving surgical procedures and having relatively mild adverse effects. In this paper we briefly review the use of 2 non-invasive brain stimulation techniques, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), as therapeutic approaches in physical and rehabilitation medicine. We also compare the effects of non-invasive central nervous system stimulation with techniques of non-invasive peripheral electrical stimulation, in order to provide new insights for future developments. Although the outcomes of these initial trials include some conflicting results, the evidence supports that rTMS and tDCS might have a therapeutic value in different neurological conditions. Studies published within the last year have examined new approaches of stimulation, such as longer intensities of stimulation, new electrode sizes for tDCS, novel coils for stimulation of deeper areas, and new frequencies of stimulation for rTMS. These new approaches need to be tested in larger clinical trials in order to determine whether they offer significant clinical effects.

Key words: transcranial magnetic stimulation, transcranial direct current stimulation, transcutaneous electrical nerve stimulation, stroke, Parkinson disease, chronic pain.

J Rehabil Med 2009; 41: 305–311

Correspondence address: Felipe Fregni, Center for Non-invasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, KS 452, Boston, MA 02215, USA. E-mail: ffregni@bidmc.harvard.edu

Submitted November 11, 2008; accepted February 17, 2009

INTRODUCTION

An ideal treatment in neuropsychiatry would be one that is targeted to specific dysfunctional areas in the brain, is associated with mild or no adverse effects, is highly effective, and is economically and reasonably feasible to use in clinical practice. Using these criteria it is clear that current treatments for neuropsychiatric disorders, especially pharmacological treatments, have significant limitations, such as a non-specific effect and moderate to severe adverse effects. Although other treatments, such as physical or behavioral therapy, are safer and more specific, they are highly dependent on the therapist's level of training and availability, as well as on the patient's co-operation. There is therefore an evident unmet clinical need for the development of new therapeutic approaches in physical and rehabilitation medicine.

A new therapeutic approach that has shown positive clinical results in the last decade in a wide range of neuropsychiatric disorders is non-invasive brain stimulation (NBS) (1–3). Two techniques of NBS appear to induce clinically relevant impact: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). These methods of brain stimulation can modulate cortical excitability focally, are associated with mild adverse effects, and, most importantly, are non-invasive and painless (4, 5).

Although investigation into the use of NBS in clinical practice is in the initial stages, with only a few, small, phase II studies having been performed, the initial evidence for significant clinical effects is encouraging. We therefore reviewed the results of randomized, double-blind, sham controlled studies testing the use of NBS in 3 areas of physical and rehabilitation medicine: pain, stroke and Parkinson's disease (PD). We chose these areas because of the relatively large number of studies. Because our focus was on the discussion of novel strategies of NBS in physical and rehabilitation medicine, we included only those publications that were relevant to this topic. In this paper we discuss our findings, and compare them with those induced by a technique of non-invasive stimulation that targets the peripheral nervous system; transcutaneous electrical nerve stimulation (TENS).

BASIC MECHANISMS OF ACTION

The investigation of stimulation with weak direct currents dates back to the 1960s and 1970s when researchers began to explore it systematically in human and animal stimulation. Animal investigation from that time demonstrates a controllable and reliable impact on the spontaneous activity and the

*This is an educational review produced in collaboration with the International Society of Physical and Rehabilitation Medicine.

 doi: 10.2340/16501977-0356

Journal Compilation © 2009 Foundation of Rehabilitation Information. ISSN 1650-1977

evoked response of neurons (6, 7). Although human use and investigation did not accompany the initial results from animal studies, recent interest in this technique has resulted in novel studies showing that tDCS stimulation can influence cortical activity in humans in a manner similar to that seen in these pioneering experiments (8, 9). During tDCS, low amplitude direct currents are applied via scalp electrodes and penetrate the skull to enter the brain. The effects of tDCS depend on the direction of the current; such that anodal stimulation induces an increase in spontaneous neuronal activity, which is observed via an increase in cortical excitability; whereas cathodal stimulation results in the opposite effect; a decrease in cortical excitability (10). Although there is substantial shunting of current in the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential and thus influence the level of excitability and modulate the firing rate of individual neurons in response to additional inputs, as shown in our recent modeling studies (11). When tDCS is applied for a sufficient duration, cortical function can be modified beyond the stimulation period (12). Although its mechanisms of action are unclear, its long-lasting effects have been associated with changes in synaptic strengthening (13).

Another option to induce electrical currents in the brain is through the use of varying magnetic fields. The advantage of using magnetic fields is that the skull does not represent a barrier, although the strength of a magnetic field decays with the square of the distance. Technological advancements led Barker et al. (14) to introduce transcranial magnetic stimulation (TMS) as a technique capable of overcoming the technical challenges, essentially the strength and time variation of a magnetic field. In TMS, in contrast to tDCS, the direction of the current is not a critical parameter. Here an important issue is the frequency of stimulation, as low-frequency stimulation appears to decrease cortical excitability and high-frequency stimulation induces an increase in cortical excitability (15, 16). Low-frequency is defined as below or equal to 1 Hz and high-frequency is usually higher than or equal to 5 Hz. For the range between 1 and 5 Hz, the effects are uncertain. The reason why the frequency has this important role is not known. In addition, some subjects show contrary effects, such as that low frequency induces an increase in cortical excitability (17), which may depend on baseline cortical excitability.

In contrast to tDCS, TMS is a neurostimulation and neuromodulation application, as it forces action potentials (given supra-threshold stimulation), while tDCS is a purely neuromodulatory intervention. TMS uses the principle of electromagnetic induction to focus induced currents in the brain (18). These currents can be of sufficient magnitude to depolarize neurons, but when the currents are applied repetitively (rTMS) they can increase or decrease cortical excitability (depending on the parameters of stimulation) that can last beyond the duration of the train of stimulation (19). In addition, tDCS and TMS have other fundamental differences, such as the focality of stimulation. tDCS is a technique with less focality, therefore inducing changes in a larger area than rTMS. It is unclear whether this might represent a disadvantage for the use of tDCS in the clinical context.

CHRONIC PAIN

NBS using rTMS appears to be effective, with mean pain relief in the range 20–45% (20–22). Although only 2 studies have evaluated the effects of tDCS on chronic pain, they show even larger results, with a mean pain relief up to 58% (23, 24). In fact, we have recently conducted a meta-analysis assessing the effects of NBS for pain, and have shown that the mean response rate for rTMS and tDCS studies is 45.3% (95% confidence interval (95% CI) 39.2–51.4) and the number of responders in the active group is significantly higher when compared with a sham stimulation group (risk ratio 2.64) (95% CI 1.63–4.30) (25).

Compared with other forms of brain stimulation, such as invasive epidural motor cortex stimulation, the results are relatively similar, as these studies show a mean pain relief of 28–47% in the largest series (26, 27) and 50–70% in the smallest series (28, 29). However, the variation in clinical effects for the rTMS studies was significant and an important source of variation in patient selection.

Because the rationale of NBS is to reverse the maladaptive changes that occur in the brain as a result of chronic pain, patients with central pain might be the best candidates for this treatment, as pain in these patients is due mainly to central nervous system dysfunction. Indeed, most studies investigated the effects of rTMS in patients with central pain, such as pain due to stroke (including thalamic stroke) and spinal cord injury (20, 22, 30–34). Similarly, anodal tDCS of the primary motor cortex has also induced significant pain reductions in chronic pain due to spinal cord injury (23).

Not only central pain has been explored, but also other neuropathic pain syndromes, such as brachial plexus lesion (30), trigeminal nerve lesion (20), neuralgia (22, 35), and peripheral lesion (33). rTMS and tDCS studies have also investigated whether pain in chronic migraine (36) and fibromyalgia (24, 37) responded to NBS. These studies all show that NBS significantly reduces pain when comparing sham vs active treatment. Finally, we also observed that rTMS can significantly reduce chronic pain associated with chronic pancreatitis (38). This evidence supports that a peripheral lesion might be only the initial event in the cascade of events that leads to maladaptive plastic changes in the central nervous system responsible for sustaining chronic pain.

Although the results were consistent across different pain syndromes, some studies report negative results. Different parameters of stimulation might explain these studies with mixed results. For instance, Irlbacher et al. (39), applying several sessions of rTMS in patients with phantom limb pain, did not find a difference between active and sham treatment. Some methodological issues might account for this negative result, such as: (*i*) a high drop-out rate (less than half of the patients completed this cross-over study); (*ii*) a short 18-day wash-out period (Khedr et al. (22) showed that 5 consecutive days of stimulation can cause analgesic effects for at least 2 weeks) and; (*iii*) the study used 500 TMS pulses per session (a lower number compared with other studies), most of which used more than 1000 pulses per session. Finally, it is possible that phantom limb pain is more resistant to treatment with rTMS, perhaps requiring higher intensities and doses of rTMS for effective analgesia compared with other types of chronic pain.

STROKE

All the randomized clinical trial studies (8 studies met our inclusion criteria) evaluating the effects of NBS in stroke showed that active stimulation of either the affected or unaffected motor cortex induces a significant improvement in motor function compared with sham stimulation. It is important to note that in most of these studies effects were indexed as a change in movement speed or strength, and thus it is not clear if this improvement means a significant clinical impact or any changes in quality of life. However, most of these studies were performed in patients with chronic stroke in whom the likelihood of any improvement is low; therefore any significant change in motor function in these patients might represent a functional benefit for them.

Because the methodology of these studies was heterogeneous, it is not possible to draw conclusions about potential clinical indications for this therapy. For instance, in regard to patient selection, studies enrolled patients with subcortical and cortical stroke, ischemic and hemorrhagic stroke and also with acute, subacute and chronic stroke. One common characteristic for all these studies is that patients had moderate to mild motor deficits. Therefore it is not known whether patients with severe motor deficits might also benefit from this therapy, although one case report seemed to suggest a possible improvement also for these patients (40). This heterogeneous group selection might indicate that the effects of NBS are not specific or that they have an unspecific component.

In 5 of these studies, the unaffected primary motor cortex was targeted with stimulation strategies to reduce cortical excitability, such as low frequency rTMS and cathodal tDCS (41–45). These studies showed a significant improvement in motor function when comparing active with sham stimulation. The effects were transient, as a single session was applied, with the exception of the study of Fregni et al. (44) in which 5 sessions were applied to the unaffected primary cortex and the effects lasted for more than 2 weeks. In 2 of these studies, cortical excitability was evaluated using single and paired pulse TMS. Takeuchi et al. (42) showed that rTMS of the unaffected hemisphere reduces the amplitude of motor-evoked potentials from the affected hemisphere and the transcallosal inhibition duration. Furthermore, in our recent study we showed that inhibition of the unaffected hemisphere is associated with a decrease in the cortical excitability in the stimulated, unaffected hemisphere and an increase in the affected hemisphere, which is correlated with motor function improvement (44).

Another strategy of stimulation is to use paradigms of stimulation to increase cortical excitability (high-frequency rTMS and anodal tDCS) in the affected (ipsilesional) hemisphere. Initially, Khedr et al. (34) applied 3 Hz rTMS to the affected hemisphere over a 10-day period to 26 patients suffering from acute ischemic stroke. Compared with sham TMS, patients receiving active rTMS showed a significant improvement as measured by disability scales; Khedr et al. (34) conclude that rTMS might be used as an add-on therapy to normal physical and drug rehabilitation in early stroke patients. Kim et al. (46) subsequently confirmed these results, showing that motor function improves in stroke patients when high frequency (10 Hz) stimulation is applied to the affected cortical motor areas. Finally, similar results were found when anodal tDCS was applied to the affected motor cortex (38, 43, 45, 47). In all of these (double-blind) studies, stimulation was performed for a short period of time only and therefore the effects were transient. Finally, in 2 of these studies the authors showed a relationship between changes in the motor function and corticomotor excitability in the affected hemisphere (46, 47).

PARKINSON'S DISEASE

A total of 14 randomized clinical trials met our inclusion criteria. Unlike stroke and pain, the methodology across the studies in PD is even more heterogeneous. One of the main problems is the variability of rTMS parameters, such as number of pulses, stimulation intensity, number of sessions, and patients' characteristics, such as stage of disease, use of medications, and stage of treatment. Therefore, in order to obtain a meaningful estimate of the effects of NBS in PD, a recent meta-analysis showed that the pooled effect size across these studies significantly favors the active compared with sham stimulation (effect size of 0.62). After this meta-analysis, a recent study in which patients were treated for 8 weeks showed that performance, as a function of time, for executing walking and complex hand movement tests gradually decreased and these effects lasted for at least one month after treatment ended (48). Finally, a recent tDCS study (only one study has been performed so far) showed that a single session of anodal, but not cathodal, tDCS of the motor cortex is associated with a significant effect on motor function and this effect is correlated with a change in motor cortex excitability (49).

One important factor when evaluating the clinical effects is the site of stimulation. Two main strategies have been used; stimulation of the primary motor cortex and prefrontal cortex. The primary motor cortex (M1) was the most common target area, and most of the studies showed that stimulation of this area is effective to improve motor function and, in addition, when sessions were applied repetitively, the effects lasted for several weeks. Some studies did not find significant effects of rTMS in improving motor function after stimulation of the primary motor cortex, such as the study of Okabe et al. (50), which included a large sample size of 81 patients. However, in this study, the authors used 0.2 Hz stimulation with a circular coil once a week for 8 weeks; these parameters might not have been satisfactory, as it has been shown that repeated sessions of rTMS (when repeated within 24 h, but not after one week) lead to cumulative long-lasting changes in cortical excitability (51).

Other areas, such as the supplementary motor cortex, did not induce motor function improvement and, indeed, induced a worsening of complex motor function as measured by spiral drawing (52). Finally, for the prefrontal cortex, although some studies show positive results these were small and quite variable (53, 54). One alternative that might show some benefit is the use of stimulation in prefrontal areas to improve cognition and treat mood disorders, as shown in previous studies (55, 56); therefore potential benefits in motor function together with a decrease in other medications to treat cognitive function might lead to a secondary improvement in motor function.

NON-INVASIVE PERIPHERAL NERVOUS SYSTEM STIMULATION FOR CHRONIC PAIN: INSIGHTS FOR BRAIN STIMULATION TECHNIQUES

TENS might give valuable insights into nervous system stimulation as this technique has been used for several decades. One interesting point is that, despite being widely used, the efficacy of TENS remains controversial as an isolated intervention to treat chronic pain (57–59). Indeed, similarly, the use of NBS may prove to be more effective if combined with other interventions; this may be especially true for tDCS, a technique of neuromodulation only.

Regarding patient population, most TENS trials have enrolled patients with peripheral pain, such as low-back pain or osteoarthritis. In fact, a recent meta-analysis concluded that electrical nerve stimulation is more effective than placebo to reduce chronic musculoskeletal pain (60). On average, electrical nerve stimulation provided nearly 3 times more pain relief than placebo (60); results that are similar to the techniques of NBS. For some patients, electrical nerve stimulation may be used as a substitute for analgesic drugs (60, 61). In addition, conventional TENS and acupuncture-like TENS have been demonstrated to be effective in controlling pain and improving joint stiffness over placebo in patients with knee osteoarthritis (62). Acupuncture-like TENS seems to be better than placebo to reduce pain intensity and to improve muscle power in patients with rheumatoid arthritis (63). Here it is interesting to discuss whether non-invasive electrical stimulation should be targeted to the affected area (i.e. peripheral vs central nervous system); or whether similar mechanisms of sensitization take place regardless of the origin of pain. In this case it might be speculated that a combination of both approaches (central and peripheral stimulation) might enhance their therapeutic effects.

Finally, the mechanisms of action by which peripheral stimulation improves pain remain unclear. Proposed mechanisms of action involve the release of endogenous opioids (64, 65) and interference in the excitability of the peripheral sensory nervous system (66, 67). Studies directly comparing both forms of brain stimulation (central vs peripheral) might provide insights into the mechanisms of action of these techniques.

RECENT ADVANCES

The number of studies using non-invasive TMS and tDCS has increased exponentially. For instance, the number of publications involving tDCS and TMS in the past year was 15 and 205, respectively. These numbers represent a significant increase compared with 15 years ago, when the number of publications was 0 and 35, respectively. Importantly, during this period, some studies on safety have been published, which suggest that both techniques have safe profiles if used according to certain guidelines of stimulation (68–70).

Transcranial direct current stimulation

Reviewing the literature of the past year for tDCS, interesting developments have taken place. Most of these studies evaluated new strategies of tDCS targeting the primary motor cortex to modulate its cortical excitability. Nitsche et al. (71) tested whether it was possible to increase the focality of tDCS, investigating whether a reduced electrode size and larger reference electrode size is associated with significant changes in motor cortex excitability. This study showed that reducing the size of the stimulating electrode focalized the effects of tDCS, and increasing the size of the reference electrode rendered this electrode functionally ineffective (71). Furubayashi et al. (72) tested the effects of short durations of tDCS applied to the motor cortex with higher intensities of stimulation (up to 5mA). This strategy does not seem to induce significant changes in the motor cortex excitability that might be advantageous for clinical use (72). Finally, Jeffery et al. (73) investigated whether tDCS at an intensity of 2 mA could induce changes in the excitability of deeper cortical structures of the motor cortex, such as the area correspondent to the innervation of the muscles of the lower leg. The results showed that anodal tDCS of this area induces significant increases in the motor cortex excitability of the tibialis anterior, whereas cathodal tDCS of the leg area does not suppress excitability.

In addition, because tDCS seems to be effective in improving motor function in healthy subjects (40) and patients after stroke (45, 47), recent studies have tried new approaches to improve motor function. Cogiamanian et al. (74) showed that anodal tDCS of the motor cortex improves muscle endurance (as indexed by maximum voluntary contraction and fatiguing isometric contraction), suggesting that this approach might be used in sports medicine and pathological conditions. Hesse et al. (75) showed that the combination of tDCS of the motor cortex with robot-assisted arm training is effective to improve motor function in patients with subcortical stroke lesion.

Finally, tDCS use has been expanded to other conditions, such as modulation of risk (76), modulation of language in healthy subjects (77) and, finally, the evaluation of sleep in conditions such as fibromyalgia (78).

Repetitive transcranial magnetic stimulation

Important advances have been made in the field of TMS in the past year. A potential useful development for clinical application is the use of H-coils, which allow direct stimulation of deeper neuronal pathways, compared with standard TMS. Levkovitz et al. (79) performed a randomized controlled feasibility and safety study in which they showed that stimulation with H-coil was well tolerated, with no adverse physical or neurological outcomes. Jung et al. (80) showed that stimulation duration is a significant parameter for rTMS and can induce different patterns of long-lasting changes in corticospinal and intracortical excitability. Along these lines, De Ridder et al. (81) have shown that burst rTMS (using different frequency ranges, such as theta (5 Hz), alpha (10 Hz) and beta (20 Hz)) can be used clinically and induces significant tinnitus suppression in subjects with chronic tinnitus. Finally, Sparing et al. (82) suggested that higher precision in coil placement can be achieved with functional MRI-guided stimulation, which was shown to be accurate within the range of millimeters. However, it is uncertain whether this strategy would lead to clinical benefits.

In addition to new strategies to enhance stimulation, several clinical trials have been performed in the past year in different neurological diseases. There were 10 publications on using rTMS for the treatment of tinnitus. Most of these trials showed that rTMS can induce significant relief in tinnitus (81, 83–86). However, these studies also showed that the effects of rTMS are transient and variable between subjects. Indeed, Klienjung et al. (87) concluded that patients with normal hearing and a short history of complaints might respond more to rTMS, as the neuroplastic changes in these patients might be less pronounced.

Parkinson's disease is another condition with a relatively high number of publications in the last year; 5 publications. The recent results for this condition follow the same trend as in previous studies using rTMS in PD, as 2 studies showed negative results (del Olmo et al. (88) showed that rTMS of the dorsolateral prefrontal cortex (DLPFC) does not induce any significant motor function improvements and Kim et al. (89) showed that the effects of rTMS on intracerebral dopamine release (as assessed by 11-C raclopride positron emission tomography) supports placebo response during rTMS only) and 2 publications showed positive results (Epstein et al. (90), in an open-label study, showed that rTMS of DLPFC induces significant motor and mood effects in PD and Khedr et al. (91) showed a significant correlation between levels of serum dopamine and motor improvement after treatment with rTMS). Use of NBS in PD is still challenging due to an elevated placebo response in this group of patients, motor fluctuations due to chronic use of levodopa, and variations in the clinical presentation of motor deficits.

In other areas, such as chronic pain and stroke, fewer studies have been published in the last year; but they are generally supportive of the clinical effects of rTMS in these conditions, such as a study suggesting that rTMS combined with muscle contraction might enhance its therapeutic effects in stroke (92), and a study showing that rTMS might induce a significant improvement in pain in fibromyalgia (93).

In conclusion, there is mounting evidence for the efficacy of NBS in various areas of physical and rehabilitation medicine. In addition, studies published in the last year have shown that different approaches to brain stimulation might induce different on-line effects. These findings are therefore encouraging, and further studies testing novel parameters of stimulation might find better approaches for the clinical use of NBS.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry 1999; 56: 300–311.
2. George MS, Nahas Z, Kozol FA, Li X, Yamanaka K, Mishory A, et al. Mechanisms and the current state of transcranial magnetic stimulation. CNS Spectr 2003; 8: 496–514.
3. Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 2007; 3: 383–393.
4. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003; 2: 145–156.
5. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003; 114: 2220–2222.
6. Bindman LJ, Lippold OC, Redfearn JW. 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 1964; 172: 369–382.
7. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 1965; 28: 166–185.
8. Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation – technical, safety and functional aspects. Suppl Clin Neurophysiol 2003; 56: 255–276.
9. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol 2003; 114: 589–595.
10. Nitsche M, Cohen L, Wasserman EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimulation 2008; 1: 206–223.
11. Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial direct current stimulation: a computer-based human model study. Neuroimage 2007; 35: 1113–1124.
12. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001; 57: 1899–1901.
13. Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol 2005; 568: 291–303.
14. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985; 1: 1106–1107.
15. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997; 48: 1398–1403.
16. Maeda F, Gangitano M, Thall M, Pascual-Leone A. Inter- and intra-individual variability of paired-pulse curves with transcranial magnetic stimulation (TMS). Clin Neurophysiol 2002; 113: 376–382.
17. Fregni F, Boggio PS, Valle AC, Otachi P, Thut G, Rigonatti SP, et al. Homeostatic effects of plasma valproate levels on corticospinal excitability changes induced by 1Hz rTMS in patients with juvenile myoclonic epilepsy. Clin Neurophysiol 2006; 117: 1217–1227.
18. Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000; 406: 147–150.
19. Pascual-Leone A, Tarazona F, Keenan J, Tormos JM, Hamilton R, Catala MD. Transcranial magnetic stimulation and neuroplasticity. Neuropsychologia 1999; 37: 207–217.
20. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Nguyen JP. Neuropathic pain controlled for more than a year by monthly sessions of

repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin 2004; 34: 91–95.
21. Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett 2004; 356: 87–90.
22. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005; 76: 833–838.
23. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain 2006; 122: 197–209.
24. Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum 2006; 54: 3988–3998.
25. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. Neurology 2008; 70: 2329–2337.
26. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, et al. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 1999; 82: 245–251.
27. Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, et al. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain 2005; 118: 43–52.
28. Herregodts P, Stadnik T, De Ridder F, D'Haens J. Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir Suppl 1995; 64: 132–135.
29. Ebel H, Rust D, Tronnier V, Boker D, Kunze S. Chronic precentral stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 1996; 138: 1300–1306.
30. Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport 2001; 12: 2963–2965.
31. Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin 2001; 31: 247–252.
32. Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G, Cocito D. Transcranial magnetic cortical stimulation relieves central pain. Stereotact Funct Neurosurg 2002; 78: 192–196.
33. Andre-Obadia N, Peyron R, Mertens P, Mauguiere F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. Clin Neurophysiol 2006; 117: 1536–1544.
34. Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology 2005; 65: 466–468.
35. Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, et al. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain 2006; 122: 22–27.
36. Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, et al. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci 2004; 227: 67–71.
37. Sampson SM, Rome JD, Rummans TA. Slow-frequency rTMS reduces fibromyalgia pain. Pain Med 2006; 7: 115–118.
38. Fregni F, DaSilva D, Potvin K, Ramos-Estebanez C, Cohen D, Pascual-Leone A, et al. Treatment of chronic visceral pain with brain stimulation. Ann Neurol 2005; 58: 971–972.
39. Irlbacher K, Kuhnert J, Roricht S, Meyer BU, Brandt SA. Central and peripheral deafferent pain: therapy with repetitive transcranial magnetic stimulation. Nervenarzt 2006; 77: 1196, 1198–1203.
40. Boggio PS, Alonso-Alonso M, Mansur CG, Rigonatti SP, Schlaug G, Pascual-Leone A, et al. 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 2006; 85: 927–930.
41. Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–1804.
42. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 2005; 36: 2681–2686.
43. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci 2007; 25: 123–129.
44. Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke 2006; 37: 2115–2122.
45. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport 2005; 16: 1551–1555.
46. Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, et al. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. Stroke 2006; 37: 1471–1476.
47. Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005; 128: 490–499.
48. Lomarev MP, Kanchana S, Bara-Jimenez W, Iyer M, Wassermann EM, Hallett M. Placebo-controlled study of rTMS for the treatment of Parkinson's disease. Mov Disord 2006; 21: 325–331.
49. Boggio PS, Castro LO, Savagim EA, Braite R, Cruz VC, Rocha RR, et al. Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett 2006; 404: 232–236.
50. Okabe S, Ugawa Y, Kanazawa I. 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 2003; 18: 382–388.
51. Baumer T, Lange R, Liepert J, Weiller C, Siebner HR, Rothwell JC, et al. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. Neuroimage 2003; 20: 550–560.
52. Boylan LS, Pullman SL, Lisanby SH, Spicknall KE, Sackeim HA. Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease. Clin Neurophysiol 2001; 112: 259–264.
53. Ikeguchi M, Touge T, Nishiyama Y, Takeuchi H, Kuriyama S, Ohkawa M. Effects of successive repetitive transcranial magnetic stimulation on motor performances and brain perfusion in idiopathic Parkinson's disease. J Neurol Sci 2003; 209: 41–46.
54. Shimamoto H, Takasaki K, Shigemori M, Imaizumi T, Ayabe M, Shoji H. Therapeutic effect and mechanism of repetitive transcranial magnetic stimulation in Parkinson's disease. J Neurol 2001; 248 Suppl 3: III48–III52.
55. Fregni F, Santos CM, Myczkowski ML, Rigolino R, Gallucci-Neto J, Barbosa ER, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75: 1171–1174.
56. Boggio PS, Fregni F, Bermpohl F, Mansur CG, Rosa M, Rumi DO, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord 2005; 20: 1178–1184.
57. Khadilkar A, Odebiyi DO, Brosseau L, Wells GA. Transcutaneous electrical nerve stimulation (TENS) versus placebo for

chronic low-back pain. Cochrane Database Syst Rev 2008; 4: CD003008.
58. Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. Cochrane Database Syst Rev 2008; 3: CD003222.
59. Robb KA, Bennett MI, Johnson MI, Simpson KJ, Oxberry SG. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. Cochrane Database Syst Rev 2008; 3: CD006276.
60. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. Pain 2007; 130: 157–165.
61. Gadsby JG, Flowerdew MW. Transcutaneous electrical nerve stimulation and acupuncture-like transcutaneous electrical nerve stimulation for chronic low back pain. Cochrane Database Syst Rev 2000; 2: CD000210.
62. Osiri M, Welch V, Brosseau L, Shea B, McGowan J, Tugwell P, et al. Transcutaneous electrical nerve stimulation for knee osteoarthritis. Cochrane Database Syst Rev 2000; 4: CD002823.
63. Brosseau L, Judd MG, Marchand S, Robinson VA, Tugwell P, Wells G, et al. Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. Cochrane Database Syst Rev 2003; 3: CD004377.
64. Han JS, Chen XH, Sun SL, Xu XJ, Yuan Y, Yan SC, et al. Effect of low- and high-frequency TENS on Met-enkephalin-Arg-Phe and dynorphin A immunoreactivity in human lumbar CSF. Pain 1991; 47: 295–298.
65. Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. J Pharmacol Exp Ther 1999; 289: 840–846.
66. Sluka KA, Bailey K, Bogush J, Olson R, Ricketts A. Treatment with either high or low frequency TENS reduces the secondary hyperalgesia observed after injection of kaolin and carrageenan into the knee joint. Pain 1998; 77: 97–102.
67. Radhakrishnan R, Sluka KA. Spinal muscarinic receptors are activated during low or high frequency TENS-induced antihyperalgesia in rats. Neuropharmacology 2003; 45: 1111–1119.
68. Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol 2007; 20: 1–28.
69. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007; 72: 208–214.
70. Lomarev MP, Kim DY, Richardson SP, Voller B, Hallett M. Safety study of high-frequency transcranial magnetic stimulation in patients with chronic stroke. Clin Neurophysiol 2007; 118: 2072–2075.
71. Nitsche MA, Doemkes S, Karakose T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 2007; 97: 3109–3117.
72. Furubayashi T, Terao Y, Arai N, Okabe S, Mochizuki H, Hanajima R, et al. Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. Exp Brain Res 2008; 185: 279–286.
73. Jeffery DT, Norton JA, Roy FD, Gorassini MA. Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. Exp Brain Res 2007; 182: 281–287.
74. Cogiamanian F, Marceglia S, Ardolino G, Barbieri S, Priori A. Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. Eur J Neurosci 2007; 26: 242–249.
75. Hesse S, Werner C, Schonhardt EM, Bardeleben A, Jenrich W, Kirker SG. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study. Restor Neurol Neurosci 2007; 25: 9–15.
76. Fecteau S, Pascual-Leone A, Zald DH, Liguori P, Theoret H, Boggio PS, et al. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. J Neurosci 2007; 27: 6212–6218.
77. Sparing R, Dafotakis M, Meister IG, Thirugnanasambandam N, Fink GR. Enhancing language performance with non-invasive brain stimulation-A transcranial direct current stimulation study in healthy humans. Neuropsychologia 2008; 46: 261–268.
78. Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Pract 2007; 7: 297–306.
79. Levkovitz Y, Roth Y, Harel EV, Braw Y, Sheer A, Zangen A. A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. Clin Neurophysiol 2007; 118: 2730–2744.
80. Jung SH, Shin JE, Jeong YS, Shin HI. Changes in motor cortical excitability induced by high-frequency repetitive transcranial magnetic stimulation of different stimulation durations. Clin Neurophysiol 2008; 119: 71–79.
81. De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A. Theta, alpha and beta burst transcranial magnetic stimulation: brain modulation in tinnitus. Int J Med Sci 2007; 4: 237–241.
82. Sparing R, Buelte D, Meister IG, Paus T, Fink GR. Transcranial magnetic stimulation and the challenge of coil placement: A comparison of conventional and stereotaxic neuronavigational strategies. Hum Brain Mapp 2008; 29: 82–96.
83. Smith JA, Mennemeier M, Bartel T, Chelette KC, Kimbrell T, Triggs W, et al. Repetitive transcranial magnetic stimulation for tinnitus: a pilot study. Laryngoscope 2007; 117: 529–534.
84. Rossi S, De Capua A, Ulivelli M, Bartalini S, Falzarano V, Filippone G, et al. Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: a randomised, crossover, double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 2007; 78: 857–863.
85. Plewnia C, Reimold M, Najib A, Reischl G, Plontke SK, Gerloff C. Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. J Neurol Neurosurg Psychiatry 2007; 78: 152–156.
86. Langguth B, Kleinjung T, Marienhagen J, Binder H, Sand PG, Hajak G, et al. Transcranial magnetic stimulation for the treatment of tinnitus: effects on cortical excitability. BMC Neurosci 2007; 8: 45.
87. Kleinjung T, Steffens T, Londero A, Langguth B. Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects. Prog Brain Res 2007; 166: 359–367.
88. del Olmo MF, Bello O, Cudeiro J. Transcranial magnetic stimulation over dorsolateral prefrontal cortex in Parkinson's disease. Clin Neurophysiol 2007; 118: 131–139.
89. Kim JY, Chung EJ, Lee WY, Shin HY, Lee GH, Choe YS, et al. Therapeutic effect of repetitive transcranial magnetic stimulation in Parkinson's disease: analysis of [(11)C] raclopride PET study. Mov Disord 2008; 23: 207–211.
90. Epstein CM, Evatt ML, Funk A, Girard-Siqueira L, Lupei N, Slaughter L, et al. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. Clin Neurophysiol 2007; 118: 2189–2194.
91. Khedr EM, Rothwell JC, Shawky OA, Ahmed MA, Foly N, Hamdy A. Dopamine levels after repetitive transcranial magnetic stimulation of motor cortex in patients with Parkinson's disease: preliminary results. Mov Disord 2007; 22: 1046–1050.
92. Pomeroy VM, Cloud G, Tallis RC, Donaldson C, Nayak V, Miller S. Transcranial magnetic stimulation and muscle contraction to enhance stroke recovery: a randomized proof-of-principle and feasibility investigation. Neurorehabil Neural Repair 2007; 21: 509–517.
93. Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007; 130: 2661–2670.