Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques

Felipe Fregni, Steven Freedman, Alvaro Pascual-Leone

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Center for Non-invasive Brain Stimulation, Department of Neurology (F Fregni MD, A Pascual-Leone MD) **and The Pancreas Center, Beth Israel Deaconess Medical Center** (F Fregni, S Freedman MD), **Harvard Medical School, Boston, USA**

Correspondence to:
Dr 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
ffregni@bidmc.harvard.edu

Background Brain stimulation is a technique that can guide brain plasticity and thus be suitable to treat chronic pain—a disorder that is associated with substantial reorganisation of CNS activity. In fact, the idea of using invasive and non-invasive brain stimulation for pain relief is not new. Studies from the 1950s investigated the use of this therapeutic method for the treatment of chronic pain. However, recent advancements in the techniques of non-invasive brain stimulation have enhanced their modulatory effects and thus become a new, attractive alternative for chronic pain treatment.

Recent developments Recent studies with non-invasive brain stimulation—eg, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)—using new parameters of stimulation have shown encouraging results. These studies explored alternative sites of stimulation, such as the secondary somatosensory cortex (rather than primary motor cortex) for the treatment of chronic visceral pain and new parameters of stimulation, such as repeated sessions of tDCS with 2 mA for the treatment of chronic central pain.

Where next? The investigation of non-invasive brain stimulation for therapeutic effects is in its at initial stages; but the preliminary data make us optimistic. Several questions still need to be addressed before any firm conclusion about this therapy is made. Other parameters of stimulation need to be further explored such as theta-burst stimulation and the combination of tDCS and rTMS. The duration of the therapeutic effects is another important issue to be considered, especially because the current devices for brain stimulation do not allow patients to receive this therapy in their homes; therefore, maintenance therapy regimens, as well as the development of portable stimulators, need to be investigated. Further trials must determine the optimum parameters of stimulation. After that, confirmatory, larger studies are mandatory.

Introduction

Chronic pain is a common disorder that has detrimental effects on physical and psychological health, quality of life, employment, and economic well-being.[1,2] In the USA, 45% of the population experiences chronic pain at some point in their lives. Chronic pain is currently extensively studied, but therapeutic options to date are limited, and duration of the symptoms tends to make pain increasingly resistant to treatment. Because medical treatments have limited effects on patients with chronic pain, patients are twice as likely to commit suicide and lifetime prevalence of suicide attempts is about 10%.[3] Therefore, there is a pressing need for the development of new therapeutic approaches.

Mechanisms of pain

Ultimately, chronic pain is sustained by complex peripheral system and CNS mechanisms. For instance, hyperalgesia and allodynia—common components of chronic pain—are examples of situations in which peripheral and central sensitisation affect the action potential threshold of nociceptors. Although hyperalgesia is a normal, adaptive response during injury and inflammatory processes, it becomes pathological in chronic pain because it remains after inflammation is controlled, mainly due to maladaptive changes within the nervous system.

Peripheral sensitisation is usually triggered by a peripheral initiating event (eg, acute inflammation, infection, or trauma) that results in changes in the physiology of peripheral nociceptors that might not revert to the baseline, normal state after resolution of the insult.

At the central level, pain leads to plastic changes in an extensive neural network that includes the spinal dorsal horn, limbic system, and cortical structures such as the somatosensory and prefrontal cortex.[4] Therefore, chronic pain might be a result of peripheral and central sensitisation, such as in chronic pain after trauma, or may be a result of central sensitisation only, such as in chronic pain after thalamic stroke.

A clear example of pain as a result of CNS changes is phantom limb pain, where, sometimes excruciating, pain is perceived in the non-existent amputated limb. Pain in chronic pancreatitis is another good example of the role of CNS mechanisms in the pathophysiology of pain, because extremely disabling, medication-resistant pain can continue after bilateral splanchnectomy and even pancreatectomy.[5] Medication will likely affect not only the neural structures responsible for sustaining pain, but also other brain regions that can give rise to side-effects or render the interventions less effective. Therefore, therapies that directly modulate brain activity in specific neural networks might be particularly suited to relieve chronic pain. Ultimately, this underlies the interest in neurostimulation approaches, which are being explored at multiple levels of the neuroaxis, including the peripheral nerves,[6] spinal cord,[7] deep brain structures,[8] and cortex.[9] Among the methods of central neurostimulation, two of them, repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are particularly appealing as they can change brain activity in a non-invasive, painless and safe way.

Non-invasive brain stimulation for the treatment of chronic pain

TMS is a method of brain stimulation that was developed in 1985.[10] It is based on a time-varying magnetic field that generates an electric current inside the skull, where it can be focused and restricted to small brain areas by appropriate stimulation coil geometry and size.[11] This current, if applied repetitively, repetitive TMS (rTMS), induces a cortical modulation that lasts beyond the time of stimulation.[11]

Although tDCS has different mechanisms of action, it induces similar modulatory effects. Several animal studies in the 1960s showed that this technique changes brain activity reliably.[12] tDCS is based on the application of a weak direct current to the scalp that flows between two relatively large electrodes—anode and cathode electrodes. Some studies have shown that the efficacy of tDCS depends critically on parameters such as electrode position and current strength.[12] In fact, application of tDCS for 13 min to the motor cortex can modulate cortical excitability for several hours.[13,14] In addition, this technique can be used to obtain clinical gains in neuropsychiatric disorders such as stroke,[15,16] epilepsy,[17] and tinnitus.[18]

The idea of using brain stimulation to treat pain syndromes is not new. A MEDLINE search using the terms "brain stimulation" and "pain", done in April 2006, yielded 4013 articles dating back to the 1950s, including work from Delgado and colleagues[19] and Melzack and colleagues.[20] However, the development in this field has been slow when compared to the development and use of drugs. This slow progression is partly due to the fact that up until the 1990s, the only approach for treatment of pain was deep brain stimulation of the thalamus and periventricular grey region through surgically implanted electrodes. Because the costs and risks of this neurosurgical approach were high, this treatment was a last resort, restricted to patients with severe refractory pain, and efficacy was questionable. However, at the beginning of the 1990s, a new and less invasive strategy of brain stimulation, epidural motor cortex stimulation, showed substantial pain improvement[21] and brought new life to the concept of brain stimulation for the treatment of chronic pain. Epidural cortical stimulation not only decreased the neurosurgical risks of brain stimulation for chronic pain, but also invited the exploration of

	Year	Technique	Site of stimulation for active treatment group	Parameters of stimulation*	Study design	Type of control†	N	Cause of pain	Effect size‡
Lefaucheur[22]	2001	rTMS	Primary motor cortex corresponding to the painful area	10 Hz, 80% MT, 1000 pulses	Cross-over	Sham	14	Trigeminal neuralgia, thalamic stroke	1.27§
Lefaucheur[23]	2001	rTMS	Primary motor cortex corresponding to the painful area	10 Hz and 1 Hz, 80% MT, 1000 pulses¶	Cross-over	Sham	18	Thalamic stroke, brainstem lesion, brachial plexus lesion	0·43 (10 Hz)/ −0·10 (1 Hz)¶
Brighina[24]	2004	rTMS	Left dorsolateral prefrontal cortex	20 Hz, 90% MT, 4800 pulses	Parallel	Sham	11	Chronic migraine	‖
Lefaucheur[25]	2004	rTMS	Primary motor cortex corresponding to the painful area	10 Hz, 80% MT, 1000 pulses	Cross-over	Sham	60	Thalamic stroke, brainstem lesion, brachial plexus lesion, spinal cord lesion, trigeminal nerve lesion	1·48
Pleger[26]	2004	rTMS	Primary motor cortex of the hand area	10 Hz, 110% MT, 120 pulses	Cross-over	Sham	10	Minor trauma, radial fracture, luxation of 2nd and 3rd fingers, fracture of navicular	**
Khedr[27]	2005	rTMS	Primary motor cortex corresponding to the painful area	20 Hz, 80%MT, 10 000 pulses	Parallel	Sham	48	Trigeminal neuralgia, post-stroke	2·20
Fregni[28]	2005	rTMS	Right secondary somatosensory cortex	1 Hz, 90% MT, 1600 pulses	Cross-over	Sham and active	5	Chronic pancreatitis (visceral pain)	1·10
Fregni[29]	2006	tDCS	Primary motor cortex corresponding to the painful area	2 mA, 20 minutes, 5 sessions	Parallel	Sham	17	Spinal cord injury	2·11
Hirayama[30]	2006	rTMS	Primary motor cortex corresponding to the painful area	5 Hz, 90%MT, 500 pulses	Cross-over	Active	20	Post-stroke, spinal cord lesion, trigeminal neuropathy, brachial plexus injury, peripheral neuroma operation, cauda equina lesion	**
Sampson[31]	2006	rTMS	Right dorsolateral prefrontal cortex	1 Hz, 110% MT, 32 000††	‡‡	‡‡	4	Fibromyalgia	§§
Johnson[32]	2006	rTMS	Left primary motor cortex corresponding to hand area	20 Hz, 95% MT, 500 pulses	Cross-over	Sham	17	Trauma (eg, heavy lifting, vehicle accident, fall), spinal disc degeneration, arthritis, skull base fracture and Crohn's disease	0·48
Andre-Obadia[33]	2006	rTMS	Primary motor cortex corresponding to hand area	1 and 20 Hz, 1600 pulses, 90% MT *	Cross-over	Sham	14	Central supratentorial or brainstem stroke, spinal cord injury, peripheral nerve lesion	0·22 (20 Hz)/ −0·70 (1 Hz) *

We included only rTMS studies using figure-of-eight coil in this table. *Parameters of stimulation are defined as frequency and intensity of stimulation (as showed by percentage of MT (motor threshold)) and total number of pulses for rTMS studies, and current intensity, duration and number of sessions for tDCS studies. †Sham indicates sham rTMS or sham tDCS and Active indicates active stimulation (TMS or tDCS) of other areas not related to pain improvement that served as active control sites. ‡Effect size (Cohen's d) was defined as the difference between pain change (between pre and post-treatment—as indexed by visual analogue scale) between placebo and active rTMS group for each study divided by the pooled standard deviation. A value of 0·5 or more indicates a moderate to large effect size. §Values for effect size calculation were derived from the graph. ¶Results from high-frequency and low-frequency stimulation are reported in this table. Note that a negative effect size indicates an effect favouring the sham group. ‖This study used a categorical variable to measure pain (headache index: number of headache attacks and number of ingested pills); therefore, it was not possible to calculate the effect size was. ** This study did not report mean and SD for the control group. ††One of the four patients received an additional 12 sessions of rTMS. ‡‡Part of a double-blind sham-controlled trial for major depression and borderline disorder—only one patient received placebo (sham stimulation). §§Only one patient received sham stimulation.

Table: Summary of the studies that used non-invasive brain stimulation for treatment of chronic pain
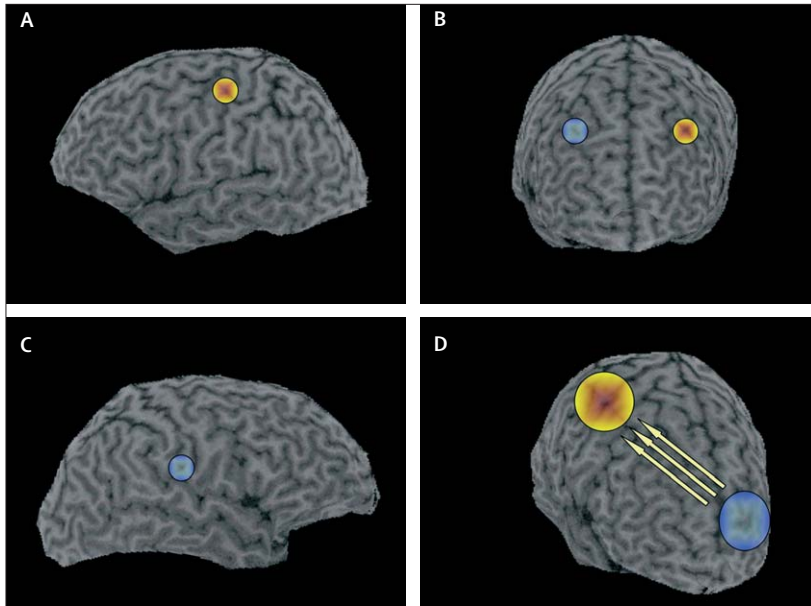
Figure: **Sites of stimulation for different techniques of non-invasive brain stimulation**
Strategy 1 was high-frequency rTMS of the primary motor cortex (A). Strategy 2 was low and high-frequency rTMS of dorsolateral prefrontal cortex (B). Strategy 3 was low-frequency rTMS of the secondary somatosensory cortex (C). Strategy 4 was anodal tDCS of the primary motor cortex (D). Stimulation with rTMS (strategies 1, 2, and 3) induces a focal change in cortical activity. Studies with this technique showed pain reduction after stimulation of the primary motor cortex with high-frequency rTMS, stimulation of the secondary somatosensory cortex with low-frequency rTMS, and stimulation of the right and left dorsolateral prefrontal cortex with low and high-frequency rTMS, respectively. Stimulation with tDCS induces a less focal change in brain activity in the areas under the cathode and anode electrodes. It has previously been shown, as depicted in this figure as strategy 4, that anodal stimulation of the primary motor cortex (red/yellow area indicates an increase in cortical excitability that is induced by brain stimulation) reduces pain substantially (arrows indicate the direction of the electric current). The blue/green area indicates a decrease in cortical excitability, which is induced by brain stimulation.[23,25-28]

non-invasive brain stimulation techniques, tDCS and rTMS, which also primarily target the brain cortex.

Initial clinical studies

The first study of rTMS in chronic pain was done by Lefaucheur and colleagues[22] in 2001. They did a placebo-controlled study in 18 patients with intractable neurogenic pain and showed that 10 Hz rTMS of the motor cortex induced substantial pain relief (as assessed by visual analogue scale) as compared with sham rTMS. 3 years later, the same group confirmed their previous results in a similar study with a larger sample size of 60 patients with intractable central pain.[23] And recently, Khedr and colleagues[24] showed that multiple consecutive sessions of rTMS are associated with substantial pain relief (indexed by visual analogue scale). The table[22–33] has a summary of studies that used non-invasive brain stimulation for pain relief.

On the basis of this evidence, we hypothesised that patients with visceral pain might also obtain pain relief from rTMS treatment because changes in activity in the somatosensory cortex are usually reported in these patients as well.[34] We did a preliminary crossover, sham-controlled study in 5 patients with chronic visceral pain due to pancreatitis. These patients received (in a random order) six sessions of rTMS, with different parameters of

stimulation, right and left secondary somatosensory cortex stimulation with 1 Hz, 20 Hz, and sham. The results showed that 1 Hz (of left and right secondary somatosensory cortex) and right somatosensory cortex (with 1 and 20 Hz) stimulation led to a significant pain reduction (indexed by pain and medication reduction; mean reduction of 36% and 31%, respectively).[28]

We have also assessed the clinical use of tDCS for chronic pain relief. Patients with chronic pain due to spinal cord injury (n=17) were randomised to receive sham or active motor tDCS (2 mA for 20 min for five consecutive days). There was a significant pain improvement after active anodal stimulation of the motor cortex, but not after sham stimulation.[29] In addition, there was a significant cumulative analgesic effect, and the peak of pain reduction on visual analogue scale was achieved after the last session of stimulation. 2 weeks after stimulation was stopped, patients still showed a trend of less pain compared with baseline in the active tDCS group.[29] The importance of this study lies in the fact that tDCS has some advantages over rTMS because it has longer-lasting modulatory effects of cortical function, is less expensive, easy to administer, and provides a reliable sham-stimulation condition to assess the specificity of the effects.

Although these studies show a substantial reductions in pain, there is a significant variability in the effect size across these studies. One important contributor to this variability is the effect of the parameters of stimulation, particularly the frequency of stimulation, number of rTMS sessions, and site of stimulation. For instance, two studies showed that 1 Hz rTMS induces a worsening (although this was not significant) in pain as compared to sham stimulation. Lefaucher and colleagues[23] reported a negative effect size of 0·1 and Andre-Obadia and colleagues[33] found an even larger negative effect size of 0·7 after stimulation of the primary motor cortex with 1 Hz rTMS. Another important parameter is the number of sessions. For the treatment of depression, the number of rTMS sessions was correlated to the magnitude of its effects.[35,36] Additional numbers of sessions might decrease the variability of response. Indeed, the largest effect size (2·20) was obtained by the study of Khedr and colleagues,[24] which had five consecutive sessions and, in addition, Fregni and colleagues,[29] in a study of five consecutive sessions of tDCS, also showed a large effect size (2·10). The number of sessions might also explain why one of the studies, Andre-Obadia and colleagues,[33] showed a non-significant difference between the 20 Hz rTMS and sham rTMS (table). Finally, although the initial evidence supports the use of excitability-enhancing methods of brain stimulation of the primary motor cortex to improve pain, other cortical areas have not been optimally explored. Dorsolateral prefrontal cortex, an area that is targeted for the treatment of depression, might offer some benefits for patients with chronic pain, as shown in the studies of Brighina and colleagues[27] and Sampson and colleagues.[31] Future studies that explore the effects of different areas as compared with

Search strategy and selection criteria

We did searches for papers on tDCS for the treatment of chronic pain and we only used those that were published in an indexed journal during January 1985 to August 2006. Where two or more published studies reported overlapping data sets, we chose the study with the largest study population. Single case reports were excluded and only those papers that were written in English were used.

the primary motor cortex, such as the recent study of Hirayama and colleagues,[30] are critical (figure).

Conclusions

The field of non-invasive brain stimulation for the treatment of pain is a new and rapidly devloping field. Although a great deal of research and confirmatory studies are still critically necessary to draw firm conclusions about the role of neurostimulation in clinical practice, we are optimistic that, in the future, rTMS and tDCS might become new therapeutic options for patients with chronic pain. New studies investigating other parameters of stimulation to achieve long-lasting effects as well as investigations that compare the effects of drugs with those of non-invasive brain stimulation are needed to increase our understanding and the clinical implications for the use of these new neuromodulatory methods.

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