Methods to focalize noninvasive electrical brain stimulation: principles and future clinical development for the treatment of pain

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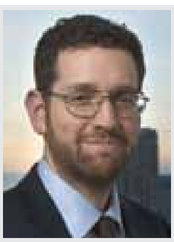
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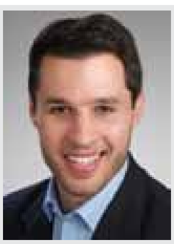
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There has been increased interest in noninvasive brain stimulation (NIBS) as a technique to investigate and treat neuropsychiatric disorders [1,2]. Usually, NIBS is targeted to specific dysfunctional cortical areas, as the case for prefrontal cortex stimulation in mood disorders [3], or regions presumed to modulate dysfunctional areas, as the case for primary motor cortex (M1) stimulation to influence thalamic activity in chronic pain syndromes [4]. The neurophysiological effects are based on modulation of cortical excitability. NIBS, using common and validated protocols, is considered safe and painless and is not associated with severe adverse effects [5]. The two main techniques of NIBS that have been currently explored are transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), though additional approaches such as transcranial alternating current stimulation, cranial electrotherapy stimulation/transcranial pulsed current stimulation and nonelectrical modalities are under investigation [6,7].

Although transcranial magnetic stimulation is an effective technique to induce focal changes in cortical excitability, it is relativity costly, requires wall-powered equipment to produce the required stimulation intensities and it may lead to seizures. The recent development of tDCS provides a more cost-effective, portable and simple approach of NIBS [3]. This technique has shown to induce significant effects on neuroplasticity as shown by animal models and human studies [8–10].

While almost every individual has experienced pain, and indeed, in some situations, such as in acute conditions, pain is advantageous as to protect against further damage, the field of medicine is still dedicating massive amounts of resources and time in order to free humanity from this form of unpleasant condition especially in chronic syndromes. In fact, for chronic refractory pain, most forms of therapeutic efforts provide only transient relief for many patients without much solution addressing the fundamental basis of the problem. The simplistic conception of pain as just a reflexive response to physical damage has evolved in the last century, nowadays, there is more focus on the brain's role as the main modulatory organ for perception, response and, thus, a possible solution of the problem by itself. Though the central mechanism involved in chronic pain remains under investigation, increasing evidence supports the use of brain stimulation in the treatment of chronic refractory pain.

There has been a great interest in exploring tDCS as a CNS-based therapeutic tool for the treatment of chronic pain. Such

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interest has been an evolution from the first neurosurgical studies showing that modulation of M1 is associated with significant reductions of pain, followed by mechanistic neuroimaging studies showing that M1 stimulation induces significant and correlated changes in thalamic activity. There have been several small studies showing the effects of tDCS on alleviating neuropathic pain and a recent meta-analysis showed that tDCS is associated with a pooled effect size in pain of 0.59 as compared with sham tDCS [11].

Traditional tDCS includes the use of two large sponge-based electrodes placed on the scalp. Cathodal stimulation is considered to induce hyperpolarization, thereby decreasing cortical excitability, and anodal stimulation induces a depolarization, thus, increasing cortical excitability. One perceived limitation for the use of tDCS is its nonfocal effects related to the use of two large sponge electrodes. Recent development has shown that it is possible to focalize the effects of tDCS through either optimization of electrode design to focalize current delivery or by integrating stimulation with cognitive/behavioral methods to produce 'functionalized' focalization. To physically induce focal delivery of current to the underlying cortex, the use of small ring-like 'high-definition' (HD) electrodes following specially designed montages have been used [12]. Recent modeling and experiential study has confirmed the focality of induced electrical currents by HD-tDCS [13]. Functionalized focal stimulation effects can also be achieved by combining tDCS with specific cognitive/behavioral methods; therefore, functional network activation/discrimination can be achieved depending on the tasks aimed to trigger selective cortical areas.

Focalizing tDCS by using arrays of small HD electrodes

One of the methods to increase focality of tDCS is the use of an array of small electrodes [14]. HD-tDCS requires specially designed electrode for consistent and well-tolerated stimulation [15]. One deployment of HD-tDCS is the 4 × 1-ring configuration where one active HD electrode is surrounded by four return electrodes of the opposite polarity [16–18]; cortical modulation is presumed to be limited the cortex circumscribed by the ring radius [19]. The polarity of the center HD electrode determines the dominant polarity of stimulation, for example center anode with four return cathodes, is predicted to produce dominantly excitation [20]. Two studies have investigated the use of HD-tDCS on chronic pain.

Borckardt *et al*. investigated whether HD-tDCS over the motor cortex would decrease pain and sensory experience. The results of the effects of HD-tDCS on sensory and pain perception show that real HD-tDCS is associated with significantly decreased heat and cold sensory thresholds, decreased thermal wind-up pain and marginal analgesic effect for cold pain thresholds. No significant effects were observed for mechanical pain thresholds or heat pain thresholds [12]. These results provided the first confirmation of the analgesic effects of HD-tDCS.

In a subsequent study testing the effects of HD-tDCS in fibromyalgia subjects, Villamar *et al*. investigated the HD-tDCS as alternative treatment for chronic pain caused by fibromyalgia [20]. The findings from this study show changes in VNS for overall pain. Overall, cathodal stimulation led to a numerically greater pain reduction compared with anodal HD-tDCS. Furthermore, only anodal stimulation led to significantly increased thresholds. No significant changes between visits were found for the Adapted QOL Scale for persons with chronic illness, BDI-II nor the pain and medication diary. In summary, this study showed that both active conditions (anodal and cathodal HD-tDCS of M1) induce significant reductions in pain.

Focalizing tDCS by combining with behavioral therapies

The relationship between function and anatomical localization within the human cortex has been well established; studies from intraoperative recordings, imaging and electrophysiological methods have validated the concept of specialized cortical structures and their association with precise functions. Using these concepts, physicians and therapists have developed methods and techniques that combine cognitive and behavioral engagements in order to promote activation of specific areas of the brain, for instance, constrained-induced movement therapy has been used to facilitate motor rehabilitation in stroke patients forcing the activation of the affected hemisphere by using the paretic limb, while the unaffected hemisphere is 'shut-down' by the limitations presented by the constrain movement on the unaffected limb. In a study conducted by Williams *et al*., authors investigated the effects of tDCS combined with unilateral motor training with contralateral hand restraint. Their results showed that tDCS enhances the effects of unilateral motor training and contralateral hand restraint on motor function. These benefits were associated with specific differences in bi-hemisferic modulation when dominant versus nondominant and tDCS effects were taken into account for rehabilitative purposes [21].

Focalizing the effects of tDCS can also be seen in other areas, such as in the occipital cortex when combining with a visual-behavioral task – vision restoration therapy. In a recent study combining computer modeling and neuroimaging data in a patient who received this combined therapy for 10 sessions, the authors showed that activation in the visual cortex was more intense in specific occipital areas [22]. Indeed the activation was higher in the left occipital cortex near the lesion when compared with the right occipital cortex, suggesting perilesional plastic changes that reflect increments in the visual function. Interestingly, computer modeling data showed diffuse activation over occipital-parietal areas – in an area that was much larger than what was shown by the functional neuroimaging study. Another important finding of this study was the significant correlation between these two cortical maps (as shown by neuroimaging and modeling study). These two studies – combining tDCS with motor training and tDCS with visual training – showed that simultaneous behavioral training focalizes the effects of tDCS to specific neural networks.

Conclusion & future directions

As exemplified above, it appears feasible to focalize the neuromodulatory effects of tDCS by positioning the montage to those areas related with specific functions. In addition, when the subject is engaged in a cognitive or behavioral tasks related with the selected lobe or hemisphere, it may be possible to enhance the facilitatory mechanisms of anodal tDCS, as when the neural networks are being active, neuroplastic phenomena can be boosted, consequently enhancing the effects of rehabilitative therapies. In chronic pain, one can envision the combination of tDCS with behavioral tasks, such as sensory retraining, as has been tested successfully [23] or with cognitive behavioral training as to modulate predominantly emotional-affective aspects of chronic pain.

tDCS is a promising technique that can be used in chronic pain syndromes and in combination with rehabilitation therapies. It remains to be established if focal tDCS, as produced by HD-tDCS or combined with behavioral therapies, would enhance clinical outcomes, though early evidence suggests that it enhances neuromodulatory effects [17] and may, thus, prolong therapeutic benefits by consolidating mechanisms of neuroplasticity. Focal stimulation would also presumably increase the specificity of neuromodulation also, thus, may reduce the development of adverse effects. Further research is needed to elucidate the full potential of focal tDCS and its applicability for clinical conditions such as chronic pain and in rehabilitation medicine.

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