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Immediate and Sustained Effects of 5-Day Transcranial Direct Current Stimulation of the Motor Cortex in Phantom Limb Pain

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Abstract: **The study explored the analgesic effects of transcranial direct current stimulation (tDCS) over the motor cortex on postamputation phantom limb pain (PLP). Eight subjects with unilateral lower or upper limb amputation and chronic PLP were enrolled in a crossover, double-blind, sham-controlled treatment program. For 5 consecutive days, anodal (active or sham) tDCS was applied over the motor cortex for 15 minutes at an intensity of 1.5 mA. The 5-day treatment with active, but not sham, tDCS induced a sustained decrease in background PLP and in the frequency of PLP paroxysms, which lasted for 1 week after the end of treatment. Moreover, on each day of active tDCS, patients reported an immediate PLP relief, along with an increased ability to move their phantom limb. Patients' immediate responses to sham tDCS, on the contrary, were variable, marked by an increase or decrease of PLP levels from baseline. These results show that a 5-day treatment of motor cortex stimulation with tDCS can induce stable relief from PLP in amputees. Neuromodulation targeting the motor cortex appears to be a promising option for the management of this debilitating neuropathic pain condition, which is often refractory to classic pharmacologic and surgical treatments.**

Perspective: ***The study describes sustained and immediate effects of motor cortex stimulation by tDCS on postamputation PLP, whose analgesic action seems linked to the motor reactivation of the phantom limb. These results are helpful for the exploitation of tDCS as a therapeutic tool for the management of neuropathic pain.***

Key words: *Phantom limb pain, transcranial direct current stimulation, motor cortex, phantom movement, neuroplasticity.*

Phantom limb pain (PLP), a pain of neuropathic origin, refers to the presence of painful sensations in an absent limb that has been removed by amputation.[12,13] PLP is a common sequela of amputation following trauma or peripheral vascular disease, with an incidence of up to 80%.[27] The management of PLP is difficult, with the condition often being refractory to classic pharmacologic and surgical treatments. In recent years, various therapeutic strategies have been proposed, but there is still little evidence-based support for their clinical effectiveness.[12,33]

Although the etiology and pathophysiological mechanisms of PLP are not yet clearly defined, theoretical and empirical works indicate that brain changes represent a major determinant, proposing maladaptive plasticity as a neural basis of PLP.[13] In animals, substantial plastic reorganization following deafferentation was shown at multiple loci, from the cortex to the spinal cord.[23,37,42] In humans, emphasis was given to the cortex, with postamputation reorganization of sensory and motor maps closely related to the development of PLP.[13,46] Cortical reorganization also involves changes in cortical excitability. Transcranial magnetic stimulation studies in upper- and lower-limb amputees show that motor threshold and intracortical inhibition

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decreases for the muscle proximal to the amputation, suggesting an increased excitability of the corticospinal neurons and a reduction of gamma-aminobutyric acid activity at the cortical level.[7,9,10,29,47] Although the relationship between motor excitability and PLP remains unclear,[29,34] these cortical excitability shifts were shown to be larger in patients with PLP than in pain-free patients.[13,24,29]

In light of this evidence, there is considerable interest in determining whether PLP could be alleviated through noninvasive brain stimulation. A large amount of research shows that neurostimulation methods targeting the primary motor cortex (M1) are effective for different types of chronic neuropathic pain when long-term drug therapy is ineffective.[30,40] However, few studies have explored these approaches in PLP. Overall, only 2 studies have been conducted with transcranial direct current stimulation (tDCS). The first showed that just a single application of anodal tDCS to M1 induces short-lived (<90 minutes) PLP relief.[4] A following single case report suggests that repeated tDCS applications may prolong the analgesic effects of tDCS on PLP.[5]

With a crossover, double-blind, sham-controlled design, we explored the effect of a 5-day treatment with anodal tDCS of the motor cortex on PLP, with the primary goal of establishing enduring analgesic effects on the intensity of background PLP (ie, pain felt constantly in the phantom limb) and on the frequency of PLP paroxysms (ie, episodes of increased PLP above the background level). We also assessed immediate, day-by-day changes of PLP and nonpainful sensations induced by tDCS, including the patients' ability to move their phantom limb. Indeed, motor components of the phantom limb seem strictly related to PLP,[17,38,46] but so far, no previous research on the analgesic effect of motor cortex stimulation by tDCS has searched for a possible concurrent modulation of the motor components of the phantom limb.

Method

Participants

Eight amputees (all right-handed before amputation) were recruited from the inpatient and outpatient populations of the Neurological Rehabilitation Unit of the Hospital "Carlo Poma" of Bozzolo (Italy) and of the Vascular Surgery Unit of the Hospital "Alessandro Manzoni" of Lecco (Italy). Seven of 8 patients suffered from unilateral lower limb amputation, while in 1 patient, the upper limb was amputed. Demographic and clinical data of the patients are reported in Table 1.

The protocol followed the guidelines of the Declaration of Helsinki and was approved by the local ethical committee of each hospital. Each patient gave informed consent before participating in the study. Inclusion criteria were as follows: 1) age 18 to 90 years, 2) normal score (>24) at the Mini-Mental State Examination,[14] 3) limb amputation at least 2 months before study enrollment, 4) stable presence of PLP for at least 2 months, and 5) written informed consent. Exclusion criteria were as follows: 1) coexistence of major neurologic, neuropsychological, and psychiatric diseases; 2) being actively enrolled in a separate study targeting pain relief; and 3) any contraindication to noninvasive brain stimulation.[48]

Before the experiment, each patient underwent a detailed interview about phantom sensations in order to assess 1) the features of phantom limb sensations; 2) the features of PLP; 3) presence of voluntary or involuntary phantom movements or of immobilized phantom postures; and 4) any other subjective descriptions of the qualities of the deafferentation pain. Patients were encouraged to describe exhaustively the quality of any subjective sensation they perceived in their phantom limb.

Additionally, the Groningen Questionnaire Problems after Amputation[27] was used to assess the following: time, side, level, and reason of amputation; duration of pain experienced before amputation; frequency of phantom sensation, phantom pain, and stump pain; amount of trouble and suffering experienced as a consequence of these sensations; type of phantom sensations; and medical treatment received for phantom pain and/or stump pain and self-medication (see Table 1).

tDCS Treatment Protocol

In a crossover, double-blind, sham-controlled design, the amputees underwent 2 weeks of treatment with tDCS comprising 1 week of active tDCS (5 days, Monday to Friday) and 1 week of sham (5 days, Monday to Friday) tDCS, counterbalanced across participants. Therefore, 4 of the 8 patients received active tDCS in the first week of treatment followed by a week with sham tDCS, and the remaining 50% of patients received the 2 stimulations in the opposite order (week 1, sham tDCS; week 2, active tDCS). Patients continued their usual drug intake during the treatment (see Table 1).

tDCS was delivered with a battery-driven constant current stimulator (BrainStim, E.M.S. s.r.l., Bologna, Italy; http://brainstim.it) using a pair of surface saline-soaked sponge electrodes placed on the patient's scalp. The anodal electrode was placed over C3 or C4 (according to the 10-20 electroencephalograph system for electrode placement) in order to stimulate M1 contralateral to the amputation, with the cathode electrode over the contralateral supraorbital area. This choice was guided by 2 main considerations: First, massive sensorimotor cortical reorganization occurs in the cerebral hemisphere contralateral to the amputation[9,13,46]; second, in order to produce analgesic effects, brain stimulation should be applied to the motor cortex contralateral to the side of pain.[29] Moreover, in the treatment of chronic pain, motor cortex stimulation with repetitive transcranial magnetic stimulation (rTMS) may be more effective when the stimulation site is adjacent to the cortical representation of the painful zone, rather than within the painful zone itself.[31] However, the low spatial resolution and diffuse current spread of tDCS does not allow focal stimulation of the hand (or leg) area in M1 as rTMS does; indeed, analgesic effects were induced by stimulating with tDCS the M1 relative to the upper limb even for sublesional pain in the lower limbs.[15]