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Short communication

Cortical neuromodulation for neuropathic pain and Parkinson disease: Where are we?

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ABSTRACT

Cortex neuromodulation is promising approach for treatment of some neurological conditions, especially neuropathic pain and Parkinson's disease. Effects of non-invasive cortical stimulation are short lived; transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) may be useful to assess the suitability for invasive cortical stimulation. Direct cortical stimulation (DCS) is the method able to provide long-lasting effects in treatment of neuropathic pain and some symptoms of Parkinson's disease through the use of totally implantable systems that ensure a chronic stimulation.

1. Introduction

Cortical neuromodulation aims to induce stimulation of the defined cortical areas in attempt to reduce chronic symptoms of neurological diseases by directly altering brain activity.

There are currently a number of standard invasive and noninvasive cortical neuromodulation methods: some have shown great promise in treating neurological disorders, while other are already accepted in clinical practice. We illustrate these methods by discussing results, advantages and disadvantages, and possible mechanisms of action.

2. Invasive cortical stimulation

Direct electrical stimulation of precentral cortex (DCS), also known as motor cortex stimulation (MCS), is an invasive neuromodulation method in which paddle lead is implanted in the epidural space or more rarely in subdural space over the motor cortex to deliver chronic electrical stimulation. Lead placement is carried out through a craniotomy or burr holes performed respectively under general and local anesthesia with sedation [35]. The stimulation waveform is a continuous biphasic pulse train delivered at an amplitude below motor threshold.

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The surgical risks of the procedure include epidural or subdural intracranial bleeding depending on the implantation site and infection. Seizures induction has been reported following DCS programming and during chronic stimulation, not necessary leading to the development of epilepsy [24].

Chronic direct stimulation of the precentral cortex is a clinically accepted treatment for medication refractory neuropathic pain [1,2,34,36].

This method was first reported by Tsubokawa in 1991 [32] for the treatment of central pain; by the time its indications have been extended to various types of peripheral and central deafferentation pain refractory to common treatments included, when indicated, spinal cord stimulation (post-stroke pain, phantom limb pain, spinal cord injury pain, postherpetic neuralgia and trigeminal neuropathic pain).

DCS has proven effective in intractable chronic pain conditions but no randomized controlled study has yet been published. A literature review by the European Federation of Neurological Societies covering more than 200 patients treated with DCS found that 50–60% of patients had significant pain relief [3]. Others scientific studies confirm that different forms of central pain and peripheral neuropathic pain can be effectively treated with DCS [37,39]. Review of the literature reports that patients with neuropathic facial pain achieved ≥ 60% pain relief with DCS. Post-stroke pain responds nearly as well, with almost two-thirds of patients obtaining good to excellent relief [24,27,36].

The mechanisms underlying the effects on neuropathic pain is actually still unknown. A corticospinal system relatively intact is necessary, but not sufficient, to achieve pain control, while success in DCS treatment does not require intact somatosensory system. It has been proposed that action mechanism may act by reinforcing the control of non-nociceptive sensory inputs on nociceptive systems at the level of the thalamus, dorsal column nuclei and spinal cord but other suggested mechanism involves supraspinal structures (cingulate gyrus, orbitofrontal cortex and brainstem) [4,10,11,28,29]. DCS-induced pain relief is associated with an improved sensory discrimination within the painful zone suggesting that stimulation of motor cortex acts on somatosensory pathways and sensory processing [24].

Reported amplitudes range from 0.5 V to 10 V, rates from 5 Hz to 130 Hz and pulse widths from 60 μs to 450 μs, increasing the intensity by 20% if necessary [5,6,23,30,37,39].

DCS of the precentral cortex is also used to treat Parkinson's disease (PD) and essential tremor (ET) [4–6,8,10,28–31]. The number of patients treated remains small but Direct Cortical Stimulation can reduce PD symptoms (tremor, rigidity, akinesia, freezing of gait, balance) and to a greater extent axial symptoms. One reason that DCS is not more widely used as treatment for PD is that, as with chronic pain, not all patients show significant symptom improvement. Furthermore DCS is not yet as effective as deep brain stimulation (DBS) for PD. Nevertheless, some authors [10,11,29] concluded that DCS is a important treatment option for a subgroup of PD patients who are contraindicated for DBS. DCS has also been used in a small number of patients to treat medically refractory tinnitus and depression with some success [12].

There are several mechanisms proposed to explain the effects of DCS on PD. The motor cortex region is the final common link between deeper circuitry coordinating movement and the spinal cord itself. It is one of the few areas in which the pyramidal and extrapyramidal systems interact. The motor cortex is connected to the basal ganglia indirectly via a cortico-striatal pathway and directly via a cortico-subthalamic circuit. DCS may exert its effect modulating the subthalamic nucleus (STN) directly or through the loop cortex-striatum-lateral globus pallidus-STN [4]. Chronic stimulation of motor cortex may alter not only the firing patterns in the basal ganglia but also, due to its location, the interactions between the pyramidal and extrapyramidal systems [12]. Finally it may modulate the activity of the supplementary motor area (SMA) or the "suppressor cortical system" [11].

In summary DCS can treat effectively neuropathic pain and PD symptoms in some patients that are refractory to pharmacological treatment and cannot be treated with other stimulation techniques. However, it is difficult to predict which patients will respond. Since the method involves a neurosurgical procedure, this has impact on its clinical application.

3. Noninvasive cortical stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive neuromodulation method that uses a magnetic field to induce current flow in the cortex by means of a figure-of-eight coil. The stimulation waveform can be single, paired, or burst pulses [4,7] usually applied repetitively (rTMS) and can be delivered at amplitudes high enough to cause limb movement when the coil is positioned over the motor cortex [33]. Two rTMS procedures are used: low-frequency rTMS (1 Hz with continuous trains of single pulses) and high-frequency rTMS (more than 5 Hz with bursts of pulses).

Because it is noninvasive, TMS has a widely used in research. TMS of the motor cortex has been explored as a treatment for both neuropathic pain and PD [13,14]. While significant effects have been reported for treating both disorders, they are often too modest to be clinically relevant [15,16] or the effects tend to be short lived [3,17]. This highlights one of the limitations of TMS: the strong magnetic field and stimulator size mean that it can only be used in laboratory or clinical setting and cannot deliver chronic stimulation.

Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are noninvasive neuromodulation methods in which two large square electrodes are placed on the scalp to deliver low amplitude currents (typically <2 mA) that are able to cross the skull by inducing effects on excitability of cortical neurons [18–20]. Main adverse effect of tDCS and tACS is the onset of burns on the scalp at the site of the stimulating electrodes.

While TMS and DCS work by using high amplitude and pulsed waveforms to initiate action potentials in axons [21], the mechanisms behind tDCS and tACS are quite different and are not completely understood. tDCS uses low amplitude direct current to cause somatic and dendritic polarization across a spatially broad neuronal population and has effects that persist after stimulation has stopped [18,22]. tACS uses low amplitude sine waves (alternating current) which also act

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