Thieme

New Results on Brain Stimulation in Chronic Pain

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ABSTRACT

Pain that has become chronic has lost its warning function and is associated with dysfunction of the so-called pain network. Systematic brain stimulation aims to normalize this network by modulating neuronal activities. Non-invasive DC stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) are considered effective in pain treatment. Here, the stimulation of the primary motor cortex (M1) plays a central role. If the pain is not adequately controlled by tDCS and rTMS, invasive procedures such as motor cortex stimulation (MCS) or deep brain stimulation are available as a last resort.

Introduction

Over the past decades, various methods of neuromodulatory stimulation have been established. Of these, the stimulation of the primary motor cortex (M1) and the dorsolateral prefrontal cortex (DLPFC) using transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are of particular interest. Both techniques allow the induction and modulation of neuroplastic changes in the cerebrum through modification of neuronal activity or resting membrane potential. As the two techniques primarily permit stimulation of cortical areas, they are less suitable for direct stimulation of deeper structures, such as the thalamus. However, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies showed that multiple deeper structures can be reached indirectly by (superficial or epidural) stimulation of M1 or DLPFC [1–3].

TMS uses the magnetic field of a coil to induce a brief electrical current in the brain, while tDCS uses constant direct current delivered via electrodes on the scalp. The primary effect of tDCS is most likely caused by de - or hyperpolarization of neuronal membrane potentials. The aftereffects of the stimulation can be influenced by pharmacological interventions either positively or negatively [4, 5]. Response to tDCS in patients with depression can be enhanced by co-application of serotonin reuptake inhibitors [6, 7]. In M1, D-cycloserine (glycine receptor agonist and thus indirect NMDA receptor agonist) can prolong tDCS aftereffects from 1 h to 24 h [5]; however, this has not yet been evaluated in pain therapy.

Application of rTMS and tDCS in Pain patients

Chronic pain induces a change of the anatomical pain network, primarily comprising DLPFC, M1, somatosensory cortex, the anterior cingulate cortex, and the thalamus. In patients with chronic back pain, a progressive decrease in neocortical gray matter (DLPFC) of 5–11 % compared to healthy subjects is observed over the years [8]. Per pain year the loss of gray matter density was approximately 1.3 cm^3.

The use of rTMS and tDCS in chronic pain patients has evolved from the concept of invasive motor cortex stimulation (MCS) using epidurally implanted electrodes in patients with chronic thalamus pain [9–11]. The MCS effect is explained by inhibition of both nociceptive afferent fibers and affective-motivational pain components via the medial thalamus and anterior cingulate cortex. The empirically established stimulation parameter space differs between rTMS (typically 5 to 20 Hz) and MCS (20 Hz and higher frequencies).

Patients with treatment-resistant pain are typically stimulated for 20 min per session with 'excitability-enhancing' 10 Hz over M1 [12, 13]. In line with MCS data, it was shown that most likely not an inhibition but an activation of M1 via its projection to the thalamus inhibits afferent pain fibers ascending there [14]. In this way, activation of thalamic nuclei can in turn modify the activity of other pain-associated structures (e.g., anterior cingulate cortex, periaqueductal gray) at least temporarily and thus inhibit e.g., pain of primarily spinal origin.

A PubMed search (search terms: rTMS/TBS (theta burst stimulation) and neuropathic/neurogenic pain) currently identified 68 studies, including 19 placebo-controlled studies with at least 10 patients with chronic neuropathic pain, receiving active low-frequency (LF) or high-frequency (HF) rTMS over M1. The analysis included a total of 688 patients [15]. Stimulation was always applied contralaterally to the pain site. The conclusions drawn from this analysis are in line with those from other reviews (e.g., [16–18]): (i) LF rTMS over M1 is most likely not effective; (ii) HF rTMS over M1 results in pain relief of more than 50 % only in one-third of the patients; (iii) repeated HF rTMS sessions (5–10 sessions, 1 session/day) increase the analgesic effect [15]. The effectiveness of one single HF rTMS session usually lasts for a few days and can be enhanced and extended by repeated stimulation [16]. A most effective protocol (site of stimulation, stimulation frequency, number of impulses per session and number of sessions) has not been determined yet. A predictive value of HF rTMS over M1 appears to show a positive correlation with invasive MCS [14, 19–22].

TBS (grouped stimulation with 3 pulses at 20-ms intervals, repetitive with 5 Hz) has either an inhibitory (cTBS, continuous) or facilitatory (iTBS, intermittent with 8-second pause after stimulations of 2 s each) action [23]. According to current data, the shorter, 'excitability-increasing' iTBS protocol is apparently not capable of inducing an analgesic effect. In addition, the responsiveness of varies types of neuropathic pain was not further differentiated [24–27]. Stimulation of DLPFC is based on the concept that, besides chronic pain, a positive effect is exerted on the depression component (e.g., [15, 28]).

In chronic pain, tDCS is less effective compared to HF rTMS. A PubMed search [search terms: tDCS AND (pain or migraine)] identified 269 studies, including 62 clinical studies with 1426 patients [29]. Central neuropathic pain conditions (including central pain after stroke and traumatic spinal injury), peripheral neuropathic pain, musculoskeletal pain (including fibromyalgia and myofascial pain); migraine, orofacial pain, chronic back pain (of lower back) and abdominal or pelvic pain were included. Application of stimulation was either to the contralateral M1 (anodal) or, in pain without side preferences, the dominant hemisphere of the left DLPFC or the primary visual cortex in migraine (cathodal) [30, 31]. In migraine, a cathodal inhibition of hyperexcitability of the primary visual cortex is assumed.

Most studies used a stimulation intensity of 1 - 2 mA and an electrode size of 35 cm^2. Session duration ranged from 10 min to 20 min/day and sessions were repeated on up to 20 consecutive days. The most common protocol consisted of anodal stimulation over M1 for 20 min on five consecutive days. The analgesic effect lasted for 2 to 6 weeks [32–37].

The evidence grade attributed to direct current stimulation is considered lower compared to that of rTMS, primarily due to the higher numbers of patients in rTMS studies [14, 15]: grade A for rTMS in the treatment of chronic neuropathic pain of the head or upper extremities and grade B for tDCS in the treatment of fibromyalgia and neuropathic pain of the lower extremities (an evidence grade A for tDCS cannot be established due to insufficient number of studies). Only one placebo-controlled study directly compared the analgesic effect of the two approaches [38]. In patients with neuropathic pain, however, rTMS (3 stimulations/day) relieved the pain associated with lumbosacral radiculopathy, whereas anodal tDCS did not.

Invasive Pain Management

One disadvantage of the non-invasive techniques is the lack of persistent response to treatment. If the duration of pain relief achieved by tDCS and rTMS is too short or if no adequate pain control can be achieved, the next step is to evaluate minimally invasive extracranial surgical interventions. Here, spinal cord stimulation (SCS) and peripheral nerve field stimulation (sPNS) are of special interest. In patients with failed back surgery syndrome (FBSS) and peripheral neuropathic pain, SCS was used with good response. SCS treatment of pain syndromes after incomplete spinal cord injuries is less successfull. In regional pain conditions, sPNS plays an increasingly important role and recent attempts of treating trigeminal pain with sPNS have been successful [39]. Should these surgical procedures fail, two invasive brain stimulation methods are available as a last resort.

1. With MCS, continuous stimulation of M1 in the area of the cortical representation of the pain region is applied. To this end, one or more electrodes are placed in most cases epidurally, but rarely also subdurally, either via burr-hole trepanation or via craniotomy. Neuronavigation and functional magnetic resonance imaging can be used to increase precision of electrode positioning. With neither a standardized technique to perform the procedure nor uniform stimulation parameters available, the comparability of clinical studies is limited [40]. In the meantime, a consensus has been established that prior to implantation of a pulse generator, the stimulation effect should be tested over a period of several days. However, here again there is no standardization with regard to trial period duration, stimulation parameters to be tested and need for placebo stimulation [41, 42]. A longer trial period may lead to an increase of infectious complications. MCS was used in numerous central and peripheral pain syndromes with variable success [43]. Best and most reproducible are the results with trigeminal neuropathic pain [41, 44]. Likewise, good results were achieved with pain

after spinal cord injury and phantom pain, whereas the success rates in patients with central pain and plexus injuries appear to be lower [45]. Except for trigeminal neuropathic pain, it is difficult to draw final conclusions about suitable indications for MCS due to the limited comparability of the studies available.

2. Deep brain stimulation (DBS) has also been used as an invasive pain therapy to treat central and peripheral pain syndromes, using various target regions (sensory thalamus, periaqueductal gray/periventricular zone, anterior cingulate cortex). Apart from the target area selected, the surgical technique does not differ from functional stereotactic procedures performed for movement disorders. Implantation of the pulse generator is performed based on the results of a trial period extending over several days, for which no standards have yet been defined, as in MCS [46]. Good results have been achieved especially in patients with peripheral neuropathic pain or failed back surgery syndrome (FBSS). Pain control achieved with DBS in patients with central pain—both after stroke and spinal injury—appears to be less favorable [47]. However, here again there is a lack of prospective, randomized trials which would allow a conclusive evaluation of the indications. From the few studies comparing MCS with DBS in the treatment of various pain syndromes, it appeared that MCS was clinically superior to DBS [40].

MCS and DBS are techniques which should only be used if conservative and less invasive surgical interventions have failed. Given the complexity of establishing an indication and their comparative rarity, these surgical procedures should only be performed at specialized centers.

Summary and Outlook

The existing clinical phase III studies with chronic pain patients suggest a potential usefulness of non-invasive transcranial stimulation. The published pain relief rates of up to 60 % are in line with those from pharmacotherapy-evaluating studies; however, it should be noted that the patients recruited for non-invasive transcranial stimulation studies were otherwise drug- or treatment-resistant pain patients, e.g., patients with fibromyalgia or chronic neuropathic pain of the head and upper extremities [15, 29]. tDCS offers special feasibility advantages compared to rTMS, as the devices are affordable and can be used at home. After the signature of the mandatory medical informed consent and instructions on how to use the device, non-invasive transcranial stimulation can be applied under supervision of medically experienced technical staff (e.g., MTAs) in the further course of treatment. In clinical practice, trial stimulation would be applied on three consecutive days; in case no clinical improvement is observed, the (currently still) compassionate use of non-invasive transcranial stimulation in these patients would be stopped.

Placebo rate is high in rTMS and tDCS studies, a phenomenon generally noted in pain studies. Complete blinding of the skin receptor stimulation during rTMS is difficult and some authors postulate that it can only be achieved by electrical costimulation. The tingling sensation underneath the tDCS electrodes decreases over time; the so-called fade-in/fade-out placebo protocol applies stimulation only at the beginning and at the end of the stimulation session. With current intensities of 2 mA instead of 1 mA this becomes even more difficult because the active stimulation group experiences light tingling during the entire stimulation period.

In case of failure of non-invasive techniques, MCS is a good therapeutic option, especially in patients with trigeminal neuropathic pain. MCS can also achieve good results in patients with pain after spinal cord injury and phantom limb pain. DBS is a treatment option of lesser importance according to current data. Definite conclusions about which indications should be regarded as promising or less promising for MCS or DBS cannot be drawn due to insufficient data.

Conflict of Interest

No conflict of interest has been declared by the authors.

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