Chapter 5

# Noninvasive Neuromodulation Methods in the Treatment of Chronic Pain

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Additional information is available at the end of the chapter

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## 1. Introduction

Non-invasive neurostimulation is recommended for patients with chronic neuropathic pain lasting more than six months.

Neurostimulation methods represent a firm place in the treatment of chronic pain. In this article, the respective mechanisms of action and efficacy of TENS(transcutaneous electrical nerve stimulation), rTMS ( repetitive transcranial magnetic stimulation), tDCS ( transcranial direct current stimulation) are described. In addition to the positive effects, side effects and complications are mentioned and discussed in detail. In conclusion, neuromodulatory (neurostimulatory) techniques are highly recommended for the treatment of different types of pharmacoresistant pain.

## 2. Neurostimulation methods

Neurostimulation, as a treatment of pain method, has been shown to be beneficial for patients suffering from pharmacoresistant chronic pain. Currently, neurostimulation methods are indicated only after exhaustion of all other therapies; however, it is expected that, in the near future, neurostimulation methods will become a first line treatment. Chronic pain is thought to occur in up to 30% of the adult population, although some authors suggest that it is less than 10%; others researchers, particularly in developed countries, put the prevalence as high as 50%. Neurostimulation methods are mainly used for chronic intractable pain, in which long-term treatment had been ineffective. Invasive or non-invasive neurostimulation is often recommended for patients with chronic neuropathic pain lasting more than six months, which was

refractory to well-established first and second-line analgesic therapy or in which first and second-line analgesic therapy produced unacceptable side effects. Most neurostimulation pain treatments are classified based on invasivity; they are classified as either invasive or non-invasive [29-32].

## 3. Invasive neurostimulation methods

- PNS - peripheral nerve stimulation SCS (spinal cord stimulation) - stimulation of the anterolateral and dorsal spinal cord tracts
- DBS - Deep brain stimulation
- MCS -Motor cortex stimulation [29]
- Stimulation of vagus nerve [37]
- Occipital nerve stimulation [22,23]

## 4. Non-invasive stimulation methods

- TENS (transcutaneous electrical nerve stimulation)
- rTMS (repetitive transcranial magnetic stimulation) [10]
- tDCS (transcranial direct current stimulation)

## 5. Transcutaneous electrical nerve stimulation (TENS)

TENS is a simple and relatively little used method with several probable mechanisms of pain relief [10]. These techniques are rather inexpensive and non-invasive, but the evidence for their effectiveness is overall of low quality [26]. The restrictive definition of TENS is the administration by surface electrodes of electric current produced by a device to stimulate cutaneous sensory nerves to reduce pain, both acute and chronic. TENS treatment targets painful regions instead of specific nerves. Based on the stimulation frequency, TENS can be subdivided in low frequency (frequency < 10 Hz) or high frequency (frequency > 10 Hz). As the biological basis of analgesia by TENS remains speculative, the 'gate control theory' of pain was the most tenable explanation but now release of endogenous opioids is the most acceptable explanation. [11]

Transcutaneous electrical nerve stimulation is known to work via multiple pathways and to have multiple indications and uses:

- TENS stimulates sensory nerves, activates the endogenous opioid system, stimulates the release of enkephalins and endorphins and increases blood flow in the stimulated areas.

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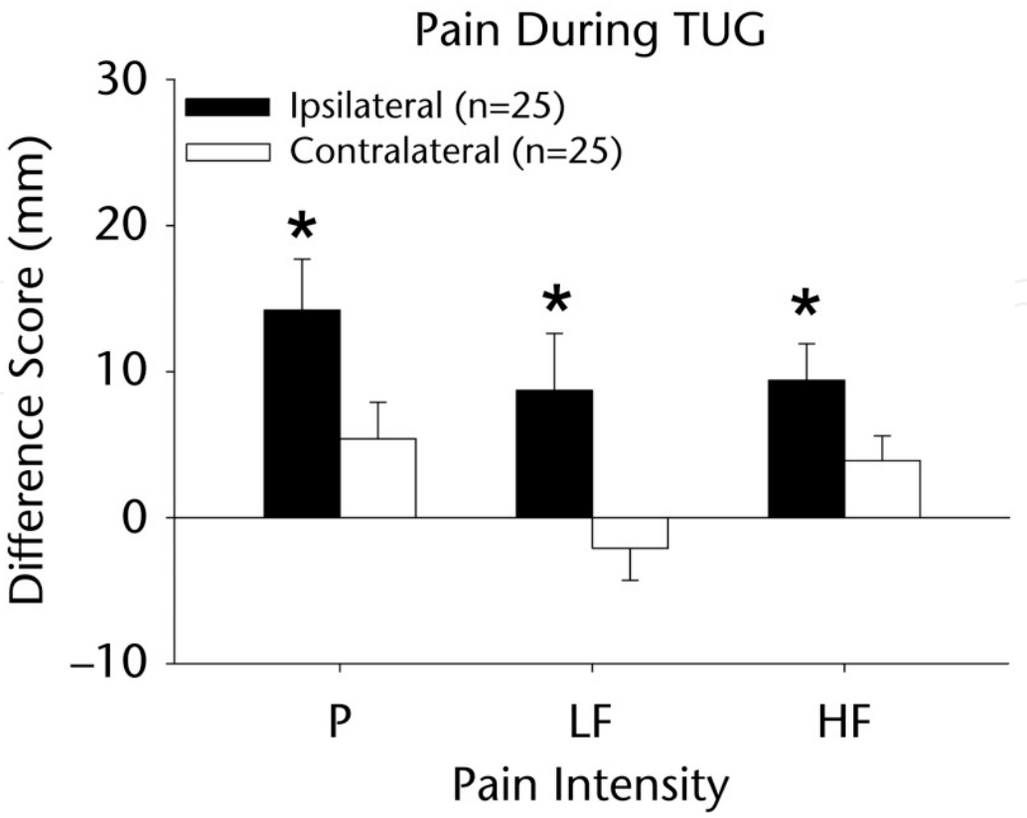
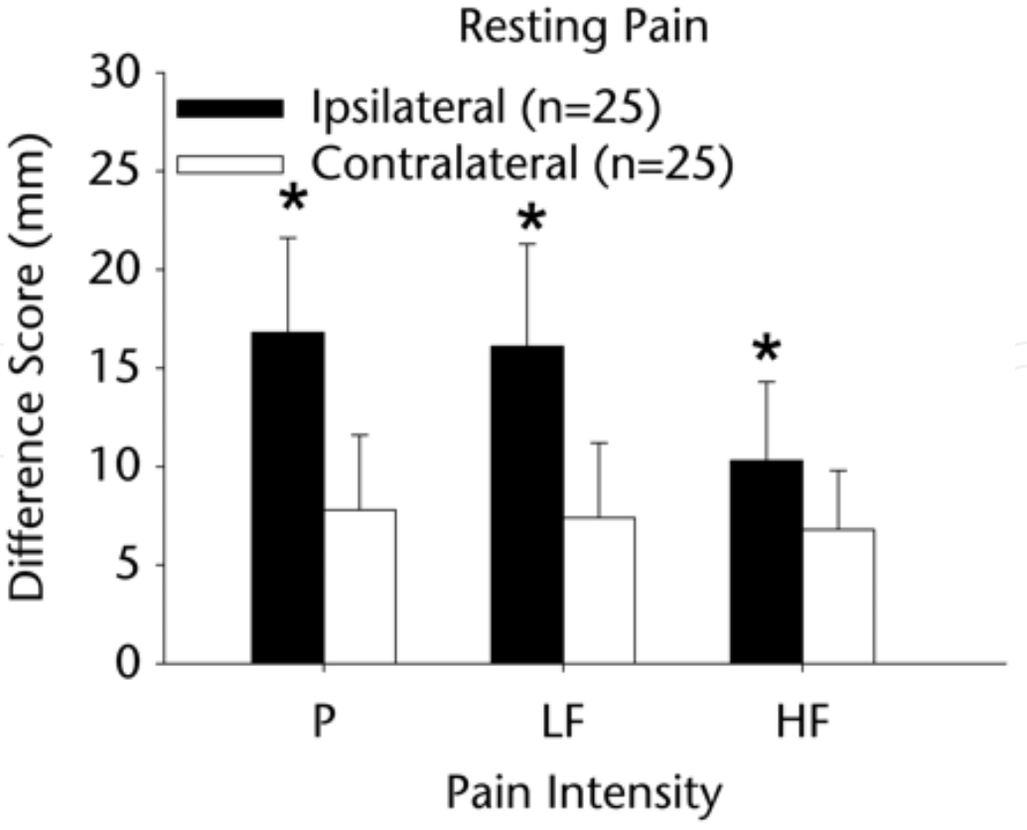
- TENS produces pain relief at both low and high frequencies.
- TENS is mediated via release of μ and δ opioids in the CNS and by a reduction in substance P.
- TENS affects the cardiovascular system: it increases heart rate and lowers blood pressure [18,24].
- TENS has been successfully used for the treatment of pelvic pain when applied to the dam and its dermatomes [37]
- TENS is used in geriatrics as valuable alternative treatment method for pharmacotherapy. [1].
- TENS can be used to treat muscle spasms and pains in specific areas such as surgical scars or post-herpetic neuralgia.
- TENS is simple to cooperate with patients and they can use it at home for self-analgesia.
- TENS can be used as electroanalgesia, for the treatment of pain during labor; it is used along the projections of Th10, Th 11, Th 12 and L1.
- TENS can be used as a complement of rehabilitation methods; threshold stimulation affects spinal mechanisms and supra-threshold stimulation affects supraspinal modulating mechanisms.
- TENS is also effective for neuropathic pain (including diabetic neuropathic pain [34], stump and phantom pain, post-herpetic neuralgia, spinal cord injury [27,5] and fibromyalgia [4]; it has also started to be used for cancer pain [19].
- TENS is contraindicated for use in the patients with implanted pacemakers

A number of complementary therapies have been found to have some efficacy among the older population, including acupuncture, TENS and massage. Such approaches can affect pain and anxiety and are worth further investigation.

Difference scores for movement-evoked pain during the Timed "Up & Go" Test (TUG) which is used in ipsilateral and contralateral knees during transcutaneous electrical nerve stimulation (TENS). Significant decreases were observed ipsilaterally for all 3 groups (placebo TENS [P], low-frequency TENS [LF], and high-frequency TENS [HF]). Data are expressed as the mean and standard error of the mean. *=significantly different from baseline [33]

Difference scores for pain at rest in ipsilateral and contralateral knees during transcutaneous electrical nerve stimulation (TENS). Significant decreases were observed ipsilaterally for all 3 groups (placebo TENS [P], low-frequency TENS [LF], and high-frequency TENS [HF]). Data are expressed as the mean and standard error of the mean. *=significantly different from baseline [33]


Pain During TUG
Ipsilateral (n=25)
Contralateral (n=25)
Difference Score (mm)
30
20
10
0
–10
*
*
*
P
LF
HF
Pain Intensity


Resting Pain
Ipsilateral (n=25)
Contralateral (n=25)
Difference Score (mm)
30
25
20
15
10
5
0
*
*
*
P
LF
HF
Pain Intensity

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In this study, participants were able to correctly identify active TENS 92% of the time. We previously reported similar responses to active TENS in healthy controls. Despite participants knowing that they received active TENS, there was no difference between active TENS and placebo TENS in subjective pain rating. Blinding of an electrical modality such as TENS has always been difficult, and few studies have reported blinding of active TENS.[33]

In summary, the present randomized clinical trial examined the effects of single treatments of HF-TENS and LF-TENS on knee OA pain and function. The use of various outcome measures, different frequencies, and an improved placebo provided insight for the management of knee OA pain with TENS. The pilot study tested a series of outcome measures designed to parallel and validate animal models of TENS and to test the effects of TENS in a true double-blind manner. Using PPT as an objective measure of pain sensitivity, showed that both HF-TENS and LF-TENS reduced primary hyperalgesia and that only HF-TENS reduced secondary hyperalgesia in people with OA. Quantitative sensory testing with cutaneous mechanical and heat pain measures was not affected by HF-TENS, LF-TENS, or placebo TENS, suggesting that TENS has no effect on cutaneous hyperalgesia. Alternatively, it is possible that the participants with OA did not have cutaneous mechanical and heat hyperalgesia. All treatments had similar but minimal effects on subjective pain measures, suggesting a placebo component of the effect of TENS. [33]

Side effects of TENS therapy:

High frequency TENS delivered at low intensities is associated with paraesthesia over the area of stimulation, and low frequency TENS delivered at high intensities is associated with a sharp flicking sensation or even muscle contractions. These sensations hamper proper blinding in controlled trials.[21]

TENS is completely contraindicated for use in patients with an implanted pacemaker.

## 6. Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) has been used for more than 20 years as treatment for various neurological disorders, including the treatment of chronic pain conditions.

rTMS is a noninvasive method that rarely has any side effects.

In 2008, rTMS of the left dorsolateral prefrontal cortex was approved for treatment of depression in the USA.

TMS can be used with a single pulse (single-pulse TMS), with a pair of applied pulses with a variable interval (paired-pulse TMS) or with repeating pulses (repetitive) rTMS.

rTMS is distinguished according to the selected frequency; it can be fast, i.e. high-frequency rTMS, which operate at frequencies of more than 1 Hz, or slow, i.e. low-frequency rTMS, which operate at frequencies of 1 Hz or less.

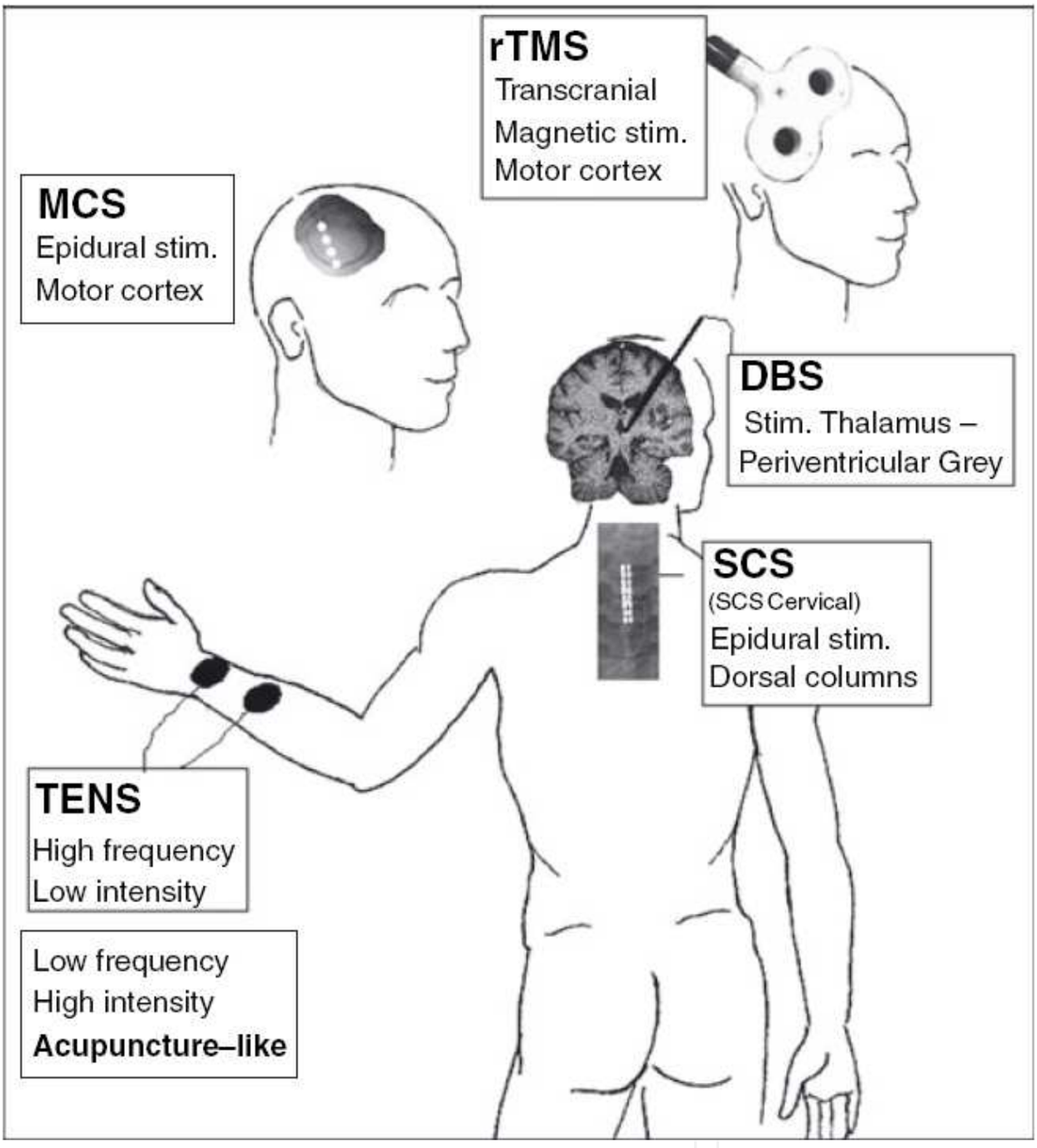


**Figure 1.** Guidelines of European Federation of Neurological Societes for the Neurostimulation Therapy in Neuropathic Pain [6].

This classification is based on a variety of physiological effects and degrees of risk associated with low and high frequency stimulation.

The effects of rTMS involved in a variety of mechanisms, including changes resembling experimental synaptic long term depression (LTD) and long-potentiating (LTP) mechanisms, activation of feedback loops, as well as changes in neuronal excitability. The treatment of pain

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using rTMS began mainly as a test to demonstrate the efficiency of cortical stimulation. The pioneers of this method were Lefaucheur et al. from Paris (2004, 2008) [11-13] and Leung et al. (2009) [17], which when using rTMS on healthy volunteers observed a decrease in sensory pain threshold.

Later it was shown that this effect was also present in patients suffering from various types of chronic pain. Studies using imaging techniques have shown that rTMS causes not only electrochemical changes in the brain, but also leads to a reorganization (changing the structure) of the cerebral cortex and other areas of the brain associated with chronic pain.

The TMS principle involves a magnetic field, with an intensity of 1-2 T, which generates an electric field that acts on the cell membrane of neurons and leads to changes in the electrochemical membrane potential.

Mechanism of action of rTMS pain treatment: The exact mechanism behind rTMS pain relief remains unknown. Stimulation of the motor cortex has been associated with pain relief in various pharmacoresistant pain syndromes. Stimulation of the motor cortex using rTMS alters the sensory threshold in healthy individuals and inhibits transmission of sensory information in the spinothalamic tract; depending on stimulation duration of each treatment, rTMS has been shown to induce a long-term increase in synaptic transmission.

Measurements of stimulation effects: In our research [10] we tested rTMS effects by making before and after rTMS using a VAS (visual analogue scale) and QST (quantitative sensory testing). QST consisted of thermal stimulation, which measured the thermal sensation threshold and tactile sensation testing using von Frey hairs. Testing must be individualized by establishing individual motor thresholds.

Contralateral motor stimulation provoked an immediate response and was associated with stimulation levels that produced relief from pain. Immediately after stimulation there is a temporary increase in pain, the changes in thermal threshold and tactile sensation. The benefits of rTMS, in the form of pain relief, are usually seen 2 to 4 days after treatment. rTMS outcomes depends on the origin and location of the treated pain and the degree of sensory deficit.

rTMS can also be used, in addition to its own analgesic effects, to determine if cortical brain stimulation would be effective in a particular patient.

### 6.1. Types of pain suitable for rTMS stimulation

Intractable chronic pain: neuropathic pain (postherpetic neuralgia), pain after stroke, deafferentation pain (very often after brachial plexus avulsion), trigeminal neuralgia, and thalamic pain. Other analgesic indications are atypical orofacial pain ) [10], spinal stenosis, low back pain, phantom pain, stump pain, KRBS, fibromyalgia, and migraines.Best practices, for neurostimulation have been standardized and are available in the European Federation of Neurological Societies for neurostimulation therapy for neuropathic pain (G. Cruccu TZ Aziz, L. Garcia-Larrea, d, P. Hansson, TS Jensen; J.-P. Lefaucheur, BA Simpson and RS Taylor, European Journal of Neurology 2007).

rTMS, used in accordance with the guidelines, is considered to be a safe and non-invasive method of neuromodulation pain therapy. It offers an important next step in the treatment of chronic intractable pain. Our research has confirmed the benefits of rTMS stimulation in patients with trigeminal and orofacial pain. For most of patients, we observed a change in the nature and a reduction in the frequency of painful episodes. Two patients in our research group became pain-free and 1 patient was indicated for cortical stimulation two years after stimulation [8-10].

The use of rTMS in the treatment of chronic intractable pain is reserved for pain that does not respond to analgesics and for pain in which the cause is difficult to remove. If it can be demonstrated to have an analgesic effect, then rTMS could be considered for inclusion in the current methods of pain treatment [30]. The advantage of magnetic stimulation is that it is a non-invasive procedure that is not time-consuming. Before rTMS can be routinely used in the treatment of chronic pain, it is necessary to accurately determine the amount and duration for each stimulation session, thereby ensuring the optimal duration of effect. From our results it is possible to conclude that the more effective rTMS was obtained with 20 Hz stimulation if compared wit our results with 10 Hz stimulation [9]. These results were measured with subjective evaluation of the pain, VAS, and with objective measurement using QTS. In objective evaluation the tactile measurement proved to be more important, while the results from measurement of thermal thresholds were not significant.The two treatment groups (active vs. sham) were comparable with respect to baseline demographic and clinical characteristics. rTMS was well tolerated, and no serious adverse effects were reported. In our study we combined both, sham or real stimulation. Another advantage over other neuromodulatory methods is the price of the equipment.

rTMS has also been tested on healthy subjects and was found to cause facilitation of motor evoked potentials, leading to an alternative interpretation of the effects of rTMS, which involves the activation of plasticity in the cerebral cortex [37]. Another possible pathophysiological explanation is that low-frequency stimulation (1 Hz) reduces the activity of excitatory circuits in the human motor cortex. Our results did not completely confirm this hypothesis.rTMS has also been investigated in depression, Parkinson's disease, spinocerebellar degeneration, epilepsy, urinary incontinence, movement disorders, chronic pain, migraines and chronic tinnitus The method did very well in comparison with epidural motor cortex stimulation and transcranial direct current electrical stimulation both in terms of effect and having a favorable cost / effectiveness ratio rTMS has also been tested in monkeys Effectiveness of rTMS also depends on the type of neuropathic pain [16,17].

Application of rTMS induces not only subjective pain relief [16,17] but also objective changes in Quantitative Sensory Testing (QST), namely changes in thermal threshold [14,15]and the threshold for tactile sensation [14,15]. Changes in the threshold of tactile sensation can be easily and reliably accessed with techniques using von Frey monofilaments and a Peltier thermal generator can be used to determine changes in thermal threshold [14,17].

Information regarding the prevalence of orofacial pain varies considerably from study to study and depends on the source of pain, however, it appears to affect between 10 to 50% of the adult population. The most common cause of facial pain is pain of dental origin, which begins after

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dental reparation or dental surgeries. Very often it is an intractable pain and pharmacological treatment is unsuccessful. Recent studies have suggested the involvement of the peripheral and central nervous system in the pathophysiology of atypical odontalgia.

Today rTMS is used with short-term success in the treatment of pain, mostly neuropathic pain. Previous studies have confirmed the ability of high (> 1 Hz) rTMS to stimulate the M1 in the treatment of facial pain. They have shown that the application of rTMS to the M1 changes the thermal pain threshold in this and related areas. Also of interest is the DLPFC (dorsolateral prefrontal cortex) coil position, which seems to have a substantial influence on neuronal circuits involved in the processing of cognitive and emotional aspects of pain.

### 6.2. Other effects of rTMS on pain

1 Hz (low frequency) rTMS reduces acute pain induced by capsaicin temporarily improves phantom pain and reduces pain in fibromyalgia High-frequency rTMS has been shown to produce changes in the pain threshold in people with chronic pain. Higher frequency rTMS (5-10 Hz) also reduces deafferentation intractable pain in spinal cord injury and in peripheral nerves. We enlarged these indications of high frequency stimulation by using 20 Hz stimulation, which was found to be very suitable for treatment of orofacial pain.

rTMS suppresses the perception of painful CRPS (Complex Regional Pain Syndrome)and suppresses neuropathic pain, in particular pain with a central origin rTMS is also effective in treating migraines with or without aura Low-frequency vertex rTMS (1 Hz) has been shown to have a prophylactic effect on migraines.

Our study confirmed that rTMS at a frequency of 20 Hz, functionally localized to the area of the motor cortex contralateral to the position corresponding to the somatotopic location of the pain source is effective in the treatment of chronic orofacial pain. Subjective evaluation of intra- and inter-group VAS scores, compared with the control group, showed both immediate and delayed treatment effects in subsequent measurements. The results of the VAS ratings are consistent with results of previous studies.Changes in thermal sensation were not statistically different between groups. Intragroup comparison confirmed the reduction of thermal threshold for hot air stimulation after repeated rTMS application. Some studies have confirmed the influence of rTMS to reduce the threshold for thermal stimulation of both cold air and hot air [14,15] Other studies however, have shown an increased thermal threshold for hot air stimulation after rTMS Inter-group comparisons of tactile sensations showed acute effects after repeated stimulation (days 2, 4 and 5) but not when measured using a longer interval (day 21). Confirmation of the influence of rTMS on QST, specifically its ability to reduce the threshold for tactile (mechanical) sensation, supports the hypothesis that modulation of tactile and thermal perception in the painful zone interacts with the analgesic effect of cortical stimulation [15,16]

Our data are consistent with previous studies which reported that the use of a higher frequency increased number of pulses during an rTMS application and an increased number of applications [17] led to increased efficacy of the method in the treatment of pain. The best frequency of stimulation for the most effective pain treatment has not yet been resolved. Our results

support the effect of 20 Hz rTMS. rTMS appears to be a safe and potentially effective tool for treatment of chronic migraine patients who showed resistance to pharmacological treatments [20 ]. Further studies are needed to assess factors underlying therapeutic effects (change in cortical excitability, better antinociceptive control).It's also to seek for optimal stimulation parameters (intensity,frequency, number and duration of stimulation sessions). Another important point may be the best cortical areas to be modulated for pain control in migraine, and the most efficacy side of stimulation, though the left side has been more frequently employed in studies on pain control.

### 6.3. Complications of rTMS

Low frequency rTMS stimulation can cause nausea, probably via stimulation of the posterior cranial fossa. rTMS of the premotor cortex reduces painful axial spasms in generalized secondary dystonia. [14-17] rTMS can also have side effects and randomly caused convulsions in control patients, one patient was reported to suffer from depression and parietal epilepsy.Side effects include induction of epileptic seizures (less than 1% of patients), which is more likely in high-frequency rTMS and rarely occurs in low-frequency rTMS. A more common problem is the formation of transient pain, which is precisely located and depends on the site of stimulation.

## 7. Transcranial direct current stimulation (tDCS)

Another non-invasive and simple neurostimulation technique is tDCS (transcranial direct current stimulation), which uses a cathode and anode, and is applied to the head using a low intensity direct current (0.029 to 0.08 mA/cm2) to stimulate the surface of the skull. tDCS is a noninvasive stimulation technique that is affordable and easy to use compared to other neuromodulation techniques [9].tDCS methods: anode stimulation increases cortical excitability, while cathodic stimulation decreases it. tDCS is a promising method for the treatment of chronic pain, as well as for patients with neuropsychiatric diseases and other neurological disorders.

### 7.1. Mechanisms of action tDCS

tDCS affects the brain's motor cortex excitability, which in humans is in area M1 (gyrus precentralis). Stimulation with the anode increases excitability of cortical brain cells by affecting the GABAergic system through depolarization. Anode stimulation reduces GABA concentrations in the cerebral cortex. Cathode stimulation reduces excitability of cortical brain cells via hyperpolarization of the glutamate system. Cathode stimulation produces a homeostatic effect. Low electric current rapidly increases the electrical conductivity of biological membranes by increasing permeability to ions and both small and large molecules. tDCS increases intracellular calcium. Neuroplasticity modulates the motor cortex through changes in opioid activity [7] glutamatergic, GABAergic, dopaminergic (D1 and D2 receptors), serotonergic and cholinergic system [25].Nicotine reduces inhibitory plastic changes after

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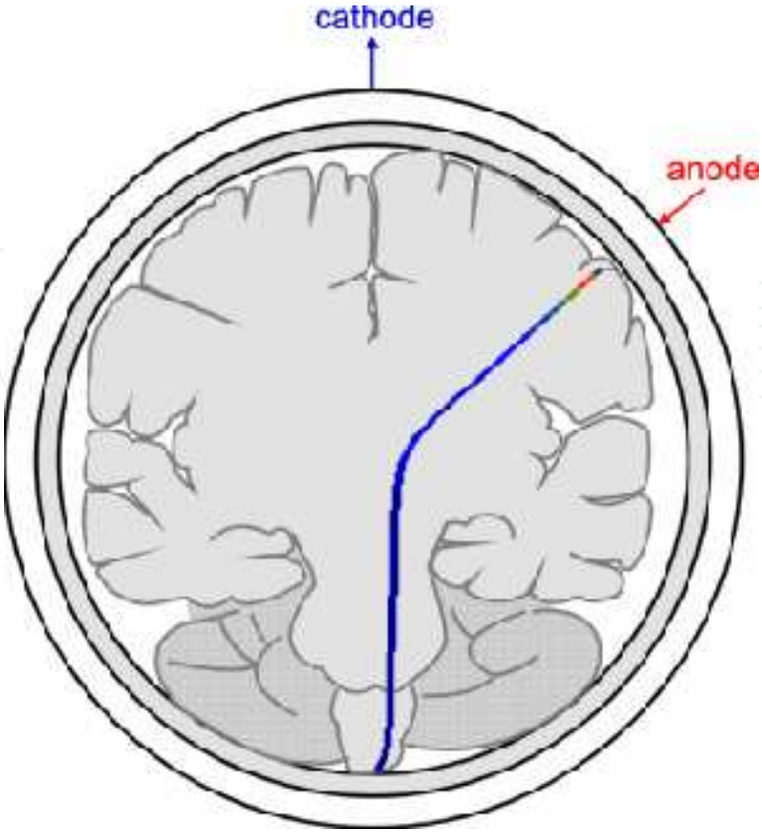


**Figure 2.** The placement of cathode and anode transcranial direct current stimulation tCDS

cathode stimulation and facilitatory plasticity after anode stimulation. tDCS has also been shown to stimulate glial cells; tDCS not only impacts neuroplasticity; tDCS is also neuroprotective.

### 7.2. Therapeutic indication tDCS

Therapeutic indication include chronic neuropathic pain [13] including refractory orofacial pain and pain after ERCP (endoscopic retrograde cholangiopancreatography), trigeminal pain, fibromyalgia [35], phantom pain [3] and back pain[28].

Therapeutic indications for psychiatric disorders include: depression (including severe depression), bipolar disorder, schizophrenia, Alzheimer's disease (here mainly it acts through GABAergic pathways during anode stimulation) and modulation of associative learning. Therapeutic indications in neurological diseases include: Parkinson's disease, postictal problems after stroke and tinnitus.

### 7.3. tDCS perspectives

In particular it is useful for stimulation of the prefrontal dorsolateral cortex and other spreading localization of tDCS stimulation. [27]. In recent Study [12] they using a randomized, crossover design; each participant was exposed to 13 minutes of sham, unilateral-anodal or bilateral

tDCS applied at 1.0 mA.In all tDCS conditions, the anode was placed over the "hot spot" of the non-dominant extensor carpi radialis longus (ECRL) muscle as determined by TMS. The order of these conditions were counterbalanced and randomized across participants, with a one week rest between each condition. This was achieved as the tDCS machine used, allowed for the use of a code to determine whether tDCS was active or inactive (sham). Within the sham condition, 50% of the unilateral stimulation and 50% of the bilateral stimulation was randomized for sham stimulation. Single and paired-pulse TMS was used to assess the after-effects of unilateral, bilateral or sham stimulation on corticomotor excitability of the right M1 and motor function of the non-dominant left ECRL. Ten single-pulse (130% of active motor threshold [AMT]), 10 paired-pulse (70% of AMT) and 10 test (test-intensity set to produce MEPs of ~1 mV) TMS stimuli were applied over the cortical area for the left ECRL at baseline, immediately following, 30 and 60 minutes post tDCS, with the order of TMS stimuli (single, paired-pulse or test) prior to and following tDCS, randomized throughout the trials (30 trials in total for each time point). Motor function was measured at each of these time points in all conditions by having participants complete a Purdue pegboard test with their left hand only. Importantly, all electrophysiological measures for each time point were measured prior to the performance of the pegboard, as post MEP facilitation and the effectiveness of SICI has been shown to be modulated immediately following the completion of the pegboard test. They examined the effects of a single-session of unilateral stimulation, bilateral and sham stimulation on modulating motor function of the non-dominant limb and indices of corticomotor plasticity. In healthy adults, the extent of motor function improvement and corticomotor plasticity were similar between unilateral and bilateral tDCS. Therefore, the physiological mechanisms regulating motor function were not different. Nevertheless, the present data indicate that tDCS induces behavioral changes in the non-dominant hand as a consequence of mechanisms associated with use-dependent cortical plasticity and is not influenced by the tDCS electrode arrangement. [12]

At a cellular level, direct current stimulation (DCS) may enhance plasticity in a given synaptic pathway while stimulated at a preferential frequency 0.1 Hz or consolidate a specific pattern of activity presented during DCS. DCS may preferentially modulate the level of potentiation in the activated pathway. DCS may facilitate long-term potentiation through membrane polarization and removal of Mg+ block but only those pathways activated during DCS (by a task or experimental stimulation) would benefit from this facilitation. DCS may be too weak and/or unspecific in isolation to enhance synaptic efficacy, but may boost ongoing (e.g., Hebbian) plasticity activated by task performance (i.e., modulation of input specific plasticity along an activated synaptic pathway while sparing quiescent synapses). In humans, transcranial electrical stimulation may also preferentially modulate networks with heightened oscillatory activity or preferentially change the progression of an active network during memory consolidation or synaptic downscaling [20]Anatomical specificity and functional specificity, through either ongoing activity-selectivity or input-selectivity, are not exclusive and may potentially be leveraged together in the development of rational tDCS protocols. In general, we propose that understanding the basis for tDCS selectivity is essential. Although we have focused our discussion to tDCS, the approaches described here would apply to other

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brain stimulation techniques including DBS, VNS, TMS, tRNS, and tACS as well as ultrasound and light based approaches [2

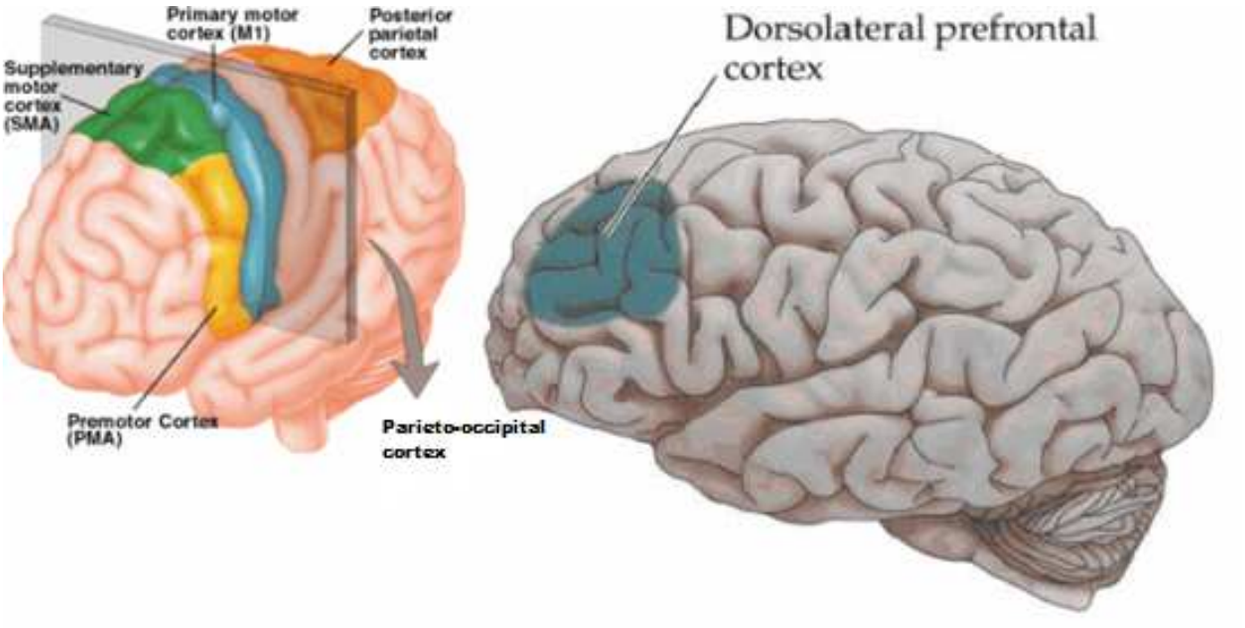


**Figure 3.** Localisation of dorsolateral prefrontal cortex which is very perspective for tDCS treatment

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