

tDCS clinical research - highlights: Pain

Neuroelectrics White Paper WP201301

Author: G. Ruffini (PhD), L. Dubreuil Vall

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[G. Ruffini](#), [L. Dubreuil Vall](#), *Neuroelectrics Barcelona SL*

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Chronic central pain is typically defined as pain that follows damage to the brain or spinal tract [D. Bowsher, "[Central pain: clinical and physiological characteristics](#)"]. The number of people who suffer chronic pain as a result of a stroke is estimated to be on the order of 1-8% of stroke patients [D. Bowsher, "[Sensory consequences of stroke](#)", G. Andersen et al., "[Incidence of central post-stroke pain](#)"]. Intriguingly, the incidence of post-stroke pain appears to be higher in younger patients [D. Bowsher, "[Central pain: clinical and physiological characteristics](#)"], suggesting that the brain's plasticity may be contributing to the pain as the brain responds to central or peripheral damage (phantom pain following amputation would be a well-known example of this [H. Flor et al., "[Phantom limb pain: a case of maladaptive CNS plasticity?](#)]).

Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) effective? Here we provide an overview/compilation of tCS studies in Pain. We have relied on Google Scholar and also [PubMed](#) to carry out the search, including the terms of tDCS, tACS, tRNS as well as Pain (since 2012 and until March 2015). For completeness we have also added some search results prior to this (papers up to March 2012) as well.

There continues to be a high intensity in the research community probing this question in addition to using tCS for pure, fundamental research. Let us review quickly what I have seen in the last year.

There quite a few encouraging results in this area, although study group sizes (the famous N) are still relatively small. I try to indicate group size and the use of a sham-controlled, double-blind experimental technique. There are some interesting positive results in **migraine and fibromyalgia**. There are negative results as well (although some of those studies employ a single session protocol, and it is fairly understood that more than a session is needed for clinical effects).

There is good progress in research with healthy subjects, with interesting insights into mechanisms. In addition, it is worth mentioning that there continues to be a lack of bad news from the safety point of view. This seems to be a common pattern of tDCS research (or tCS, in fact). This is definitely good for the field!

In what follows we concentrate on relevant, study-oriented papers with patients, and leave reviews to the end. In order to make the reading lighter, we have edited the abstracts a bit (please click on the title link if you are interested in the paper).

1. Update 2014-2015

In general, the results found in our search in 2015 are positive: tDCS is found to be safe and efficacious in various degrees. There is a wide variety of studies, most of them with small size. There is also a large number of studies with healthy subjects exploring more basic mechanisms. Most of the studies report positive, but small effects of tDCS.

The strongest results are in fibromyalgia and migraine. The number of (consistently positive) studies and involved subjects is relatively large (N=236 and N=151 respectively).

Rocha S, Melo L, Boudoux C, Foerster A, Araújo D, Monte-Silva K, Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: A pilot randomized controlled trial., J Neurol Sci. 2015 Feb 15;349(1-2):33-9

The aims of this paper are (i) to compare the excitability of visual cortex in migraine patients with **healthy** volunteers; and (ii) if an abnormal excitability has been found, to modulate cortical excitability in migraine patients with transcranial direct current stimulation (tDCS) and observe their clinical and neurophysiological effects. The study was divided into two steps. A cross-sectional study (step 1) was conducted to compare the cortical excitability of 23 migraineurs (11 with and 12 without aura) on 11 healthy individuals. On step 2, a randomized, double blinded, controlled pilot trial was carried on with **19 migraineurs**, randomly divided into: experimental and control group. During 12 sessions, experimental and group received active tDCS to visual cortex and control group received sham tDCS. The headache diary was applied for a total of 90days (before, during and after tDCS sessions). Phosphene threshold (PT) induced by transcranial magnetic stimulation was recorded to measure the excitability of the visual cortex before and after each session. Step 1 showed higher level of cortical excitability between migraineurs when compared to healthy volunteers; therefore, cathodal tDCS was applied over visual cortex in step 2. After tDCS application, a significant decrease was observed in a number of migraine attacks, painkiller intake and duration of each attack just in experimental group. The analysis of PT indicated no difference in cortical excitability after tDCS. **Findings of the study suggested that inhibitory tDCS on visual cortex might be an alternative and non-pharmacological treatment for migraine prophylaxis.**

Viganò A, D'Elia TS, Sava SL, Auvé M, De Pasqua V, Colosimo A, Di Piero V, Schoenen J, Magis D., Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine, J Headache Pain. 2013 Mar 11;14(1):23

To study the effects of anodal tDCS on visual cortex activity in healthy volunteers (HV) and episodic migraine without aura patients (MoA), and its potentials for migraine prevention. We recorded pattern-reversal visual evoked potentials (VEP) before and after a 15-min session of anodal tDCS over the visual cortex in 11 HV had a significant preventive anti- migraine effect, proofing the concept that the low preactivation level of the visual cortex in migraine patients can be corrected by an activating neurostimulation. The therapeutic results indicate that a larger sham-controlled trial using the same tDCS protocol is worthwhile. and 13 MoA interictally. Then **10 MoA** patients reporting at least 4 attacks/month subsequently participated in a therapeutic study, and received 2 similar sessions of tDCS per week for 8 weeks as migraine preventive therapy. In HV as well as in MoA, anodal tDCS transiently increased habituation of the VEP N1P1 component. VEP amplitudes were not modified by tDCS. **Preventive treatment with anodal tDCS turned out to be beneficial in MoA: migraine attack frequency, migraine**

days, attack duration and acute medication intake significantly decreased during the treatment period compared to pre-treatment baseline (all $p < 0.05$), and this benefit persisted on average 4.8 weeks after the end of tDCS.

CONCLUSIONS: Anodal tDCS over the visual cortex is thus able to increase habituation to repetitive visual stimuli in healthy volunteers and in episodic migraineurs, who on average lack habituation interictally. Moreover, 2 weekly sessions of anodal tDCS

Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, Punjaruk W, Thinkhamrop B, Auvichayapat N., Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial., J Med Assoc Thai. 2012 Aug;95(8): 1003-12.

To determine whether 20 consecutive days of the left M1 can be an effective prophylactic treatment for migraine. Forty-two episodic migraine patients who had never received any prophylactic treatment, failed prophylactic treatment, or discontinued treatment due to adverse events were recruited in the present study. Patients were randomized to receive either active tDCS or sham tDCS 1mA, 20 m for 20 consecutive days and followed up for 12 weeks. Differences between and within groups were determined using repeated measures ANOVA. The level of significance was set at $p < 0.05$. **Thirty-seven patients participated in the final analyses** (active: $n = 20$, sham: $n = 17$). Between-groups comparison of attack frequency, pain intensity, and abortive medications used were performed at 4, 8, and 12 weeks after treatment. **The results showed statistically significant reduction in attack frequency and abortive medications at week 4 and 8 after treatment. The pain intensity was statistically significant reduced at week 4, 8, and 12.** All patients tolerated the tDCS well without any serious adverse events. **CONCLUSION:** The present study suggests that anodal M1 tDCS may be a safe and useful clinical tool in migraine prophylaxis. The mechanism of action of anodal tDCS on neuromodulation in migraine patients needs further investigation.

Fagerlund AJ, Hansen OA, Aslaksen PM., Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. Pain. 2015 Jan;156(1):62-71.

Previous studies suggest that transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) reduces chronic pain levels. In this randomized controlled trial, we investigated the effects of 5 consecutive 20-minute sessions of 2-mA anodal tDCS directed to the M1 in 48 patients (45 females) with fibromyalgia. Changes in pain, stress, daily functioning, psychiatric symptoms, and health-related quality of life were measured. Pain and stress were measured 30 days before treatment, at each treatment, and 30 days after treatment by using short message service on mobile phones. Patients were randomized to the active or sham tDCS group by receiving individual treatment codes associated either with the sham or active tDCS in the stimulator. Adverse effects were registered using a standardized form. **A small but significant improvement in pain was observed under the active tDCS condition but not under the sham condition.** Fibromyalgia-related daily functioning improved in the active tDCS group compared with the sham group. The stimulation was well tolerated by the patients, and no significant difference in the adverse effects between the groups was observed. The results suggest that tDCS has the potential to induce statistically significant pain relief in patients with fibromyalgia, with no serious adverse effects, but small effect sizes indicate that the results are unlikely to reflect clinically important changes.

Foerster BR, Nascimento TD, DeBoer M, Bender MA, Rice IC, Truong DQ, Bikson M, Clauw DJ, Zubieta JK, Harris RE, DaSilva AF., Excitatory and inhibitory brain metabolites as targets of motor

cortex transcranial direct current stimulation therapy and predictors of its efficacy in fibromyalgia., Arthritis Rheumatol. 2015 Feb;67(2):576-81.

Transcranial direct current stimulation (tDCS) has been shown to improve pain symptoms in fibromyalgia (FM), a central pain syndrome whose underlying mechanisms are not well understood. This study was undertaken to explore the neurochemical action of tDCS in the brain of patients with FM, using proton magnetic resonance spectroscopy (1H-MRS). **Twelve** patients with FM underwent sham tDCS over the left motor cortex (anode placement) and contralateral supraorbital cortex (cathode placement) for 5 consecutive days, followed by a 7-day washout period and then active tDCS for 5 consecutive days. Clinical pain assessment and 1H-MRS testing were performed at baseline, the week following the sham tDCS trial, and the week following the active tDCS trial. **RESULTS: Clinical pain scores decreased significantly between the baseline and active tDCS time points (P = 0.04).** Levels of glutamate + glutamine (Glx) in the anterior cingulate were significantly lower at the post-active tDCS assessment compared with the post-sham tDCS assessment (P = 0.013), and the decrease in Glx levels in the thalami between these time points approached significance (P = 0.056). From baseline to the post-sham tDCS assessment, levels of N-acetylaspartate (NAA) in the posterior insula increased significantly (P = 0.015). There was a trend toward increased levels of γ -aminobutyric acid (GABA) in the anterior insula after active tDCS, compared with baseline (P = 0.064). Baseline anterior cingulate Glx levels correlated significantly with changes in pain score, both for the time period from baseline to sham tDCS ($\beta_1 = 1.31$, $P < 0.001$) and for the time period from baseline to active tDCS ($\beta_1 = 1.87$, $P < 0.001$). The present findings suggest that GABA, Glx, and NAA play an important role in the pathophysiology of FM and its modulation by tDCS.

Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, Fregni F, Focal modulation of the primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation., J Pain. 2013 Apr;14(4):371-83

Fibromyalgia is a prevalent chronic pain syndrome characterized by altered pain and sensory processing in the central nervous system, which is often refractory to multiple therapeutic approaches. Given previous evidence supporting analgesic properties of noninvasive brain stimulation techniques in this condition, this study examined the effects of a novel, more focal method of transcranial direct current stimulation (tDCS), using the 4×1-ring configuration of high-definition (HD)-tDCS, on overall perceived pain in fibromyalgia patients. In this patient- and assessor-blind, sham-controlled, crossover trial, **18 patients** were randomized to undergo single 20-minute sessions of anodal, cathodal, and sham HD-tDCS at 2.0 mA in a counterbalanced fashion. The center electrode was positioned over the left primary **motor** cortex. Pain scales and sensory testing were assessed before and after each intervention. A finite element method brain model was generated to predict electric field distribution. We found that both active stimulation conditions led to significant reduction in overall perceived pain as compared to sham. This effect occurred immediately after cathodal HD-tDCS and was evident for both anodal and cathodal HD-tDCS 30 minutes after stimulation. Furthermore, active anodal stimulation induced a significant bilateral increase in mechanical detection thresholds. These interventions proved well tolerated in our patient population.

Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, Punjaruk W, Thinkhamrop B, Auvichayapat N., Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial., J Med Assoc Thai. 2012 Aug;95(8): 1003-12.

Forty-two episodic migraine patients who had never received any prophylactic treatment, failed prophylactic treatment, or discontinued treatment due to adverse events were recruited in the present study. Patients were randomized to receive either active tDCS or sham tDCS 1mA, 20 m for 20 consecutive days and followed up for 12 weeks. Differences between and within groups were determined using repeated measures ANOVA. The level of significance was set at $p < 0.05$. **RESULTS:** Thirty-seven patients participated in the final analyses (active: $n = 20$, sham: $n = 17$). Between-groups comparison of attack frequency, pain intensity, and abortive medications used were performed at 4, 8, and 12 weeks after treatment. **The results showed statistically significant reduction in attack frequency and abortive medications at week 4 and 8 after treatment.** The pain intensity was statistically significant reduced at week 4, 8, and 12. All patients tolerated the tDCS well without any serious adverse events. **CONCLUSION:** The present study suggests that anodal M1 tDCS may be a safe and useful clinical tool in migraine prophylaxis. The mechanism of action of anodal tDCS on neuromodulation in migraine patients needs further investigation.

Dasilva AF1, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, Bajwa Z, Datta A, Bikson M, Fregni F, tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine., Headache. 2012 Sep;52(8):1283-95.

We investigated in a sham-controlled trial the analgesic effects of a 4-week treatment of transcranial direct current stimulation (tDCS) over the primary motor cortex in chronic migraine. In addition, using a high-resolution tDCS computational model, we analyzed the current flow (electric field) through brain regions associated with pain perception and modulation. **Thirteen** patients with chronic migraine were randomized to receive 10 sessions of active or sham tDCS for 20 minutes with 2 mA over 4 weeks. Data were collected during baseline, treatment and follow-up. For the tDCS computational analysis, we adapted a high-resolution individualized model incorporating accurate segmentation of cortical and subcortical structures of interest. There was a significant interaction term (time vs group) for the main outcome (pain intensity) and for the length of migraine episodes (ANOVA, $P < .05$ for both analyses). Post-hoc analysis showed a significant improvement in the follow-up period for the active tDCS group only. Our computational modeling studies predicted electric current flow in multiple cortical and subcortical regions associated with migraine pathophysiology. Significant electric fields were generated, not only in targeted cortical regions but also in the insula, cingulate cortex, thalamus, and brainstem regions. **Our findings give preliminary evidence that patients with chronic migraine have a positive, but delayed, response to anodal tDCS of the primary motor cortex. These effects may be related to electrical currents induced in pain-related cortical and subcortical regions.**

Riberto M, Marcon Alfieri F, Monteiro de Benedetto Pacheco K, Dini Leite V, Nemoto Kaihama H, Fregni F, Rizzo Battistella L., Efficacy of transcranial direct current stimulation coupled with a multidisciplinary rehabilitation program for the treatment of fibromyalgia., Open Rheumatol J. 2011;5:45-50.

23 patients were randomized to receive weekly sessions of multidisciplinary rehabilitation approach combined with sham or anodal tDCS of M1. Patients were evaluated for pain with VAS and for quality of life with SF-36, fibromyalgia pain questionnaire and health assessment questionnaire by a blinded rater before and after the 4 month period of rehabilitation. **RESULTS:** Patients tolerated tDCS treatment well, without adverse effects. Patients who received active treatment had a significantly greater reduction of SF-36 pain domain scores ($F((2,21))=6.57$; $p=0.006$) and a tendency of higher improvement in Fibromyalgia

Impact Questionnaire (FIQ) scores after ($p=0.056$) as compared with sham tDCS/standard treatment, but no differences were observed in the other domains. **CONCLUSIONS:** Although active tDCS was associated with superior results in one domain (SF-36 pain domain), the lack of significance in the other domains does not fully support this strategy (weekly tDCS) combined with a multidisciplinary approach.

Mendonca ME, Santana MB, Baptista AF, Datta A, Bikson M, Fregni F, Araujo CP., Transcranial DC stimulation in fibromyalgia: optimized cortical target supported by high-resolution computational models., J Pain. 2011 May;12(5):610-7.

In this study we aimed to determine current distribution and short-term analgesic effects of transcranial direct current stimulation (tDCS) in fibromyalgia using different electrode montages. For each electrode montage, clinical effects were correlated with predictions of induced cortical current flow using magnetic resonance imaging-derived finite element method head model. Thirty patients were randomized into 5 groups (Cathodal-M1 [primary motor cortex], Cathodal-SO [supra-orbital area], Anodal-M1, Anodal-SO, and Sham) to receive tDCS application (2 mA, 20 minutes) using an extracephalic montage. Pain was measured using a visual numerical scale (VNS), pressure pain threshold (PPT), and a body diagram (BD) evaluating pain area. There was significant pain reduction in cathodal-SO and anodal-SO groups indexed by VNS. For PPT there was a trend for a similar effect in anodal-SO group. Computer simulation indicated that the M1-extracerebral montage produced dominantly temporo-parietal current flow, consistent with lack of clinical effects with this montage. Conversely, the SO-extracerebral montage produced current flow across anterior prefrontal structures, thus supporting the observed analgesic effects. Our clinical and modeling findings suggest that electrode montage, considering both electrodes, is critical for the clinical effects of M1-tDCS as electric current needs to be induced in areas associated with the pain matrix. These results should be taken into consideration for the design of pain tDCS studies.

Antal A, Kriener N, Lang N, Boros K, Paulus W., Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine., Cephalalgia. 2011 May;31(7):820-8.

This painless and non-invasive method was applied for 6 weeks over the visual cortex (V1), delivered three times per week. **Thirty patients** were assigned to cathodal or to sham stimulation, and 26 patients participated in the final analyses (cathodal: $n = 13$, sham: $n = 13$). During the first 3 weeks both groups received only placebo stimulation. Measures of attack frequency and duration, intensity of pain and number of migraine-related days were recorded 2 months before, during and 2 months post-treatment. **RESULTS:** Patients treated by cathodal tDCS showed a significant reduction in the duration of attacks, the intensity of pain and the number of migraine-related days post-treatment as compared to the baseline period, but not in the frequency of the attacks. However, compared to the sham group, only the intensity of the pain was significantly reduced post-stimulation. No patients experienced severe adverse effects. **CONCLUSION:** Our results suggest that the application of cathodal stimulation over the V1 might be an effective prophylactic therapy in migraine, at least with regard to pain control.

Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, Boggio PS, Fregni F., Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial., J Pain Manag. 2009;2(3):353-361.

Fibromyalgia has been recognized as a central pain disorder with evidence of neuroanatomic and neurophysiologic alterations. Previous studies with techniques of noninvasive brain stimulation--transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS)--have shown that

these methods are associated with a significant alleviation of fibromyalgia-associated pain and sleep dysfunction. Here we sought to determine whether a longer treatment protocol involving 10 sessions of 2 mA, 20 min tDCS of the left primary motor (M1) or dorsolateral prefrontal cortex (DLPFC) could offer additional, more long-lasting clinical benefits in the management of pain from fibromyalgia. **Forty-one** women with chronic, medically refractory fibromyalgia were randomized to receive 10 daily sessions of M1, DLPFC, or sham tDCS. Our results show that M1 and DLPFC stimulation both display improvements in pain scores (VAS) and quality of life (FIQ) at the end of the treatment protocol, but only M1 stimulation resulted in long-lasting clinical benefits as assessed at 30 and 60 days after the end of treatment. **CONCLUSIONS:** This study demonstrates the importance of the duration of the treatment period, suggesting that 10 daily sessions of tDCS result in more long lasting outcomes than only five sessions. Furthermore, this study supports the findings of a similarly designed rTMS trial as both induce pain reductions that are equally long-lasting.

Roizenblatt S1, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, Boggio PS, Valle AC., Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study., Pain Pract. 2007 Dec;7(4):297-306.

To investigate whether active anodal transcranial direct current stimulation (tDCS) (of dorsolateral prefrontal cortex [DLPFC] and primary motor cortex [M1]) as compared to sham treatment is associated with changes in sleep structure in fibromyalgia. **Thirty-two patients** were randomized to receive sham stimulation or active tDCS with the anode centered over M1 or DLPFC (2 mA, 20 minutes for five consecutive days). A blinded evaluator rated the clinical symptoms of fibromyalgia. All-night polysomnography was performed before and after five consecutive sessions of tDCS. Anodal tDCS had an effect on sleep and pain that was specific to the site of stimulation: such as that M1 and DLPFC treatments induced opposite effects on sleep and pain, whereas sham stimulation induced no significant sleep or pain changes. Specifically, whereas M1 treatment increased sleep efficiency (by 11.8%, $P = 0.004$) and decreased arousals (by 35.0%, $P = 0.001$), DLPFC stimulation was associated with a decrease in sleep efficiency (by 7.5%, $P = 0.02$), an increase in rapid eye movement (REM) and sleep latency (by 47.7%, $P = 0.0002$, and 133.4%, $P = 0.02$, respectively). **In addition, a decrease in REM latency and increase in sleep efficiency were associated with an improvement in fibromyalgia symptoms (as indexed by the Fibromyalgia Impact Questionnaire).** Finally, patients with higher body mass index had the worse sleep outcome as indexed by sleep efficiency changes after M1 stimulation.

Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, Bravo R, Rigonatti SP, Freedman SD, Nitsche MA, Pascual-Leone A, Boggio PS., A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia., Arthritis Rheum. 2006 Dec;54(12):3988-98.

Thirty-two patients were randomized to receive sham stimulation or real tDCS with the anode centered over the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC) (2 mA for 20 minutes on 5 consecutive days). A blinded evaluator rated the patient's pain, using the visual analog scale for pain, the clinician's global impression, the patient's global assessment, and the number of tender points. Other symptoms of fibromyalgia were evaluated using the Fibromyalgia Impact Questionnaire and the Short Form 36 Health Survey. Safety was assessed with a battery of neuropsychological tests. To assess potential confounders, we measured mood and anxiety changes throughout the trial. Anodal tDCS of the primary motor cortex induced significantly greater pain improvement compared with sham stimulation and

stimulation of the DLPFC ($P < 0.0001$). Although this effect decreased after treatment ended, it was still significant after 3 weeks of followup ($P = 0.004$). A small positive impact on quality of life was observed among patients who received anodal M1 stimulation. This treatment was associated with a few mild adverse events, but the frequency of these events in the active-treatment groups was similar to that in the sham group. Cognitive changes were similar in all 3 treatment groups. **Our findings provide initial evidence of a beneficial effect of tDCS in fibromyalgia, thus encouraging further trials.**

2. Update 2012-2013

2.1 Earlier data (up to March 2012)

In general, the results found in our search as of March 2012 were positive: tDCS was found to be safe and efficacious in various degrees.

Our results are in agreement with a recent meta-analysis including 6 tDCS studies which reports that “The available evidence suggests that tDCS applied to the motor cortex may have short-term effects on chronic pain” [O’Connell2010]. Some examples follow:

- A clinical trial of anodal tDCS (2 mA over 5 consecutive days) over the motor cortex has shown a reduction in pain scores in patients who had a spinal cord injury [Fregni2006b]. Not only did the five-day course of treatment result in a reduction in pain scores that lasted as long as the 16-day follow-up period, but the effect of each session was cumulative over the five stimulation sessions, hinting that patient-specific doses of treatment may be possible.
- Similar results have been shown for the pain of fibromyalgia [Fregni2006c, Roizenblatt2007]. The pain threshold of healthy volunteers has also been raised with anodal tDCS of the motor cortex, although this was associated with a reduction in perceptual sensitivity [Boggio2008b].
- In [Fregni2006d], a RTC study with 32 patients, the authors found that anodal tDCS of the primary motor cortex induced significantly greater pain improvement compared with sham stimulation and stimulation of the DLPFC ($P < 0.0001$).
- In the review by Knotkova [Knotkova2010], it is concluded that the findings on tDCS in patients with pain are promising, showing an analgesic effect of tDCS, and observations up to date justify the use of tDCS for the treatment of pain in selected patient populations.
- In [Mendonca2011], a study to determine current distribution and short-term analgesic effects of transcranial direct current stimulation (tDCS) in fibromyalgia using different electrode montages, it is concluded that there was significant pain reduction in cathodal-Supraorbital and anodal-Supraorbital groups indexed by Visual numerical scale. For Pressure pain threshold there was a trend for a similar effect in anodal-Supraorbital group.
- Other studies from the literature include:
 - In a pilot study [Borckhardt2011], the authors concluded that tDCS appears to be safe, has minimal side effects, and may reduce postprocedural analgesia requirements and subjective pain ratings.
 - Results suggest [Antal2011] that the application of cathodal stimulation over the V1 might be an effective prophylactic therapy in migraine, at least with regard to pain control.
 - Anodal tDCS led to a greater improvement in VAS ratings than sham tDCS, evident even three to four weeks post-treatment [260].
 - The available evidence suggests that tDCS applied to the motor cortex may have short-term effects on chronic pain [O’Connell2010].

- Although there is less evidence on tDCS as compared with TMS, the findings on tDCS in patients with pain are promising, showing an analgesic effect of tDCS, and observations up to date justify the use of tDCS for the treatment of pain in selected patient populations [[Knotkova2010](#)].
- Following anodal but not sham tDCS over the motor cortex, there was a significant pain improvement as assessed by VAS for pain and McGill questionnaire, and of overall quality of life [[Mori2010](#)].
- Findings provide initial evidence of a beneficial effect of tDCS in fibromyalgia, thus encouraging further trials: tDCS produced a 50% reduction of fibromyalgia pain (after five 20-minute treatments) [[Fregni2006c](#)].
- There was a significant pain improvement after active anodal stimulation of the motor cortex, but not after sham stimulation - there was a significant pain improvement after tDCS stimulation of the motor cortex.” [[Fregni2006b](#)].
- Cathodal stimulation of the primary motor cortex significantly diminished mild pain sensation only when laser-stimulating the hand contralateral to the side of tDCS [[Csifcsak2008](#)].
- Cathodal tDCS over somatosensory cortex significantly diminished pain perception and the amplitude of the N2 component when the contralateral hand to the side of tDCS was laser-stimulated, whereas anodal and sham stimulation conditions had no significant effect [[Antal2008](#)].
- In a pilot study (21 subjects in an RTC trial), [[Borckhardt2011](#)], reports that tDCS appears to be safe, has minimal side effects, and may reduce postprocedural analgesia requirements and subjective pain ratings. Real tDCS was associated with 22% less total hydromorphone use, versus sham.
- Fenton et al [[Fenton2009](#)] in a study to determine the efficacy and safety of tDCS for the management of refractory chronic pelvic pain, report that overall and pelvic pain scores were significantly lower after active compared with sham treatment, as were disability and traumatic stress scores. Active tDCS treatment induces a modest pain reduction in refractory chronic pelvic pain patients as compared with sham tDCS treatment.
- In [[Soler2010](#)], the aim of the study (39 patients RTC) was to evaluate the analgesic effect of transcranial direct current stimulation of the motor cortex and techniques of visual illusion, applied isolated or combined. The authors concluded: The combination of transcranial direct current stimulation and visual illusion reduced the intensity of neuropathic pain significantly more than any of the single interventions. Patients receiving transcranial direct current stimulation and visual illusion experienced a significant improvement in all pain subtypes, while patients in the transcranial direct current stimulation group showed improvement in continuous and paroxysmal pain, and those in the visual illusion group improved only in continuous pain and dysaesthesias. At 12 weeks after treatment, the combined treatment group still presented significant improvement on the overall pain intensity perception, whereas no improvements were reported in the other three groups.

2.1 Positive results (2012-2013)

Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, Punjaruk W, Thinkhamrop B, Auvichayapat N. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial., J Med Assoc Thai. 2012 Aug;95(8): 1003-12.

Past evidence had shown that consecutive motor cortex (M1) stimulation with anodal tDCS was effective to relieve central pain. **37 migraine patients** participated in the final analyses (active: n = 20, **sham**: n = 17).

Between-groups comparison of attack frequency, pain intensity, and abortive medications used were performed at 4, 8, and 12 weeks after treatment. *The results showed statistically significant reduction in attack frequency and abortive medications at week 4 and 8 after treatment. The pain intensity was statistically significant reduced at week 4, 8, and 12.* All patients tolerated the tDCS well without any serious adverse events. *The present study suggests that anodal M1 tDCS may be a safe and useful clinical tool in migraine prophylaxis. The mechanism of action of anodal tDCS on neuromodulation in migraine patients needs further investigation.*

Dasilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, Bajwa Z, Datta A, Bikson M, Fregni F. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine., Headache. 2012 Sep;52(8):1283-95. doi: 10.1111/j.1526-4610.2012.02141.x.

We investigated in a **sham-controlled** trial the analgesic effects of a 4-week treatment of transcranial direct current stimulation (tDCS) over the primary motor cortex in chronic migraine. In addition, using a high-resolution tDCS computational model, we analyzed the current flow (electric field) through brain regions associated with pain perception and modulation. **13 patients with chronic migraine** were randomized to receive 10 sessions of active or sham tDCS for 20 minutes with 2 mA over 4 weeks. *There was a significant interaction term (time vs group) for the main outcome (pain intensity) and for the length of migraine episodes (ANOVA, $P < .05$ for both analyses). Post-hoc analysis showed a significant improvement in the follow-up period for the active tDCS group only. Our findings give preliminary evidence that patients with chronic migraine have a positive, but delayed, response to anodal tDCS of the primary motor cortex. These effects may be related to electrical currents induced in pain-related cortical and subcortical regions.*

Kumru H, Soler D, Vidal J, Navarro X, Tormos JM, Pascual-Leone A, Valls-Sole J. The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: an evoked potentials and quantitative thermal testing study., Eur J Pain. 2013 Jan;17(1):55-66. doi: 10.1002/j.1532-2149.2012.00167.x.

Neuropathic pain (NP) is common in spinal cord injury (SCI) patients. One of its manifestations is a lowering of pain perception threshold in quantitative thermal testing (QTT) in dermatomes rostral to the injury level. tDCS combined with visual illusion (VI) improves pain in SCI patients. We studied whether pain relief with tDCS + VI intervention is accompanied by a change in contact heat- evoked potentials (CHEPs) or in QTT. We examined **18 patients with SCI and NP** before and after 2 weeks of daily tDCS + VI intervention. **20 SCI patients without NP and 14 healthy subjects served as controls.** We assessed NP intensity using a numerical rating scale (NRS) and determined heat and pain thresholds with thermal probes. CHEPs were recorded to stimuli applied at C4 level, and subjects rated their perception of evoked pain using NRS during CHEPs. *Two weeks of tDCS + VI induced significant changes in CHEPs, evoked pain and heat pain threshold in SCI patients with NP. These neurophysiological tests might be objective biomarkers of treatment effects for NP in patients with SCI.*

Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, Fregni F. Focal modulation of the primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation., J Pain. 2013 Apr;14(4):371-83. doi: 10.1016/j.jpain.2012.12.007.

Fibromyalgia is a prevalent chronic pain syndrome characterized by altered pain and sensory processing in the central nervous system, which is often refractory to multiple therapeutic approaches. Given previous evidence supporting analgesic properties of noninvasive brain stimulation techniques in this condition, this study examined the effects of a novel, more focal method of transcranial direct current stimulation (tDCS), using the 4×1-ring configuration of high-definition (HD)-tDCS, on overall perceived pain in fibromyalgia

patients. **In this patient- and assessor-blind, sham-controlled, crossover trial, 18 patients** were randomized to undergo single 20-minute sessions of anodal, cathodal, and sham HD-tDCS at 2.0 mA in a counterbalanced fashion. The center electrode was positioned over the left primary motor cortex. *We found that both active stimulation conditions led to significant reduction in overall perceived pain as compared to sham. This effect occurred immediately after cathodal HD-tDCS and was evident for both anodal and cathodal HD-tDCS 30 minutes after stimulation.*

Borckardt, Jeffrey J. PhD; Reeves, Scott T. MD, MBA; Robinson, Stefanie M. BS; May, Joshua T. BS; Epperson, Thomas I. MD; Gunselman, Ryan J. MD; Schutte, Harold Del MD; Demos, Harry A. MD; Madan, Alok PhD, MPH; Fredrich, Sarah BS; George, Mark S. MD. Transcranial Direct Current Stimulation (tDCS) Reduces Postsurgical Opioid Consumption in Total Knee Arthroplasty (TKA), Clinical Journal of Pain; November 2013 - Volume 29 - Issue 11 - p 925–928

Results from this pilot feasibility (N=40) study suggest that tDCS may be able to reduce post-TKA opioid requirements. Forty patients undergoing unilateral TKA were randomly assigned to receive a total of 80 minutes of real (n=20) or sham tDCS (n=20) with the anode over the knee representation of the motor strip (C1h or C2h corresponding to the target knee) and cathode over the right dorsolateral prefrontal cortex (F3; located by the EEG 10-20 System). Patient-controlled analgesia (hydromorphone) use was tracked during the ~48 hours postsurgery. *Although these results are preliminary, the data support further research in the area of adjunctive cortical stimulation in the management of postsurgical pain.*

Knotkova H, Portenoy RK, Cruciani RA. Transcranial Direct Current Stimulation (tDCS) Relieved Itching in a Patient With Chronic Neuropathic Pain., Clin J Pain. 2013 Jul;29(7):621-2.

This **case report** presents a first note on beneficial effects of tDCS on itching associated with chronic neuropathic pain in a patient diagnosed with syringomyelia. Although there was no change in pain intensity or quality during or after tDCS, *the treatment resulted in a reduction in itch to a mild, tolerable intensity that persisted for 3 to 4 months after each course, before returning to the pretreatment level.* The patient has agreed to a plan of care that will incorporate neurostimulation every 4 to 6 months, as long as its effectiveness continues. This case provides a rationale for future studies of neuromodulatory treatments for itch, and indicates a potential clinical use of neuromodulation in patients with unrelieved itching.

Bolognini N, Olgiati E, Maravita A, Ferraro F, Fregni F. Motor and parietal cortex stimulation for phantom limb pain and sensations., Pain. 2013 Aug;154(8):1274-80

Limb amputation may lead to chronic painful sensations referred to the absent limb, ie phantom limb pain (PLP), which is likely subtended by maladaptive plasticity. The present study investigated whether tDCS, a noninvasive technique of brain stimulation that can modulate neuroplasticity, can reduce PLP. In **2 double-blind, sham-controlled experiments in subjects with unilateral lower or upper limb amputation**, we measured the effects of a single session of tDCS (2 mA, 15 min) of the primary motor cortex (M1) and of the posterior parietal cortex (PPC) on PLP, stump pain, nonpainful phantom limb sensations and telescoping. *Anodal tDCS of M1 induced a selective short-lasting decrease of PLP, whereas cathodal tDCS of PPC induced a selective short-lasting decrease of nonpainful phantom sensations; stump pain and telescoping were not affected by parietal or by motor tDCS. These findings demonstrate that painful and nonpainful phantom limb sensations are dissociable phenomena.* PLP is associated primarily with cortical excitability shifts in the sensorimotor network; increasing excitability in this system by anodal tDCS has an analgesic effect on PLP. Conversely, nonpainful phantom sensations are associated to a hyperexcitation of PPC that

can be normalized by cathodal tDCS. *This evidence highlights the relationship between the level of excitability of different cortical areas, which underpins maladaptive plasticity following limb amputation and the phenomenology of phantom limb, and it opens up new opportunities for the use of tDCS in the treatment of PLP.*

2.2 Negative results (after 2012)

Dubois PE, Ossemann M, de Fays K, De Bue P, Gourdin M, Jamart J, Vandermeeren Y. Postoperative analgesic effect of tDCS in lumbar spine surgery: a randomized control trial., Clin J Pain. 2013 Aug; 29(8):696-701.

We tested the potential of tDCS to reduce morphine consumption or pain perception during the postoperative period. **59** ASA I to II patients undergoing lumbar spine surgery were randomized to receive anodal (n=20), cathodal (n=20), or **sham** (n=19) tDCS in the recovery room in a **double-blind** manner. Morphine consumption administered through patient-controlled analgesia (PCA) was the primary outcome; pain perception as measured by visual analog scale was the secondary outcome. *There were no statistically significant differences between the 3 groups of patients, either for PCA morphine consumption or for pain scores.*

Paul J. Wrigleya, Sylvia M. Gustina, Leigh N. McIndoe, Rosemary J. Chakiath, Luke A. Henderson, Philip J. Siddall. Long standing neuropathic pain following spinal cord injury is refractory to transcranial direct current stimulation: a randomized controlled trial., Pain Journal, Volume 154, Issue 10, October 2013, Pages 2178–2184

We found that, contrary to previous reports, after **5 tDCS treatment periods**, mean pain intensity and unpleasantness rating were not significantly different from initial assessment. *That is, in this trial tDCS did not provide any pain relief in subjects with neuropathic SCI pain (n = 10). A similar lack of effect was also seen after sham treatment. Because the injury duration in this study was significantly greater than that of previous investigations, it is possible that tDCS is an effective analgesic only in individuals with relatively recent injuries and pain.*

O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, De Souza LH, Maskill DW, Sharp A, Moseley GL.. Transcranial direct current stimulation of the motor cortex in the treatment of chronic nonspecific low back pain: a randomized, double-blind exploratory study. , Clin J Pain. 2013 Jan; 29(1):26-34.

The goal was to test the proof of principle that active anodal tDCS applied to the motor cortex reduces pain significantly more than sham stimulation in a group of **participants with chronic nonspecific low back pain**. The study utilized a within-participants sham-controlled, interrupted time series design. A sample of **8 participants** was recruited. After 3 days of baseline measures, patients entered a 15-day experimental period (Mondays to Fridays) for 3 consecutive weeks. During this period each patient received sham stimulation daily until a randomly allocated day when active stimulation was commenced. Active stimulation was then given daily for the remaining days of the experimental period. Both the participants and the assessors were blinded. The primary outcomes were average pain intensity and unpleasantness in the last 24 hours measured using a visual analogue scale. Secondary outcomes included self-reported disability, depression and anxiety, a battery of cognitive tests to monitor for unwanted effects of stimulation, and patients' perceptions of whether they had received active or sham stimulation. Data were analyzed using generalized estimating equations. *Results do not provide evidence that tDCS is effective in the treatment of chronic back pain. The*

use of a small convenience sample limits the generalizability of these findings and precludes definitive conclusions on the efficacy of tDCS in chronic nonspecific low back pain.

Kerstin Luedtke , Arne May, Tim P. Jürgens. No effect of a single session of transcranial direct current stimulation on experimentally induced pain in patients with chronic low back pain—an exploratory study. , PLOS, November 26, 2012.

The present study investigated the effect of a **single session** of anodal, cathodal and sham stimulation (15 mins/1 mA) over the primary motor cortex on the perceived intensity of repeated noxious thermal and electrical stimuli and on elements of quantitative sensory testing (thermal pain and perception thresholds) applied to the right hand in **15 patients with chronic low back pain**. The study was conducted in a **double-blind sham-controlled and cross-over design**. *No significant alterations of pain ratings were found. Further studies applying repetitive tDCS to patients with chronic pain are required to fully answer the question whether experimental pain perception may be influenced by tDCS over the motor cortex.*

2.3 Interesting research (after 2012)

Jensen MP, Sherlin LH, Askew RL, Fregni F, Witkop G, Ganas A, Howe JD, Hakimian S. Effects of non-pharmacological pain treatments on brain states., Clin Neurophysiol. 2013 Oct;124(10):2016-24.

30 individuals with spinal cord injury and chronic pain were given an EEG and administered measures of pain before and after five procedures (hypnosis, meditation, tDCS, neurofeedback, and a control **sham tDCS** procedure). Each procedure was associated with a different pattern of changes in brain activity, and all active procedures were significantly different from the control procedure in at least three bandwidths. *Very weak and mostly non-significant associations were found between changes in EEG-assessed brain activity and pain. The results provide new findings regarding the unique effects of four non-pharmacological treatments on pain and brain activity. This study used a **single tDCS** session, and found no clinical impact.*

Portilla AS, Bravo GL, Miraval FK, Villamar MF, Schneider JC, Ryan CM, Fregni F. A feasibility study assessing cortical plasticity in chronic neuropathic pain following burn injury. J Burn Care Res. 2013 Jan-Feb;34(1):e48-52.

The aim of this article is to evaluate the neuroplastic changes associated with chronic neuropathic pain following burn injury and modulation feasibility using tDCS. This is a **crossover, double-blinded** case series involving **3 patients with chronic neuropathic pain following burn injury**. Participants were randomly assigned to undergo **single sessions** of both sham and active anodal tDCS over the primary motor cortex, contralateral to the most painful site. Excitability of the motor cortex was assessed before and after each stimulation session with the use of transcranial magnetic stimulation. *An overall decrease in cortical excitability was seen after active tDCS only, as characterized by a decrease in intracortical facilitation and amplitude of motor evoked potentials and an increase in intracortical inhibition. Clinical outcomes did not change after a single session of tDCS.* Results are consistent with previous studies showing that patients with chronic neuropathic pain have defective intracortical inhibition. *This case series shows early evidence that chronic pain following burn injury may share similar central neural mechanisms, which could be modulated using tDCS.*

Reidler JS, Mendonca ME, Santana MB, Wang X, Lenkinski R, Motta AF, Marchand S, Latif L, Fregni F. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects., J Pain. 2012 May;13(5):450-8

Pain modulation can be achieved using neuromodulatory tools that influence various levels of the nervous system. tDCS, for instance, has been shown to reduce chronic pain when applied to the primary motor cortex. In contrast to this central neuromodulatory technique, diffuse noxious inhibitory controls (DNIC) refers to endogenous analgesic mechanisms that decrease pain following the introduction of heterotopic noxious stimuli. We examined whether combining top-down motor cortex modulation using anodal tDCS with a bottom-up DNIC induction paradigm synergistically increases the threshold at which pain is perceived. **The pain thresholds of 15 healthy subjects** were assessed before and after administration of active tDCS, **sham** tDCS, cold-water-induced DNIC, and combined tDCS and DNIC. *We found that both tDCS and the DNIC paradigm significantly increased pain thresholds and that these approaches appeared to have additive effects.* Increase in pain threshold following active tDCS was positively correlated with baseline N-acetylaspartate in the cingulate cortex and negatively correlated with baseline glutamine levels in the thalamus as measured by magnetic resonance spectroscopy. *These results suggest that motor cortex modulation may have a greater analgesic effect when combined with bottom-up neuromodulatory mechanisms, presenting new avenues for modulation of pain using noninvasive neuromodulatory approaches. This article demonstrates that both noninvasive motor cortex modulation and a descending noxious inhibitory controls paradigm significantly increase pain thresholds in healthy subjects and appear to have an additive effect when combined. These results suggest that existing pain therapies involving DNIC may be enhanced through combination with noninvasive brain stimulation.*

Zandieh A, Parhizgar SE, Fakhri M, Taghvaei M, Miri S, Shahbabaie A, Esteghamati S, Ekhtiari H. Modulation of Cold Pain Perception by Transcranial Direct Current Stimulation in Healthy Individuals. Neuromodulation. 2013 Jul-Aug;16(4):345-8; discussion 348

Anodal, cathodal (2 mA), or **sham** tDCSs were applied on the primary motor cortex of **22 healthy** subjects in a random order. A cold pressor test was performed ten minutes after initiation of stimulation. Pain threshold and tolerance were defined as time latencies to the onset of pain perception and to the withdrawal from cold stimulus, respectively. Furthermore, pain intensity (on a scale from 0 to 10) was rated at tolerance. The authors found that *Anodal stimulation of the primary motor area can be utilized to alleviate cold pain perception in healthy individuals.*

DosSantos MF, Love TM, Martikainen IK, Nascimento TD, Fregni F, Cummiford C, Deboer MD, Zubieta JK, Dasilva AF. Immediate effects of tDCS on the μ -opioid system of a chronic pain patient. Front Psychiatry. 2012 Nov 2;3:93

We developed a unique protocol where tDCS of the motor cortex is performed during positron emission tomography (PET) scan using a μ -opioid receptor (μ OR) selective radiotracer, [(11)C]carfentanil. This is one of the most important central neuromechanisms associated with pain perception and regulation. The active session directly improved in 36.2% the threshold for experimental cold pain in the trigeminal allodynic area, mandibular branch, but not the TNP patient's clinical pain. *Interestingly, the single active tDCS application considerably decreased μ ORBP(ND) levels in (sub)cortical pain-matrix structures compared to sham tDCS, especially in the posterior thalamus.* Suggesting that the μ -opioidergic effects of a single tDCS session are subclinical at immediate level, and repetitive sessions are necessary to revert ingrained neuroplastic changes related to the chronic pain. To our knowledge, *we provide data for the first*

time in vivo that there is possibly an instant increase of endogenous μ -opioid release during acute motor cortex neuromodulation with tDCS.

Mancini F1, Bolognini N, Haggard P, Vallar G. tDCS modulation of visually induced analgesia. J Cogn Neurosci. 2012 Dec;24(12):2419-27.

Multisensory interactions can produce analgesic effects. In particular, viewing one's own body reduces pain levels, perhaps because of changes in connectivity between visual areas specialized for body representation, and sensory areas underlying pain perception. We tested the causal role of the extrastriate visual cortex in triggering visually induced analgesia by modulating the excitability of this region with tDCS. Anodal, cathodal, or **sham** tDCS (2 mA, 10 min) was administered to **24 healthy participants** over the right occipital or over the centro-parietal areas thought to be involved in the sensory processing of pain. Participants were required to rate the intensity of painful electrical stimuli while viewing either their left hand or an object occluding the left hand, both before and immediately after tDCS. *We found that the analgesic effect of viewing the body was enhanced selectively by anodal stimulation of the occipital cortex. The effect was specific for the polarity and the site of stimulation. The present results indicate that visually induced analgesia may depend on neural signals from the extrastriate visual cortex.*

Jürgens TP, Schulte A, Klein T, May A. Transcranial direct current stimulation does neither modulate results of a quantitative sensory testing protocol nor ratings of suprathreshold heat stimuli in healthy volunteers. Eur J Pain. 2012 Oct;16(9):1251-63

Little is known regarding tDCS effects on nociception in healthy volunteers. In the present study, we examined the effects of anodal, cathodal and **sham** stimulation of the left primary motor cortex in **17 healthy volunteers** on modalities of a comprehensive quantitative sensory testing protocol (including thermal and mechanoreceptive detection and pain thresholds) and on a repetitive heat pain paradigm mimicking clinical pain. The study was conducted in a single-blind crossover fashion. tDCS was applied at 1 mA for 15 min. *We could not detect any relevant modulation of somatosensory and pain variables in quantitative sensory testing. In addition, no significant alteration of enhanced pain ratings to repetitive noxious heat stimuli (heat hyperalgesia) was found. However, As pain processing in chronic pain patients might differ, tDCS could exert its antinociceptive effects depending on the activation level of the nociceptive system.*

Mylius V, Jung M, Menzler K, Haag A, Khader PH, Oertel WH, Rosenow F, Lefaucheur JP. Effects of transcranial direct current stimulation on pain perception and working memory. Eur J Pain. 2012 Aug;16(7):974-82

Previous studies have shown that non-invasive stimulation of the dorsolateral prefrontal cortex (DLPFC) could modulate experimentally induced pain and working memory (WM) in healthy subjects. However, the two aspects have never been assessed concomitantly. The present study was set up to investigate the effects of tDCS of the DLPFC on thermal pain and WM in the same population of healthy volunteers. In a randomized and balanced order of different sessions separated by 1 week, 20 min of 2 mA anodal, cathodal or **sham** tDCS were applied to the left or right DLPFC in two separate experiments. **12 healthy volunteers** were enrolled for each stimulated hemisphere. Warm and cold detection thresholds, heat and cold pain thresholds as well as heat pain tolerance thresholds were measured before, during and following tDCS. WM was assessed by a 2-back task applied once during cortical stimulation. *Anodal tDCS of the right DLPFC led to an increase of tolerance to heat pain.* The present data show an involvement of the DLPFC in the processing of pain and WM. There was no correlation between these findings, *suggesting that the analgesic effects of cortical stimulation are not associated with cognitive processing.*

Maeoka H, Matsuo A, Hiyamizu M, Morioka S, Ando H. Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: a study using electroencephalographic power spectrum analysis. *Neurosci Lett.* 2012 Mar 14;512(1):12-6

Pain is a multidimensional experience with sensory-discriminative, cognitive-evaluative and affective-motivational components. Emotional factors such as unpleasantness or anxiety are known to have influence on pain in humans. The aim of this **single-blinded, cross over study** was to evaluate the effects of tDCS on emotional aspects of pain in pain alleviation. **15 subjects** (5 females, 10 males) volunteered to participate in this study. In an oddball paradigm, three categories of 20 pictures (unpleasant, neutral, and pleasant) served as rare target pictures from the International Affective Picture System (IAPS). The power of the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-25 Hz), and gamma (30-40 Hz) frequency bands in the three categories were measured using electroencephalography during an oddball paradigm at pre- and post-anodal or sham tDCS above the left dorsolateral prefrontal cortex (DLPFC). *Results showed that the beta band power was significantly increased, and the alpha band power was significantly decreased during unpleasant pictures after anodal tDCS compared with sham tDCS.* Furthermore, regarding unpleasant pictures, subjective reports of Self Assessment Manikin (SAM) for emotional valence after anodal tDCS showed a significant decrease of unpleasantness. *Therefore, emotional aspects of pain may be effectively alleviated by tDCS of the left DLPFC as was shown not only by subjective evaluation, but also by objective observation of cerebral neural activity. This processing may be mediated by facilitation of the descending pain inhibitory system through enhancing neural activity of the left DLPFC.*

Reidler JS1, Mendonca ME, Santana MB, Wang X, Lenkinski R, Motta AF, Marchand S, Latif L, Fregni F. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. *J Pain.* 2012 May;13(5):450-8

We examined whether combining top-down motor cortex modulation using anodal tDCS with a bottom-up diffuse noxious inhibitory controls (DNIC) induction paradigm synergistically increases the threshold at which pain is perceived. **The pain thresholds of 15 healthy subjects** were assessed before and after administration of active tDCS, sham tDCS, cold-water-induced DNIC, and combined tDCS and DNIC. *We found that both tDCS and the DNIC paradigm significantly increased pain thresholds and that these approaches appeared to have additive effects. Increase in pain threshold following active tDCS was positively correlated with baseline N-acetylaspartate in the cingulate cortex and negatively correlated with baseline glutamine levels in the thalamus as measured by magnetic resonance spectroscopy. These results suggest that motor cortex modulation may have a greater analgesic effect when combined with bottom-up neuromodulatory mechanisms.*

Krause B, Márquez-Ruiz J, Cohen Kadosh R. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance?. *Front Hum Neurosci.* 2013 Sep 24;7:602

Transcranial direct current stimulation (tDCS) is a promising tool for cognitive enhancement and neurorehabilitation in clinical disorders in both cognitive and clinical domains (e.g., chronic pain, tinnitus). Here we suggest the potential role of tDCS in modulating cortical excitation/inhibition (E/I) balance and thereby inducing improvements. We suggest that part of the mechanism of action of tDCS can be explained by non-invasive modulations of the E/I balance.

Alm PA, Dreimanis K. Neuropathic pain: transcranial electric motor cortex stimulation using high frequency random noise. Case report of a novel treatment. J Pain Res. 2013 Jun 24;6:479-8

Electric motor cortex stimulation has been reported to be effective for many cases of neuropathic pain, in the form of epidural stimulation or tDCS. A novel technique is transcranial random noise stimulation (tRNS), which increases the cortical excitability irrespective of the orientation of the current. The aim of this study was to investigate the effect of tRNS on neuropathic pain in a small number of subjects, and in a case study explore the effects of different stimulation parameters and the long-term stability of treatment effects. THE STUDY WAS DIVIDED INTO THREE PHASES: (1) a **double-blind crossover study**, with 4 subjects; (2) a **double-blind extended case study** with one responder; and (3) open continued treatment. The motor cortex stimulation consisted of alternating current random noise (100-600 Hz), varying from 0.5 to 10 minutes and from 50 to 1500 μ A, at intervals ranging from daily to fortnightly. **1 out of 4 participants showed a strong positive effect** (also compared with direct-current-sham, $P = 0.006$). Unexpectedly, this effect was shown to occur also for very weak (100 μ A, $P = 0.048$) and brief (0.5 minutes, $P = 0.028$) stimulation. The effect was largest during the first month, but remained at a highly motivating level for the patient after 6 months.

Laste G, Caumo W, Adachi LN, Rozisky JR, de Macedo IC, Filho PR, Partata WA, Fregni F, Torres IL. After-effects of consecutive sessions of tDCS in a rat model of chronic inflammation. Exp Brain Res. 2012 Aug;221(1):75-83

tDCS induces cortical excitability changes in animals and humans that can last beyond the duration of stimulation. Preliminary evidence suggests that tDCS may have an analgesic effect; however, the timing of these effects, especially when associated with consecutive sessions of stimulation in a controlled animal experiment setting, has yet to be fully explored. To evaluate the effects of tDCS in inflammatory chronic pain origin immediately and 24 h after the last treatment session, complete Freund's adjuvant (CFA) was injected (100 μ l) in the right footpad to induce inflammation. On the 15th day after CFA injection, **rats** were divided into two groups: tDCS ($n = 9$) and sham ($n = 9$). The tDCS was applied for 8 days. The hot plate and Von Frey tests were applied immediately and 24 h after the last tDCS session. Eight 20-min sessions of 500 μ A anodal tDCS resulted in antinociceptive effects as assessed by the hot plate test immediately ($P = 0.04$) and 24 h after the last tDCS session ($P = 0.006$), for the active tDCS group only. There was increased withdrawal latency in the Von Frey test at 24 h after the last session ($P = 0.01$). *Our findings confirm the hypothesis that tDCS induces significant, long-lasting, neuroplastic effects and expands these findings to a chronic pain model of peripheral inflammation, thus supporting the exploration of this technique in conditions associated with chronic pain and peripheral inflammation, such as osteoarthritis.*

Spezia Adachi LN, Caumo W, Laste G, Fernandes Medeiros L, Ripoll Rozisky J, de Souza A, Fregni F, Torres IL. Reversal of chronic stress-induced pain by tDCS in an animal model. Brain Res. 2012 Dec 13;1489:17-26

tDCS has been suggested as a therapeutic tool for pain syndromes. Although initial results in human subjects are encouraging, it still remains unclear whether the effects of tDCS can reverse maladaptive plasticity associated with chronic pain. The stress group was exposed to CRS for 11 weeks for the establishment of hyperalgesia and mechanical allodynia as shown by the hot plate and von Frey tests, respectively. **Rats** were then divided into four groups control, stress, stress+sham tDCS and stress+tDCS. Anodal or sham tDCS was applied for 20min/day over 8 days and the tests were repeated. *These results support the notion that tDCS reverses the detrimental effects of chronic stress on the pain system and decreases TNF α levels in the hippocampus.*

2.4 Reviews (after 2012)

Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. Pain Pract. 2013 Feb;13(2):131-45

This is a review paper to systematically review the literature to date applying rTMS or transcranial direct current stimulation (tDCS) for patients with fibromyalgia syndrome (FMS). Electronic bibliography databases screened included PubMed, Ovid MEDLINE, PsychINFO, CINAHL, and Cochrane Library. The keyword "fibromyalgia" was combined with ("transcranial" and "stimulation") or "TMS" or "tDCS" or "transcranial magnetic stimulation" or "transcranial direct current stimulation". **Nine of 23** studies were included; brain stimulation sites comprised either the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC). Five studies used rTMS (high-frequency-M1: 2, low-frequency-DLPFC: 2, high-frequency-DLPFC: 1), **while 4 applied tDCS** (anodal-M1: 1, anodal-M1/DLPFC: 3). **Eight were double-blinded, randomized controlled trials.** Most (80%) rTMS studies that measured pain reported significant decreases, **while all (100%) tDCS studies with pain measures reported significant decreases.** Greater longevity of significant pain reductions was observed for excitatory M1 rTMS/tDCS. *Studies involving excitatory rTMS/tDCS at M1 showed analogous pain reductions as well as considerably fewer side effects compared to FDA approved FMS pharmaceuticals. The most commonly reported side effects were mild, including transient headaches and scalp discomforts at the stimulation site. rTMS/tDCS should be considered when treating patients with FMS, particularly those who are unable to find adequate symptom relief with other therapies. Further work into optimal stimulation parameters and standardized outcome measures is needed to clarify associated efficacy and effectiveness.*

Moreno-Duarte I, Morse LR, Alam M, Bikson M, Zafonte R, Fregni F. Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury. Neuroimage. 2014 Jan 15;85 Pt 3:1003-13.

We aimed to review initial efficacy, safety and potential predictors of response by assessing the effects of neural stimulation techniques to treat SCI pain. **RESULTS: 8 clinical trials** and one naturalistic observational study (nine studies in total) met the inclusion criteria. Among the clinical trials, **three studies assessed the effects of tDCS**, two of CES, two of rTMS and one of TENS. *No significant adverse effects were reported in these studies. We found an important variability in these results across studies. There is a clear need for the development of methods to decrease treatment variability and increase response to neural stimulation for pain treatment.*

Plow EB, Pascual-Leone A, Machado A. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. J Pain. 2012 May;13(5):411-24.

This critical review focuses on factors contributing to poor therapeutic utility of invasive and noninvasive brain stimulation in the treatment of chronic neuropathic and pain of noncancerous origin. *Through key clinical trial design and conceptual refinements, retention and consistency of response may be improved, potentially facilitating the widespread clinical applicability of such approaches.*