Effectiveness of transcraneal direct current stimulation (tDCS) for the treatment of fibromyalgia: Comparison of cortical targets effects on main fibromyalgia symptoms

Introduction

1. Transcranial direct current stimulation: a non-invasive brain stimulation tool

Transcranial direct current stimulation (tDCS) is a promising technique that allows to non-invasively modulate brain activity by applying a low intensity current (1 to 2 mA) (Nitsche et al 2008) via scalp electrodes. Stimulation effects and after-effects depend on the current polarity under each electrode. Indeed, motor cortex stimulation studies have shown that with standard parameters (1 to 2 mA, for 10 to 20 minutes, using 25 to 35cm² electrodes), anodal stimulation enhances cortical excitability (i.e. is "excitatory"), while cathodal stimulation decreases cortical excitability (i.e. is inhibitory) (Nitsche et al 2008, Dayan et al 2013). tDCS is also capable of modulating behaviour. For example, anodal stimulation of motor cortex has been shown to increase motor skill learning (Reis et al 2009); the initial gain in performance was still evident 3 months later. Long-term effects are thought to reflect neuromodulation of gabaergic and glutamatergic synapses (Stagg and Nitsche, 2011). tDCS stimulation is a well tolerated and innocuous treatment procedure, that may be occasionally accompanied by minor discomfort, such as stinging, burning or vibration skin sensations under the electrode placements, and rarely by headache, that in any case shows good response to analgesic medication.

Compared to the other main neuro-modulatory technique (rTMS, or repetitive transcranial magnetic stimulation), tDCS is simple to use, portable and less expensive. This makes tDCS a potentially powerful therapeutic tool, especially if it can be used directly at the patient's home (Pérez-Borrego et al 2014), also allowing placebo conditions in a simple way. Moreover, its fields of application appear wide, as shown by the number of papers reviewed recently that aim to use tDCS in stroke rehabilitation (Boggio et al., 2008; Fregni et al., 2007; Hummel et al 2008), or in the treatment of pathologies such as depression (Nitsche et al 2009) or chronic pain (O'Connell et al 2010).

2. Cortical stimulation for pain relief and modulation of pain perception

Different neuro-modulatory approaches, both invasive and non-invasive, have been successfully tested as potential therapeutic tools for chronic pain disorders (Lefaucheur et al 2014). The two methods presented above (transcranial direct current stimulation, or tDCS, and repetitive transcranial magnetic stimulation, or TMS) have been increasingly utilized, particularly due to their non-invasive nature and their ability to modify the excitability of cortical neural circuits. When delivered to the primary motor cortex (M1), these techniques are capable of modifying pain perception, possibly via modulation of M1-thalamic inhibitory networks (Houzé et al 2013, Polania, Paulus & Nitsche, 2012), as well as other cortico-cortical and cortico-subcortical projections (Boggio et al., 2008; Polania et al., 2012).

Fibromyalgia is a common cause of diffuse, chronic musculoskeletal pain in adults, with an estimated prevalence between 2 and 5% in the general population (Neumann & Buskila, 2003). Even though its aetiology and pathophysiology are not fully understood, current evidence suggests that, similarly to other chronic pain syndromes, this is a disorder of pain regulation characterized by altered pain and sensory processing in the central nervous system, likely due to maladaptive plasticity in pain-related neural circuits (Henry et al, 2011; Woolf, 2011). Thus, the use of neuro-stimulation approaches is of particular relevance in fibromyalgia, a chronic pain disorder where pain can be characterized by a lack of inhibitory control over somatosensory processing (Valle et al, 2009; Villamar et al, 2013) and that is often refractory to multiple therapeutic strategies.

Some studies have explored the analgesic effects of tDCS in chronic pain, including fibromyalgia, both stimulating M1 (Fregni et al., 2006; Riberto et al., 2011; Roizenblatt et al., 2007; Valle et al., 2009, Villamar et al., 2013) and/or the dorso-lateral prefrontal cortex (DLPFC, F3) (Fregni et al., 2006; Roizenblatt et al., 2007; Valle et al., 2010). However, a recent meta-analysis has stressed the poor methodological quality of most previous studies, leading to non-significant results of tDCS for pain relief, and the need for larger, rigorously designed studies, particularly of longer courses of stimulation (O'Connell et al Cochrane Rev 2014). Given that the results on the efficacy of tDCS for pain relief are contradictory, this study aims to obtain more information on its therapeutic use, and to respond to two important challenges of this area of research: (a)

the need of more ***sham-controlled studies with a sufficient number of patients and long follow-up****; (b) the need to explore* ***novel targets in pain-related brain regions, such as the operculo-insular cortex.***

The specific objectives of the study are: 1) to compare the analgesic effect of M1 active tDCS vs sham tDCS in a group of patients with fibromyalgia; 2) to analyze long-term effects (6, 12 month) of tDCS treatment on pain and associated symptoms; 3) to check the effect of DLPFC active tDCS vs sham tDCS on cognitive function (assessed by neuropsychological tests and EEG measures); 4) to determine the optimum tDCS stimulation place (M1, OIC or DLPFC) for each of the four group of symptoms considered (pain relief, improvement of sleep quality, amelioration of affective state and cognitive dysfunction) in fibromyalgia patients.

Methods

Participants. Fibromyalgia (FM) patients will be informed about the study in the Neurology service of the Universitary Hospital Complex of Santiago de Compostela (CHUS) or in the Rheumatology service of the Hospital Complex of Pontevedra. Also, we have a pool of 543 patients that participated in the Genetic study of Fibromyalgia that were already informed about the tDCS project.

The first contact with the patients will be telephonically. Patients that agree to participate will be scheduled for a first evaluation session. Once informed about the characteristics of the tDCS, the results of previous studies with chronic pain patients, and safety aspects, a written informed consent will be required if they agree to participate. We plan to recruit around 92 middle-age FM female patients (range 25-65 y.), using strict inclusion and exclusion criteria. Inclusion criteria are: fulfillment of both the ACR criteria of 1990 (Wolfe et al., 1990) and 2010 (Wolfe et al., 2010); moderate to high severity of the disease (indicated by a FIQ score ≥70 or a VAS Pain ≥ 7); presence of cognitive dysfunction (item 2 “cognitive troubles” of the Symptom Severity Score ≥2). Exclusion criteria are: no immune system pathology or comorbidities that could explain the main symptomatology of FM; risk factors for the tDCS procedure, such as the existence of a history of prevous convulsions (epilepsy or family history); use of anticonvulsant treatment (such as pregabalin, caarbamazepine or

gabapentin); substance abuse; psychiatric diseases (other than depression and anxiety); brain damage, dementia and Parkinson disease.

Procedure. Once signed the informed consent, patients will be cited for a first clinical evaluation. This would comprise a complete clinical evaluation including the ACR 1990 and 2010 criteria for FM, and algometry of tender points to measure pain threshold and tolerance, as well as a number of self-reported and neuropsychological tests (see Materials for a description).

If the patient fulfills the ACR criteria, then the treatment with tDCS stimulation will be delivered in 15 sessions of 20 minutes each, scheduled in 5 days per week during 3 weeks. To assess possible adverse effects of the tDCS, we will administer a questionnaire at the end of each session (see appendix). To ensure an adequate medical attention in case of adverse affects or unexpected events, the tDCS will be always apply in a hospital or health center.

The total sample will be randomly assigned to any of the four groups:

Group 1: Placebo
Group 2: Active anodal tDCS at M1
Group 3: Active anodal tDCS at OIC
Group 4: Active anodal tDCS at DLPFC

Clinical evaluation will be performed again at the end of the treatment (after 3 weeks) and in the follow-ups at 6 and 12 months to assess the evolution of the main symptoms.

All the details about the procedure and treatment are presented in Table 2 and 3.

Phase	*Clinical interview*	*Algometry of tender points*	*Self-reported questionnaires and neuropsychologial assessment*	*EEG (resting and during neuropsychological tests)*
1. First Clinical evaluation	10 min	5 min	50 min	50 min
2. Post-treatment evaluation	10 min	5 min	50 min	50 min
3. Six-month follow-up	10 min	5 min	50 min	50 min
3. 12- month follow-up	10 min	----	-----	-----

Table 2. Details of the clinical evaluation for FM patients.

	Session 1 Pre-treatment	*Session 2-16 Treatment*	*Session 17 Post-treatment*
Group 1 (Placebo)	*Clinical, neuropsychological, EEG assessment (115 min)*	*Sham tDCS (20 min)*	*Clinical, neuropsychological, EEG assessment (115 min)*
Group 2 (M1)	*Clinical, neuropsychological, EEG assessment (115 min)*	*Active tDCS (20 min)*	*Clinical, neuropsychological, EEG assessment (115 min)*
Group 3 (COI)	*Clinical, neuropsychological, EEG assessment (115 min)*	*Active tDCS (20 min)*	*Clinical, neuropsychological, EEG assessment (115 min)*
Group 4 (DLPFC)	*Clinical, neuropsychological, EEG assessment (115 min)*	*Active tDCS (20 min)*	*Clinical, neuropsychological, EEG assessment (115 min)*

Table 3. Details of the whole procedure (assessment + treatment) for FM patients.

Materials.

Clinical Assessment. We will conduct an extensive clinical interview that include the evaluation of the central features of Fibromyalgia: pattern and intensity of pain, presence of mood disorders, sleep problems, fatigue, stiffness, headache, anxiety and cognitive dysfunction, and presence of comorbidities, among others. The sociodemographic variables included will be marital status, years of education, current work and occupational status.

Algometry. Pain threshold and tolerance, at the 18 tender points proposed by the ACR (1990), will be measured by a trained investigator using pressure algometry (Wagner Force One, Model FDI). Pressure pain threshold (kg) is defined as the minimum force applied that induces pain, and pressure pain tolerance (kg) as the maximum pain-pressure value that is born at each point. A tender point is counted as positive when the patient felt pain at pressures below 4 kg, given that it has been established that healthy women usually start to perceive pain from pressures of 4 kg [1]. For each participant, we will calculate the total count of positive tender point (tender point count), and the mean pain pressure threshold and tolerance for the 18 points.

Self-reported scales. Visual Analogue Scales (VAS) created ad-hoc will be used to assess pain and key symptoms of FM, and disease evolution. Patients will fill in various self-reported questionnaires to examine sleep quality, depression, quality of life and functional consequences of the disease. The questionnaires used were the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al, 1989), the Beck Depression Inventory (BDI) (Beck, Steer y Garbin, 1988), the Hospital Anxiety and Depression Scale (HADS) (Zigmond y Snaith, 1983), the Fibromyalgia Impact Questionnaire (FIQ) (Bennett, 2005), the Memory Everyday Failures (MFE) (Sunderland, Harris and Gleave, 1984), the Fibromyalgia Survey Questionnaire (FSQ) (Wolfe et al., 2011), and the Short Form 36 Health Survey (SF-36) (Ware, 2000). All the questionnaires were administered in their corresponding Spanish-validated versions.

We will also administer a battery of neuropsychological tests to assess working memory and interference:

- Direct and inverse digits of the Wechsler Memory Scale-III
- Spatial location of the the Wechsler Memory Scale-III
- 2-back task
- Multi-source interference task (MSIT)
- Auditory consonant trigram test

Brain electrical activity will be recording in resting and during the performance of cognitive tasks.

Outcome measures

To assess the effectiveness of the treatment, we will consider four groups of symptoms, each with defined outcome measures.

I. Pain, fatigue (mean threshold by algometry, FIQ items 5 and 6)
II. Mood state (HADS score)
III. Cognitive dysfunction (MFE score)
IV. Sleep disorders (PSQI score)

A 20% of change between the pre and post treatment in any of the groups will be consider an index of a clinical improvement.

tDCS stimulation: A tDCS device will be used to perform stimulation. Electrodes will be placed on the subjects' scalp (10-20 International System sites) on the appropriate positions to stimulate the motor cortex (two electrodes, one over C3, the other contralateral supraorbital), the dorsolateral prefrontal cortex or the operculo-insular cortex (optimized multi-electrode montage). Current (2 mA max) will be gradually ramped up and down at the beginning and at the end of the stimulation period, which will be 20 minutes long. In the Sham sessions the current will be 0 mA during the interval between the initial and the final ramps.

Statistical Analyses. ANOVAs with treatment (4 levels) will be performed for the main outcome variables. Also, we will analyze the impact of treatment on general quality of life, functional impact and EEG parameters.

References

Alonso J, Prieto L, Antó JM (1995) [The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results]. Med Clin (Barc) 104:20771-20776

Andersen P, Eccles JC, Sears TA (1962) Presynaptic inhibitory action of cerebral cortex on the spinal cord. Nature 194:740-1

Andrade C. (2013) Once- to twice-daily, 3-year domiciliary maintenance transcranial direct current stimulation for severe, disabling, clozapine-refractory continuous auditory hallucinations in schizophrenia. J ECT. (3):239-42

Antal A, Polania R, Schmidt-Samoa C, Dechent P, Paulus W. (2011) Transcranial direct current stimulation over the primary motor cortex during fMRI. Neuroimage 55(2):590-6.

Baudewig J, Nitsche MA, Paulus W, Frahm J. (2001) Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med, 45(2):196-201.

Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck Depression Inventory: Twenty-five years of the valuation. Clinical Psychology Review 8:77-100

Benison AM, Chumachenko S, Harrison JA, Maier SF, Falci SP, Watkins LR, Barth DS. (2011) Caudal granular insular cortex is sufficient and necessary for the long-term maintenance of allodynic behavior in the rat attributable to mononeuropathy. J Neurosci. 31(17):6317-28

Bennett R (2005) The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 23 (5 Suppl 39):S154-162

Boggio PS, Zaghi S, Lopes M, Fregni F (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol 15:1124-1130

Bolognini N, Rossetti A, Maravita A, Miniussi C. (2011) Seeing touch in the somatosensory cortex: a TMS study of the visual perception of touch. Hum Brain Mapp, 32(12):2104-14

Brunelin J1, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, Saoud M, Mechri A, Poulet E. (2012) Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am. J. Psychiatry, 169(7):719-24.

Buysse DJ, Charles F, Reynolds TH, Berman SR, Kupfer DJ (1989) The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research 28 (2):193–213

Ciampi de Andrade D, Galhardoni R, Pinto LF, Lancelotti R, Rosi J Jr, Marcolin MA, Teixeira MJ. (2012) Into the island: a new technique of non-invasive cortical stimulation of the insula. Neurophysiol Clin. 42(6):363-368

Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M (2009). Gyri-precise head model of transcranial DC stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul 2:201-207

Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. (2013) Noninvasive brain stimulation: from physiology to network dynamics and back. Nat Neurosci. 16(7):838-44.

Dum RP, Levinthal DJ, Strick PL. (2009) The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. J Neurosci. 29(45):14223-35

Fierro B, De Tommaso M, Giglia F, Giglia G, Palermo A, Brighina F. (2010) Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: modulatory effects on motor cortex excitability. Exp Brain Res. 203(1):31-8

Fiorio M, Haggard P. (2005) Viewing the body prepares the brain for touch: effects of TMS over somatosensory cortex. Eur J Neurosci. 22(3):773-7.

Fregni, F., Gimenes, R., Valle, A. C., Ferreira, Rocha, R. R., Natalle, L., Bravo, R., Rigonatti, S. P., Freedman, S. D., Nitsche, M. A., Pascual-Leone, A., Boggio P. S. (2006). A Randomized, Sham-Controlled, Proof of Principle Study of Transcranial Direct Current Stimulation for the Treatment of Pain in Fibromyalgia. *Arthritis & Rheumatism 54* (12), 3988–3998.

Fregni, F., Freedman, S., Pascual-Leone, A. (2007). Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol ; 6 :188-191

Fregni F, Potvin K, Dasilva D, Wang X, Lenkinski RE, Freedman SD, Pascual-Leone A. (2011) Clinical effects and brain metabolic correlates in non-invasive cortical neuromodulation for visceral pain. Eur J Pain 15(1):53-60

Frot M, Faillenot I, Mauguière F. (2014) Processing of nociceptive input from posterior to anterior insula in humans. Hum Brain Mapp. doi: 10.1002/hbm.22565

García-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguière F, Sindou M, Laurent B. (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain. 83(2):259-73

Graff-Guerrero A, González-Olvera J, Fresán A, Gómez-Martín D, Méndez-Núñez JC, Pellicer F. (2005) Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. Brain Res Cogn Brain Res.25(1):153-60

Henry DE, Chiodo AE, Yang W (2011). Central nervous system reorganization in a variety of chronic pain states: A review. PM R 3:1116-1125

Houzé B, Bradley C, Magnin M, Garcia-Larrea L. (2913) Changes in the cortical representation of the hand and in pain perception induced by repetitive magnetic stimulation of the motor cortex. Cereb Cortex ; 23(11):2667-76.

Hummel FC, Celnik P, Pascual-Leone A, Fregni F, Byblow WD, Buetefisch CM, Rothwell J, Cohen LG, Gerloff C. (2008) Controversy: Noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. Brain Stimul. 1(4):370-82

Kwon YH1, Jang SH. (2011) The enhanced cortical activation induced by transcranial direct current stimulation during hand movements. Neurosci Lett.;492(2):105-8.

Ladeira A, Fregni F, Campanhã C, Valasek CA, De Ridder D, Brunoni AR, Boggio PS. (2011) Polarity-dependent transcranial direct current stimulation effects on central auditory processing. PLoS One. 6(9):e25399.

Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS (2005) How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci 22:495–504.

Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L (2014) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. doi: 10.1016/j.clinph.2014.05.021.

Macías JA, Royuela R (1996) La versión española del Índice de Calidad de Sueño de Pittsburgh. Informaciones Psiquiátricas 146 (465-472)

Mathys C, Loui P, Zheng X, Schlaug G. (2010) Non-invasive brain stimulation applied to Heschl's gyrus modulates pitch discrimination. Front Psychol 1:193

Maule F, Barchiesi G, Brochier T, Cattaneo L. (2013) Haptic Working Memory for Grasping: the Role of the Parietal Operculum. Cereb Cortex. 2013 Sep 17. [Epub ahead of print]

Monterde S, Salvata I, Montulla S, Fernández-Ballart J (2004) Validación de la versión española del Fibromyalgiam Impact Questionnaire. Rev Esp Reumatol 31 (9):507-513

Murphy K, Harris AD, Diukova A, Evans CJ, Lythgoe DJ, Zelaya F, Wise RG. (2011) Pulsed arterial spin labeling perfusion imaging at 3 T: estimating the number of subjects required in common designs of clinical trials. Magn Reson Imaging. 2011 Dec;29(10):1382-9.

Neuling T, Rach S, Wagner S, Wolters CH, Herrmann CS. (2012) Good vibrations: oscillatory phase shapes perception. Neuroimage 63(2):771-8

Neumann L, Buskila D (2003). Epidemiology of fibromyalgia. Curr Pain Headache Rep 7:362-368

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A. (2008) Transcranial direct current stimulation: State of the art 2008. Brain Stimul. 1(3):206-23

Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. (2009) Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol. 219(1):14-9

O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. (2010) Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev. 8;(9):CD008208

Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D (2007). Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 130:2661-2670.

Pérez-Borrego YA, Campolo M, Soto-León V, Rodriguez-Matas MJ, Ortega E, Oliviero A. (2014) Pain treatment using tDCS in a single patient: tele-medicine approach in non-invasive brain simulation. Brain Stimul. 7(2):334-5

Polanía R, Paulus W, Antal A, NitscheMA (2011) Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. Neuroimage 54:2287–2296

Polania R, Paulus W, Nitsche MA (2012). Modulating corticostriatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp 33:2499-2508

Pomares FB, Faillenot I, Barral FG, Peyron R. (2013) The 'where' and the 'when' of the BOLD response to pain in the insular cortex. Discussion on amplitudes and latencies. Neuroimage 64:466-75

Poreisz C, Boros K, Antal A, Paulus W. (2007) Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull. 72(4-6):208-14

Raij T, Karhu J, Kicić D, Lioumis P, Julkunen P, Lin FH, Ahveninen J, Ilmoniemi RJ, Mäkelä JP, Hämäläinen M, Rosen BR, Belliveau JW. (2008) Parallel input makes the brain run faster. Neuroimage 40(4):1792-7

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Celnik PA, Krakauer JW (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A 106:1590 –1595.

Riberto, M., Alfieri, F. M., Pacheco, K. M., Leite, V. D., Kaihami, H. N., Fregni, F., Battistella, L. M. (2011). Efficacy of Transcranial Direct Current Stimulation Coupled with a Multidisciplinary Rehabilitation Program for the Treatment of Fibromyalgia. *The Open Rheumatology Journal, 5*, 45-50.

Roizenblatt, S., Fregni, F., Gimenez, R., Wetzel, T., Rigonatti, S. P., Tufik, S., Boggio, P. S., Valle, A. C. (2007). Site-specific Effects of Transcranial Direct Curren t Stimulation on Sleep and Pain in Fibromyalgia: A Randomized, Sham-controlled Study. *Pain Practice, 7*(4), 297–306. doi: 10.1111/j.1533-2500.2007.00152.x

Sanz J, Vázquez C (1998) Fiabilidad, validez y datos normativos del Inventario para la Depresión de Beck. Psicothema 2:303-318

Stagg CJ, Nitsche MA (2011) Physiological basis of transcranial direct current stimulation. Neuroscientist 17:37–53.

Stagg CJ, O'Shea J, Kincses ZT, Woolrich M, Matthews PM, Johansen-BergH (2009) Modulation of movement-associated cortical activation by transcranial direct current stimulation. Eur J Neurosci 30:1412–1423.

Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, Tracey I. (2013) Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci. 2013 Jul 10;33(28):11425-31.

Tang MF, Hammond GR. (2013) Anodal transcranial direct current stimulation over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding. Eur J Neurosci. 38(5):2802-11.

Valmunen T1, Pertovaara A, Taiminen T, Virtanen A, Parkkola R, Jääskeläinen SK. (2009) Modulation of facial sensitivity by navigated rTMS in healthy subjects. Pain 142(1-2):149-58.

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

Villamar, M. F., Wivatvongvana, P., Patumanond, J., Bikson, M., Truong, D. Q., Datta, A., Fregni, F. (2013). Focal Modulation of the Primary Motor Cortex in Fibromyalgia Using 4x1-Ring High-Definition Transcranial Direct Current Stimulation (HD-tDCS): Immediate and Delayed Analgesic Effects of Cathodal and Anodal Stimulation. *The Journal of Pain 14*(4), 371-383. doi:10.1016/j.jpain.2012.12.007.

Wang, Z. (2012). Improving cerebral blood flow quantification for arterial spin labeled perfusion MRI by removing residual motion artifacts and global signal fluctuations, Magnetic Resonance Imaging, 30, 1409-15.

Ware JE (2000) SF-36 health survey update. Spine 25:3130–3139

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. (1990) The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 33:160-72.

Wolfe F, Clauw D, Fitzcharles MA, Goldenberg D, Katz RS, Mease P, et al. (2010) The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. Arthritis Care Res. 62:600-10.

Woolf CJ (2011). Central sensitization: Implications for the diagnosis and treatment of pain. Pain 152:S2-15

Zheng X, Alsop DC, Schlaug G (2011) Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. Neuroimage 58:26 –33.