# Title page

**Efficacy of transcranial direct current stimulation in women with provoked vestibulodynia**

Annie MORIN, MSc[1]

Guillaume LEONARD, pht, PhD [1]

Véronique GOUGEON, MSc[1]

Marie-Pierre CYR, Mpht[1]

Guy WADDELL, MD[2]

Yves-André BUREAU, MD[2]

Isabelle GIRARD, MD[2]

Mélanie MORIN, pht, PhD[1]*

* Corresponding author

[1] School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke, 3001 12th Avenue North, Sherbrooke, Québec, Canada

[2] Department of Obstetrics Gynecology, Faculty of Medicine and Health Sciences, Université de Sherbrooke, 3001 12th Avenue North, Sherbrooke, Québec, Canada

**Conflict of interest statement**
The authors report no conflict of interest.

**Trial registration**
Clinicaltrials.gov, NCT02543593; clinicaltrials.gov/ct2/show/NCT02543593; registration date: September 4, 2015.

**Short title:** Brain stimulation in women with vestibulodynia.

**Condensation:** Transcranial brain stimulation does not reduce pain intensity during intercourse in women with provoked vestibulodynia compared to sham stimulation.

**Word count:** Abstract: 474 words; Main text: 2998 words.

## Abstract

### Background

Provoked vestibulodynia (PVD) is a highly prevalent condition characterized by acute recurrent pain located at the vaginal entrance in response to pressure application or attempt of vaginal penetration. Despite a wide variety of treatments offered to women with PVD, a high proportion of women are refractory to conventional treatment. Transcranial direct-current stimulation (tDCS) is a non-invasive brain stimulation technique that has been shown effective for improving various chronic pain conditions. Growing evidence suggests that the central nervous system (CNS) could play a key role in PVD. Targeting the CNS could be a promising treatment avenue for women suffering from PVD.

### Objective

The purpose of this study was to evaluate and compare the efficacy of active and sham tDCS in reducing pain intensity during intercourse in women with PVD.

### Study design

We conducted a triple-blind, parallel group, randomized controlled trial (RCT). Women, aged between 17-45 years and diagnosed with PVD by a gynecologist using a validated protocol were randomized to 10 sessions of either active tDCS (intensity = 2mA) or 10 sessions of sham tDCS, over a 2-week period. Both active and sham tDCS were applied for 20 minutes, with the anode positioned over the primary motor cortex (M1), and the cathode, over the contralateral supraorbital area. Outcome measures were collected at baseline, 2 weeks after treatment and at 3-month follow-up by an evaluator blinded to group assignation. The primary objective was pain intensity during intercourse, as assessed with a numerical rating scale. Secondary outcomes focused on sexual function and distress, vestibular sensitivity, psychological distress, treatment

satisfaction and patient impression of change. Statistical analyses were conducted on the intention-to-treat basis, and treatment effects were evaluated using a mixed linear model for repeated measures.

**Results**

A total of 40 women were randomly assigned to received either active (n=20) or sham (n=20) tDCS treatments between November 2014 and February 2016. Baseline characteristics were similar between active and sham tDCS groups. Active tDCS did not significantly reduced pain during sexual intercourse compared to sham tDCS 2 weeks after treatment (p=0.84) and at follow-up (p=0.09). Mean [95% CI] baseline and 2-week assessment pain intensity were respectively 6.8 [5.9 - 7.7] and 5.6 [4.7 - 6.5] for active tDCS (p=0.03) versus 7.5 [6.6 - 8.4] and 5.7 [4.8 - 6.6] for sham tDCS (p=0.001). Non-significant differences between the two groups were also found in regards to sexual function and distress after treatment (p>0.20) and at follow-up (p>0.10). Overall, at 2-week assessment 68% women assigned to active tDCS reported being very much, much or slightly improved compared to 65% of women assigned to sham tDCS (p=0.82), and still comparable at follow-up 42% versus 65%, respectively (p=0.15).

**Conclusion**

Findings suggest that active tDCS is not more effective than sham tDCS for reducing pain in women with PVD. Likewise, no significant effects were found on sexual function, vestibular sensitivity or psychological distress.

**Trial registration**

Clinicaltrials.gov NCT02543593; registration date: September 4, 2015.

## Key words

Chronic pain, Dyspareunia, Pain thresholds, Provoked vestibulodynia, Psychological distress, Randomized controlled trial, Sexual dysfunction, Transcranial direct-current stimulation.

## Introduction

Chronic pain associated to female reproductive system is a neglected health problem.[1] By age 40, nearly 10% of women will develop vulvar pain symptoms.[2] Provoked vestibulodynia (PVD), the most frequent cause of pre-menopausal dyspareunia,[3] is characterized by a recurrent sharp pain at vulvar entrance (vestibule) in response to pressure or vaginal penetration attempt. The current medical approach for PVD relies on empirical treatment options, including localized (i.e. topical lidocaine , physical therapy), systemic (i.e. tricyclic antidepressants, anticonvulsants), psychotherapeutic (i.e. cognitive behavioral therapy, sex therapy), and ultimately, surgical (vestibulectomy) interventions.[4]

Women with PVD not only exhibit increased vulvar sensibility, but also have lower pain threshold and tolerance to other body regions, not restricted to the vestibule area.[5-7] Because PVD pathophysiology has been suggested to not be limited to the vulvar vestibule, central pain processing alterations similar to other chronic pain syndrome, like fibromyalgia,[8,9] irritable bowel syndrome,[10] and idiopathic back pain[11] might be involved.

More recently, neuromodulation treatment options namely transcranial direct-current stimulation (tDCS) has been proposed as another favorable therapeutic step for women with vulvodynia.[12] However, the evidence supporting the use of tDCS in this population is lacking. Treatments targeting the nervous system could be a promising therapeutic approach to reduce pain during

intercourse for women with PVD given the central nervous system (CNS) alterations postulated in this population.[5-7]

To our knowledge, the effect of tDCS for reducing pain in women with vulvodynia has only been documented in one case study,[13] which described remarkable long-lasting pain relief using tDCS in a woman suffering from severe chronic vulvar pain refractory to many empirical treatments. Based on Cecilio et al's observations,[13] it could be hypothesized that active tDCS treatment compared to sham would significantly reduce pain during intercourse in women with PDV (2-week post-treatment and 3-month follow-up compared to baseline assessment).

The main purpose of this study was to evaluate and compare the efficacy of active and sham tDCS in reducing pain intensity during intercourse in women with PVD. We also compared the effects of both interventions for sexual function, vestibular sensitivity, psychological distress, treatment satisfaction and patient's global impression of change.

## Materials and Methods

### *Study design*

A triple-blind (assessor, patient, and treatment provider) randomized placebo-controlled trial was conducted. Eligible women were randomly assigned to receive either active or sham tDCS. Outcome assessments were conducted at baseline, 2 weeks after treatment and 3 months after treatment. The study protocol received ethical approval from the *Comité d'éthique de la recherche en santé chez l'humain du CHUS*, Sherbrooke, Québec. Each participant provided written informed consent before participating in the study. The study protocol was registered at clinicaltrials.gov (NCT02543593) and published in the journal Trials.[14]

***Participants***

Premenopausal women aged between 17-40 years old suffering from pain during sexual intercourse were recruited at the Research Center of the *Centre hospitalier universitaire de Sherbrooke* between November 2014 and February 2016. Participants' eligibility was first authenticated during a telephone interview with the research coordinator. Thereafter, to further assess eligibility and confirm PVD diagnosis, a gynecological assessment was performed by a gynecologist of the research team (GW, YB or IG) following a standardized protocol.[15,16] Women were found eligible if they experienced, in the last 6 months, moderate to severe pain (>5/10) in at least 90% of attempted sexual intercourse. Women with other urogynecological conditions (e.g. urinary tract or vaginal infection) or pelvic pathology associated with pelvic pain (e.g. deep dyspareunia), having additional health issues or contraindications to tDCS (i.e. family history of epilepsy) were excluded from participating in the study.

***Intervention***

Participants were randomized to receive 10 sessions of either active/anode or sham/placebo tDCS over a period of fourteen days. tDCS treatments were given once a day, during weekdays (Monday to Friday). Each session lasted 20 minutes[17-21] and was administered by a research professional experienced in tDCS. The treatment provider was not involved in patient assessment and was blinded to the treatment allocation by selecting a preset program of the tDCS device (NeuroConn DC stimulator, Model 0008, Ilmenau, Germany). Two electrodes were applied to the subject's scalp; the anode was placed over the motor cortex (M1)[22] and the cathode over the contralateral supraorbital area.[17-19,21,22] Saline solution (77mM NaCl) was used to soak the synthetic sponge electrode covers (35cm$^2$). For the active tDCS condition, the intensity of the

stimulation was set at 2 mA for the entire duration of treatment.[13,17,23] These parameters have been used with many subjects in several laboratories without side effects (see[24] for review) apart from a slight sensation and erythema under the electrodes and possible headache in the hours following the treatment. For the sham tDCS condition, the electrodes were positioned in the same areas as for the active group. The intensity was set at 2 mA for the first 30 seconds of treatment,[21] after which the stimulation stopped automatically. Just as for the experimental group (active tDCS), participants in the control group (sham tDCS) were advised that a brief tingling sensation may be felt at the beginning of the treatment. This method was effective for preserving subject and investigator blinding in previous studies.[25,26]

***Data collection***

Outcome assessment

As recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT),[27,28] multiple dimensions of pain have been targeted in order to adequately evaluate the effectiveness of tDCS in reducing pain during intercourse in women with PVD. Baseline characteristics were collected during a structured interview at pretreatment assessment. Assessments were collected at baseline, 2-weeks and follow-up, except for patient's treatment satisfaction and impression of change (collected after the end of treatments only). Participants received CAD$20 after each assessment visit for a possible total of CAD$60.

Pain during intercourse

Participants were asked to evaluate their mean pain intensity during intercourse since the last assessment on a 0-10 verbal numeric rating scale ($NRS_{0-10}$), 0 being no pain, and 10 the worst pain ever experienced.

Questionnaires

Standardized and validated questionnaires included pain quality (McGill-Melzack Pain Questionnaire),[29,30] sexual functioning (Female Sexual Function Index),[31] sexual distress (Female Sexual Distress Scale),[32] sexual satisfaction (Global Measure of Sexual Satisfaction),[33] and patient's treatment satisfaction and impression of change (Patient's Global Impression of Change questionnaire)[34,35] were also completed. Psychological distress included questionnaires focusing on vaginal penetration (Vaginal Penetration Cognition Questionnaire),[36] catastrophizing (Pain Catastrophizing Scale),[37] anxiety (State-Trait Anxiety Inventory of Spielberger and Pain Anxiety Symptoms Scale),[38,39] and depression (Beck Depression Inventory)[40].

Vestibular sensitivity

The third International Consultation on Sexual Medicine underlined the importance of assessing vestibular sensitivity.[41] Our laboratory recently developed an algometer to measure vulvar pain threshold and tolerance in women with PVD. A gradual pressure (0 to 1000 grams) was applied to three distinct points of the vestibule at the 3, 6 and 9 o'clock positions.[42] Each pressure point was applied randomly (e.g. 3,6,9 or 3,9,6 or 6,9,3.). During this procedure, each participant was asked to indicate when they started to feel pain (pressure pain threshold; PPT) and, subsequently, the maximal pressure they could tolerate (pressure pain tolerance; PPTol).[43] Both PPT and PPTol were identified using a Computerized Visual analog scale (COVAS) throughout the test. PPT

was determined when the participant started to move the COVAS from 0 (no pain), and PPTol was established when the participant reached 10 (most intense pain tolerable). This assessment has shown good reliability and validity.[42]

Adverse events

To report participants' adverse events during tDCS treatment, at each treatment session, the treatment provider noted participants' side effects; subjects were also asked to report any adverse events experienced during or after each tDCS session in a 2-week diary.

***Sample size calculation***

A sample size of 34 participants was judged sufficient to detect a clinical minimal significant difference of 2[27,44] on the NRS ($\alpha$=0.05; $\beta$=0.80, standard deviation of 2.0, based on the data from previous tDCS reports[21,45]). This estimation of treatment effect was conservative considering that tDCS demonstrated an overall effect on pain reduction of 4.3 points[46] in various chronic pains and that the available case study in a woman with vulvodynia showed a reduction of 10 points.[13] To account for potential dropouts, a total of 40 subjects were recruited. This estimated dropout rate (<15%) was based on available studies and our own RCT experience in women with PVD.[47-49]

***Randomization and blinding***

After the baseline assessment, the participants were randomized into either the active or sham tDCS treatment (ratio 1:1) using random permuted block sizes of two and four. The allocation was managed by an independent individual of our research team following a computer-generated

randomization list drawn up by an independent statistician. Participants, investigators, physiotherapist assessors and treatment provider remained blinded to group allocation and therefore, could not influence the process in any way.

### *Statistical Analysis*

Baseline sample characteristics are presented using descriptive statistics. Analyses were done in intention-to-treat. The effects of treatment on pain, sexual function and psychological distress were examined using a mixed linear model for repeated measures. One of the factors was the GROUP (treatment group: active tDCS and control group: sham tDCS), while the repeated factor was TIME (baseline, 2-week post-treatment, and 3-month follow-up assessments). Treatment efficacy was judged on the basis of a significant GROUP*TIME interaction.[50] For some data-sets, logarithmic transformation was required to correct the distribution to normal (Pain quality, Vaginal control cognition, Anxiety-State, Depression, and Algometer). After analysis, results were converted back to their original scale. The difference between the two groups regarding satisfaction and PGIC was also assessed using mixed linear model for repeated measures. All statistical analyses were conducted at a significance level of 0.05 using Bonferroni adjustment for time factor. Analyses were conducted with SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill, USA).

## Results

### *Participants*

A total of 202 patients were screened for study eligibility from November 2014 through February 2016. Of these, 111 women were excluded due to ineligibility, and 42 refused to participate prior

to gynecological assessment. Another 6 women were excluded at gynecologist assessment due to deep dyspareunia diagnosis (n=3), and negative Q-tips test (n=3). After receiving their PVD diagnosis, three additional women refrained to take part in the study. As a result, 40 participants were consented, scheduled for baseline assessment, randomly assigned to receive active tDCS (n=20) or sham tDCS (n=20), and reschedule for 2-week and follow-up assessments. One participants' data could not be considered in the analyses because she did not attempt any vaginal penetration after receiving treatments. All participants were fully compliant to study treatment and assessments as planned in the study protocol. None of the active or sham group received other therapeutic interventions during the study. Figure 1 shows the trial flow diagram.

Baseline characteristics are presented in Table 1. Participants' characteristics were well matched for both treatment groups in regard to age, education, civil status, pain intensity and frequency, age at first intercourse attempt, number of sexual partners, relationship and pain duration, PVD subtype, and use of oral contraceptive.

***Primary outcome***

Mean pain intensity scores during intercourse for each assessment are illustrated in Figure 2. Women assigned to both interventions reported a significant pain intensity reduction from baseline to post-treatment assessment (reduction of 1.2 points in active, 95% CI 0.4-2.1; p=.03 and 1.8, 95% CI 0.8-2.8 in sham tDCS; p=.001). In addition, women assigned to sham treatment reported a significant pain intensity reduction from baseline to follow-up assessment (reduction of 2.5 points, 95% CI 1.4-3.7; p<.001). However, there was no statistical significant difference between treatment groups at each assessment (p=.84 and .09), respectively.

***Secondary outcomes***

Non-significant differences were found at baseline between the two groups in the secondary outcomes except for state-anxiety which was higher in the active tDCS group than in the placebo group. A significant reduction of sexual distress, catastrophizing, pain anxiety and improvement in sexual function were observed in both treatments from baseline to follow-up assessments. Again, there was no statistical difference between women assigned to active and sham tDCS (p-values>.08). Even though there was a significant difference between groups at post-treatment in catastrophizing (p=.02), pain anxiety (p=.03), and at follow-up in pain quality (p=.004), active tDCS did not result in a significant advantage in any measured outcome at any time point, compared to sham tDCS. Questionnaire scores are presented in Table 2. Interestingly, patient treatment satisfaction and impression of change were similar between groups (p-values>.14).

As shown in Table 3, compared to sham, active tDCS did not significantly improve vestibular sensitivity (PPT and PPTol) at any assessments (p-values>.07), although pressure pain tolerance measured at the 6 o'clock position at follow-up assessment who was higher in sham group (p=.02).

***Blinding integrity***

Treatment blinding was effective for participants but not for the tDCS operator (see Table 4). Forty-two percent of women in active, and 45% of women in sham treatment group correctly identified which treatment they received (p=.5).[26,45] However, tDCS operator correctly identified active treatment in 84%, and sham treatment in 60% of the cases (p=.008).

***Adverse effects***

Mild and transitory side-effects, commonly found in the literature about tDCS intervention,[24] were reported by participants in both groups (see Table 5). During treatment sessions, participant assigned to sham treatment reported more tingling sensation under the cathode (p=.02), while burning sensation under the cathode and erythema[24] under the anode were observed more often by participants assigned to active treatment (both p=.04). In opposition, there was no difference between groups regarding reported adverse events between treatment sessions, such as fatigue (p=.30), headache (p=.60),[24] dizziness (p=.50) or nausea (p=.20).

## Comment

To our knowledge, this is the first RCT evaluating tDCS efficacy for reducing pain in women with PVD. Our results show that active tDCS does not significantly reduce pain during intercourse nor improve sexual function or distress, vestibular sensitivity or psychological distress, compared to sham/placebo.

Although tDCS has been shown effective to reduce pain in multiple chronic pain conditions,[18,19,23,53-55] its efficacy to reduce pain during intercourse in women with PVD was not found substantiated. While women assigned to sham treatment reported a clinically significant pain intensity reduction from baseline to follow-up assessment (reduction of 2.5 points), this was not observed in the active group. Notably, the pain intensity reduction did not significantly or clinically differ between groups. The absence of group difference is not a sample size issue, as we had adequate statistical power to detect clinically relevant differences; hence type II error is not a valid explanation for our findings.

Our results coincide with a recently updated Cochrane review now showing non-significant difference between active and sham tDCS in chronic pain reduction.[56] Our trial also challenges the observation of tDCS efficacy in reducing vulvar pain as published by Cecilio et al.[13] However, it must be highlighted that the woman described in Cecilio et al.'s case study was suffering from generalized unprovoked vulvodynia. Because these are two different subtypes of vulvodynia, it is possible that tDCS might be effective in one condition but not in the other. Previous authors clearly showed the analgesic effect of tDCS in fibromyalgia,[23] spinal cord injury,[18,21] and post-stroke pain[53,57] using RCTs. It is possible that tDCS has greater effect for unprovoked types of pain, as observed by Cecilio et al.,[13] than for provoked pain conditions like PVD.

Mechanisms underlying placebo analgesia are only partly understood. It has been shown that expectation of relief contributes to placebo responses.[63] Another possible explanation is the support provided throughout the study. PVD is indeed a meaningful threat that interferes with many aspects of women's lives (i.e. sexual satisfaction, sexual self-esteem, psychological and sexual distress).[64] Given that PVD is often misdiagnosed or even ignored, women participating in our study have had prompt access to a gynecologist, which should normally take at least a year in Quebec's health care system. Meeting the same physiotherapist at each assessment and the same treatment provider on a daily basis over a two-week period, both female specialized in vulvar pain, allowed the participants to discuss of their sexual problematic with confidence. This may partially explain the changes observed in both interventions for sexual functioning, sexual distress, catastrophizing, and pain anxiety. Behavioral approaches such as systematic

desensitization and attentive listening were respectively found effective for pain management in vaginismus[65] and elderly.[66]

A substantial portion of women with PVD is reported to present pain hypersensitivity at both vulvar[5-7] and extra-genital regions (i.e. forearm, arm, fingers, thigh, shin),[6,7] suggesting that not only peripheral sensitization but also generalized central abnormalities are involved in PVD.[67] As proposed by Zhang et al.,[68] similar chronic pain alterations exist in several patients with vulvodynia. However, in their publication, the authors did not distinguish women with provoked pain from those with unprovoked pain. To determine whether PVD-subgroups can benefit more than others from tDCS, the relationship between the hypoalgesic effect noted after tDCS treatments and other variables such as emotional component of pain and central processing alteration should be investigated.

The strength of our study relies on its rigorous methodology. We minimised potential bias by including a recommended credible sham treatment, randomizing treatment allocation, and blinding the participants, treatment provider, outcome assessor, and statistician. In addition, to avoid information bias, we followed several authors' suggestions[74,75] stating that the treatment assessor blinding is compromised at 2 mA intensity. Therefore, in our study, the treatment provider was not involved in any outcome assessments. Despite all these efforts made to minimise bias our trial still have some limitations. Women's menstrual cycle was not controlled during the study, even though it is known that pain perception changes across menstrual cycle.[76] However, this variability in subject's pain evaluation and perception should be balanced between groups due to randomized treatment allocation. Another limitation might be attributable to

inconsistency in pain evaluation and information bias, especially when the participant had to recall relatively distant experiences. To counterbalance this potential memory bias, subjects were asked to complete a 4-week logbook (during the treatment period and two weeks after) in which they had to report if they experienced any pain in the vulvar region, whether related to intercourse.

## Conclusion

Active tDCS did not confer benefits over sham tDCS in pain or function in women with PVD. Although it remains possible that a subpopulation of women with PVD could benefit from tDCS, our findings do not support the use of tDCS for these patients.

## Abbreviations

BDI, Beck Depression Inventory; CNS, central nervous system; COVAS, computerized visual analog scale; CHUS, Centre hospitalier universitaire de Sherbrooke; FSDS, Female sexual distress scale; FSFI, Female sexual function index; GMSS, Global measure of sexual satisfaction; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; M1, motor cortex; mA, milliamperes; MPQ, McGill Pain Questionnaire; NRS, numeric rating scale; PASS, Pain anxiety symptoms scale; PCS, Pain catastrophizing scale; PGIC, Patient's global impression of change; PPT, Pressure pain thresholds; PPTol, Pressure pain tolerance; PVD, Provoked vestibulodynia; RCT, Randomized controlled trial; STAI, State-Trait anxiety inventory of Spielberger; tDCS, transcranial direct-current stimulation; VPCQ, Vaginal penetration cognition questionnaire.

## Competing interest

The authors have no conflicts of interest to declare.

## Authors' contributions

AM, GL and MM conceived the study and helped draft the manuscript. VG, MPC, GW, YAB and IG provided assistance in study design and implementation. All authors read and approved the final manuscript.

## Acknowledgments

This research is funded by an operating grant from the Research Center of the CHUS. Drs. Morin and Léonard are supported by a Junior 1 research scholar of the Fonds de la recherche du Québec – Santé (FRQ–S).

## Previous presentation

Some of the data have been previously published as an abstract (and presented as an oral presentation): A. Morin, G. Léonard, V. Gougeon, M.P. Cyr, G. Waddell, Y.A. Bureau, I. Girard, M. Morin. Randomized controlled trial comparing active transcranial direct-current stimulation and sham stimulation in reducing pain in women with provoked vestibulodynia. 23rd Biennial Conference on Diseases of the Vulva & Vagina, 9-10 September 2016, Chicago, Illinois, USA.

## References

1. Walling MK, Reither RCCppI. Psychological aspects of women's reproductive health Edited by Michael W. O'Hara, Robert C. Reiter, Susan R. Johnson, Alison Milburn, and Jane Engeldinger. New York: Springer Publishing Company, Inc., 1995. 298 pages. *Journal of nurse-midwifery.* 1997;42(2):124-125.

2. Harlow BL, Kunitz CG, Nguyen RHN, Rydell SA, Turner RM, Maclehose RF. Prevalence of symptoms consistent with a diagnosis of vulvodynia: Population-based estimates from 2 geographic regions. *American Journal of Obstetrics and Gynecology.* 2014;210(1):40.e41-40.e48.
3. Marinoff SC, Turner ML. Vulvar vestibulitis syndrome. *Dermatologic clinics.* 1992;10(2):435-444.
4. Stockdale CK, Lawson HW. 2013 Vulvodynia Guideline update. *Journal of lower genital tract disease.* 2014;18(2):93-100.
5. Sutton KS, Pukall CF, Chamberlain S. Pain ratings, sensory thresholds, and psychosocial functioning in women with provoked vestibulodynia. *Journal of sex & marital therapy.* 2009;35(4):262-281.
6. Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. *Obstetrics and gynecology.* 2004;104(1):126-133.
7. Granot M, Friedman M, Yarnitsky D, Zimmer EZ. Enhancement of the perception of systemic pain in women with vulvar vestibulitis. *BJOG : an international journal of obstetrics and gynaecology.* 2002;109(8):863-866.
8. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. *The Journal of rheumatology.* 2004;31(2):364-378.
9. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis and Rheumatism.* 2002;46(5):1333-1343.
10. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology.* 2000;118(5):842-848.
11. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis and Rheumatism.* 2004;50(2):613-623.
12. De Andres J, Sanchis-Lopez N, Asensio-Samper JM, et al. Vulvodynia-An Evidence-Based Literature Review and Proposed Treatment Algorithm. *Pain Pract.* 2016;16(2):204-236.
13. Cecilio SB, Zaghi S, Cecilio LB, Correa CF, Fregni F. Exploring a novel therapeutic approach with noninvasive cortical stimulation for vulvodynia. *American Journal of Obstetrics and Gynecology.* 2008;199(6):e6-7.
14. Morin A, Léonard G, Gougeon V, et al. Efficacy of transcranial direct-current stimulation (tDCS) in women with provoked vestibulodynia: study protocol for a randomized controlled trial. *Trials.* 2016;17(1):1-10.
15. Friedrich EG, Jr. Vulvar vestibulitis syndrome. *The Journal of reproductive medicine.* 1987;32(2):110-114.
16. Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI. Vulvar vestibulitis syndrome: reliability of diagnosis and evaluation of current diagnostic criteria. *Obstetrics and gynecology.* 2001;98(1):45-51.
17. Simis M, Reidler JS, Duarte Macea D, et al. Investigation of Central Nervous System Dysfunction in Chronic Pelvic Pain Using Magnetic Resonance Spectroscopy and Noninvasive Brain Stimulation. *Pain practice : the official journal of World Institute of Pain.* 2014.
18. Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain.* 2006;122(1-2):197-209.
19. Kim YJ, Ku J, Kim HJ, et al. Randomized, sham controlled trial of transcranial direct current stimulation for painful diabetic polyneuropathy. *Annals of rehabilitation medicine.* 2013;37(6):766-776.

20. Reidler JS, Mendonca ME, Santana MB, et al. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. *The journal of pain : official journal of the American Pain Society.* 2012;13(5):450-458.
21. Soler MD, Kumru H, Pelayo R, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain : a journal of neurology.* 2010;133(9):2565-2577.
22. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology.* 2001;57(10):1899-1901.
23. Fregni F, Gimenes R, Valle AC, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis and Rheumatism.* 2006;54(12):3988-3998.
24. Fregni F, Nitsche MA, Loo CK, et al. Regulatory Considerations for the Clinical and Research Use of Transcranial Direct Current Stimulation (tDCS): review and recommendations from an expert panel. *Clin Res Regul Aff.* 2014;32(1):22-35.
25. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2006;117(4):845-850.
26. Russo R, Wallace D, Fitzgerald PB, Cooper NR. Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. *Brain stimulation.* 2013;6(6):946.
27. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113(1-2):9-19.
28. Katz J, Melzack R. Measurement of pain. *The Surgical clinics of North America.* 1999;79(2):231-252.
29. Dworkin RH, Corbin AE, Young JP, Jr., et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003;60(8):1274-1283.
30. Fitzcharles MA, Ste-Marie PA, Panopalis P, Menard H, Shir Y, Wolfe F. The 2010 American college of rheumatology fibromyalgia survey diagnostic criteria and symptom severity scale is a valid and reliable tool in a French speaking fibromyalgia cohort. *BMC musculoskeletal disorders.* 2012;13:179.
31. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *Journal of sex & marital therapy.* 2000;26(2):191-208.
32. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *Journal of sex & marital therapy.* 2002;28(4):317-330.
33. Lawrance K, Byers ES. Sexual satisfaction in long-term heterosexual relationship: The Interpersonal exchange model of sexual satisfaction. *Personal Relationships.* 1995;2:267-285.
34. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *Journal of manipulative and physiological therapeutics.* 2004;27(1):26-35.
35. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94(2):149-158.
36. Klaassen M, Ter Kuile MM. Development and initial validation of the vaginal penetration cognition questionnaire (VPCQ) in a sample of women with vaginismus and dyspareunia. *The journal of sexual medicine.* 2009;6(6):1617-1627.
37. Goldfinger C, Pukall CF, Gentilcore-Saulnier E, McLean L, Chamberlain S. A prospective study of pelvic floor physical therapy: pain and psychosexual outcomes in provoked vestibulodynia. *The journal of sexual medicine.* 2009;6(7):1955-1968.

38. Gauthier J, Bouchard S. Adaptation canadienne-française de la forme révisée du State–Trait Anxiety Inventory de Spielberger. [A French-Canadian adaptation of the revised version of Spielberger's State–Trait Anxiety Inventory.]. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement.* 1993;25(4):559-578.
39. McCracken LM, Dhingra L. A short version of the Pain Anxiety Symptoms Scale (PASS-20): preliminary development and validity. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur.* 2002;7(1):45-50.
40. Beck AT, Steer RA, Brown GK. *BDI-II, Beck depression inventory: manual.* San Antonio, Tex; Boston: Psychological Corp; 1996.
41. van Lankveld JJ, Granot M, Weijmar Schultz WC, et al. Women's sexual pain disorders. *The journal of sexual medicine.* 2010;7(1 Pt 2):615-631.
42. Cyr MP, Morin M, Pinard A, Dubois O, Bourbonnais D. Reliability and validity of a new instrument for vestibular pain assessment in women with provoked vestibulodynia. *J Sex Med.* 2014;11(suppl 4):213-237.
43. Cyr M-P, Bourbonnais D, Pinard A, Dubois O, Morin M. Reliability and Convergent Validity of the Algometer for Vestibular Pain Assessment in Women with Provoked Vestibulodynia *Pain Medicine.* 2015.
44. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain.* 2000;88(3):287-294.
45. Borckardt JJ, Romagnuolo J, Reeves ST, et al. Feasibility, safety, and effectiveness of transcranial direct current stimulation for decreasing post-ERCP pain: a randomized, sham-controlled, pilot study. *Gastrointestinal endoscopy.* 2011;73(6):1158-1164.
46. Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2014;125(9):1847-1858.
47. Bergeron S, Binik YM, Khalife S, et al. A randomized comparison of group cognitive--behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain.* 2001;91(3):297-306.
48. Foster DC, Kotok MB, Huang LS, et al. Oral desipramine and topical lidocaine for vulvodynia: a randomized controlled trial. *Obstetrics and gynecology.* 2010;116(3):583-593.
49. Morin M, Dumoulin C, Bergeron S, et al. Randomized clinical trial of multimodal physiotherapy treatment compared to overnight lidocaine ointment in women with provoked vestibulodynia: Design and methods. *Contemporary clinical trials.* 2016;46:52-59.
50. Neter J, Wasserman W, Kutner MH. *Applied linear statistical models.* Vol 3rd. Boston: Irwin; 1990.
51. Paquet M, Bois K, Rosen NO, Mayrand MH, Charbonneau-Lefebvre V, Bergeron S. Why Us? Perceived Injustice is Associated With More Sexual and Psychological Distress in Couples Coping With Genito-Pelvic Pain. *J Sex Med.* 2016;13(1):79-87.
52. Rosen NO, Muise A, Bergeron S, Impett EA, Boudreau GK. Approach and Avoidance Sexual Goals in Couples with Provoked Vestibulodynia: Associations with Sexual, Relational, and Psychological Well-Being. *The Journal of Sexual Medicine.* 2015;12(8):1781-1790.
53. Antal A, Terney D, Kuhnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. *Journal of pain and symptom management.* 2010;39(5):890-903.
54. Mori F, Codeca C, Kusayanagi H, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *The journal of pain : official journal of the American Pain Society.* 2010;11(5):436-442.

55. Valle A, Roizenblatt S, Botte S, et al. 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 management.* 2009;2(3):353-361.
56. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. *The Cochrane database of systematic reviews.* 2014;4:CD008208.
57. Bae SH, Kim GD, Kim KY. Analgesic effect of transcranial direct current stimulation on central post-stroke pain. *The Tohoku journal of experimental medicine.* 2014;234(3):189-195.
58. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *The Lancet Neurology.* 2007;6(2):188-191.
59. Antal A, Paulus W. [Transcranial magnetic and direct current stimulation in the therapy of pain]. *Schmerz (Berlin, Germany).* 2010;24(2):161-166.
60. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: State of the art 2008. *Brain stimulation.* 2008;1(3):206-223.
61. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology.* 2000;527 Pt 3:633-639.
62. Marchand S. *Le pénomène de la douleur.* Montréal: Éditions de la Chenelière; 2009.
63. !!! INVALID CITATION !!! 68-70.
64. Gates EA, Galask RP. Psychological and sexual functioning in women with vulvar vestibulitis. *Journal of psychosomatic obstetrics and gynaecology.* 2001;22(4):221-228.
65. Flanagan E, Herron KA, O'Driscoll C, Williams AC. Psychological treatment for vaginal pain: does etiology matter? A systematic review and meta-analysis. *J Sex Med.* 2015;12(1):3-16.
66. Takai Y, Uchida Y. Frequency and type of chronic pain care approaches used for elderly residents in Japan and the factors influencing these approaches. *Japan journal of nursing science : JJNS.* 2009;6(2):111-122.
67. Pukall CF, Strigo IA, Binik YM, Amsel R, Khalife S, Bushnell MC. Neural correlates of painful genital touch in women with vulvar vestibulitis syndrome. *Pain.* 2005;115(1-2):118-127.
68. Zheng Z, Zolnoun DA, Francisco EM, Holden JK, Dennis RG, Tommerdahl M. Altered central sensitization in subgroups of women with vulvodynia. *The Clinical journal of pain.* 2011;27(9):755-763.
69. Charron J, Rainville P, Marchand S. Direct comparison of placebo effects on clinical and experimental pain. *The Clinical journal of pain.* 2006;22(2):204-211.
70. Marchand S, Gaumond I. Placebo and nocebo in the treatment of pain: Their presence is inevitable but their actions can be manipulated. *Douleur et Analgésie.* 2014;27(4):198-202.
71. Beaulieu P, Lussier D, Porreca F, Dickenson A. Pharmacology of Pain. Seattle : IASP Press2010:451-473.
72. Leonard G, Lafrenaye S, Goffaux P. Randomized placebo-controlled cross-over designs in clinical trials: a gold standard to be reassessed. *Current medical research and opinion.* 2012;28(2):245-248.
73. Sanga P, Polverejan E, Wang S, Kelly KM, Thipphawong J. Efficacy, Safety, and Tolerability of Fulranumab as an Adjunctive Therapy in Patients With Inadequately Controlled, Moderate-to-Severe Chronic Low Back Pain: A Randomized, Double-blind, Placebo-controlled, Dose-Ranging, Dose-Loading Phase II Study. *Clinical therapeutics.* 2016.
74. O'Connell NE, Cossar J, Marston L, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2mA. *PloS one.* 2012;7(10):e47514.
75. Palm U, Reisinger E, Keeser D, et al. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain stimulation.* 2013;6(4):690-695.

76. Riley JL, 3rd, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. *Pain.* 1999;81(3):225-235.

## Tables

### Table 1 – Baseline characteristics by treatment group

| Variable | Active tDCS (n=20) | Sham tDCS (n=20) |
|---|---|---|
| Age at randomization, y[a] | 22 (20 – 24) | 22 (20 – 24) |
| Education, n (%) | | |
| Elementary | 1 (5) | 0 |
| High school | 4 (20) | 5 (25) |
| Professional study diploma | 1 (5) | 1 (5) |
| College | 12 (60) | 9 (45) |
| Baccalaureate | 2 (10) | 5 (25) |
| Civil status, n (%) | | |
| Relationship | 11 (55) | 11 (55) |
| Civil union | 8 (40) | 8 (40) |
| Married | 1 (5) | 1 (5) |
| Pain intensity, $NRS_{0-10}$[a] | 6.5 (6.0 – 7.9) | 7.0 (7.0 – 8.8) |
| Age at first intercourse attempt, y[a] | 16 (15 – 18) | 17 (15 – 18) |
| Sexual partners, n | 3 (1 – 5) | 3 (1 – 5) |
| Relationship duration, y[a] | 2.8 (1.7 – 4) | 2.3 (1.2 – 4.3) |
| Pain duration, y[a] | 3.0 (1.6 – 5.0) | 2.0 (1.6 – 4.0) |
| Intercourse frequency, wk[a] | 0.8 (0.3 – 2.9) | 1.0 (0.2 – 2.0) |
| Oral contraceptive, n (%) | 20 (100) | 19 (95) |
| PVD Subtype, n (%) | | |
| Primary | 5 (25) | 5 (25) |
| Secondary | 15 (75) | 15 (75) |

**Table 2 – Pain, sexual function, psychological distress, treatment satisfaction and patient global impression of change by treatment group**

| | Treatment group | | |
|---|---|---|---|
| | Active tDCS[a] | Sham tDCS[a] | Difference between groups |
| **Outcomes** | **n = 19** | **n = 20** | ***P* value**[b] |
| Pain quality[c] | | | |
| Baseline | 23.6 (17.8 - 31.4) | 22.8 (17.3 - 30.0) | .85 |
| 2-week assessment | 22.5 (17.0 - 29.9) | 17.3 (13.1 - 22.8) | .19 |
| Follow-up assessment | 22.3 (16.8 - 29.6) | 12.4 (9.4 - 16.3)*** | .004†† |
| Sexual functioning[d] | | | |
| Baseline | 20.4 (17.8 - 23.0) | 20.1 (17.6 - 22.6) | .87 |
| 2-week assessment | 23.9 (21.3 - 26.5)** | 22.2 (19.7 - 24.7) | .35 |
| Follow-up assessment | 23.4 (20.8 - 26.0)* | 23.9 (21.3 - 26.4)** | .79 |
| Sexual distress[e] | | | |
| Baseline | 30.1 (24.2 - 35.9) | 27.1 (21.4 - 32.8) | .47 |
| 2-week assessment | 23.4 (17.6 - 29.2)* | 18.8 (13.1 - 24.4)** | .26 |
| Follow-up assessment | 20.8 (15.0 - 26.6)** | 15.4 (9.7 - 21.0)*** | .19 |
| Sexual satisfaction[f] | | | |
| Baseline | 21.4 (18.3 - 24.5) | 21.7 (18.7 - 24.7) | .88 |
| 2-week assessment | 22.8 (19.7 - 25.9) | 24.2 (21.2 - 27.2) | .52 |
| Follow-up assessment | 23.2 (20.1 - 26.3) | 25.8 (22.7 - 28.8)* | .24 |
| Vaginal control cognition[g] | | | |
| Baseline | 3.6 (3.0 - 4.1) | 4.3 (3.8 - 4.6) | .07 |
| 2-week assessment | 4.1 (3.6 - 4.5) | 4.5 (4.1 - 4.8) | .17 |
| Follow-up assessment | 4.1 (3.6 - 4.5) | 4.5 (4.2 - 4.8) | .15 |
| Catastrophizing[h] | | | |
| Baseline | 29.3 (24.0 -34.5) | 23.6 (18.5 - 28.7) | .13 |
| 2-week assessment | 25.4 (20.2 - 30.6) | 16.4 (11.3 - 21.5)* | .02† |
| Follow-up assessment | 21.6 (16.4 - 26.8)** | 15.8 (10.7 - 20.8)** | .12 |
| Anxiety-Trait[i] | | | |
| Baseline | 43.1 (38.1 - 48.2) | 39.6 (34.6 - 44.5) | .32 |
| 2-week assessment | 39.4 (34.4 - 44.5) | 37.6 (32.6 - 42.5) | .60 |
| Follow-up assessment | 38.2 (33.1 - 43.2)* | 35.7 (30.7 - 40.6) | .48 |
| Anxiety-State[i] | | | |
| Baseline | 39.9 (35.4 - 44.9) | 33.2 (29.6 - 37.3) | .03† |
| 2-week assessment | 35.2 (31.3 - 39.7) | 32.8 (29.2 - 36.8) | .39 |
| Follow-up assessment | 34.0 (30.2 - 38.3)* | 30.0 (26.7 - 33.7) | .14 |
| Pain anxietyk[j] | | | |
| Baseline | 42.7 (34.4 - 51.0) | 33.9 (25.8 - 41.9) | .13 |
| 2-week assessment | 37.6 (29.3 - 45.9) | 24.4 (16.3 - 32.4)** | .03† |
| Follow-up assessment | 32.4 (24.1 - 40.7)*** | 22.0 (13.9 - 30.1)*** | .08 |
| Depression[k] | | | |
| Baseline | 7.1 (4.8 - 10.6) | 6.2 (4.2 - 9.1) | .62 |
| 2-week assessment | 5.3 (3.5 - 7.9) | 5.5 (3.7 - 8.1) | .92 |
| Follow-up assessment | 5.0 (3.4 - 7.5) | 4.1 (2.8 - 6.1)* | .48 |
| Impression of change[l], n (%) | | | |
| 2-week assessment | 13 (68) | 13 (65) | .82 |
| Follow-up assessment | 8 (42) | 13 (65) | .15 |
| Satisfaction[m], n (%) | | | |
| 2-week assessment | 11 (58) | 14 (70) | .42 |
| Follow-up assessment | 8 (42) | 14 (70) | .14 |

**Table 3 – Pressure pain thresholds/tolerance by treatment group**

| | Treatment group | | |
|---|---|---|---|
| | **Active tDCS**[a] | **Sham tDCS**[a] | **Difference between groups** |
| **Outcomes** | **n = 19** | **n = 20** | ***P* value**[b] |
| PPT, g[c] | | | |
| Position no3 | | | |
| Baseline | 112.6 (83.4 - 152.0) | 120.4 (89.9 - 161.3) | .75 |
| 2-week assessment | 118.5 (87.4 - 160.7) | 137.8 (102.4 - 185.4) | .48 |
| Follow-up assessment | 108.6 (80.1 - 147.4) | 149.5 (111.6 - 200.2) | .14 |
| Position no6 | | | |
| Baseline | 112.5 (84.3 - 150.) | 120.3 (90.5 - 159.9) | .74 |
| 2-week assessment | 116.2 (86.7 - 155.7) | 169.0 (127.1 - 224.7) | .07 |
| Follow-up assessment | 125.8 (93.9 - 168.6) | 166.5 (125.6 - 220.5) | .17 |
| Position no9 | | | |
| Baseline | 94.5 (69.4 - 128.9) | 111.4 (82.3 - 150.7) | .45 |
| 2-week assessment | 84.7 (61.4 - 116.7) | 128.5 (94.5 - 174.6) | .07 |
| Follow-up assessment | 96.5 (70.5 - 132.3) | 130.3 (96.3 - 176.3) | .18 |
| PPTol, g[c] | | | |
| Position no3 | | | |
| Baseline | 94.5 (69.4 - 128.9) | 111.4 (82.3 - 150.7) | .45 |
| 2-week assessment | 84.7 (61.4 - 116.7) | 128.5(94.5 - 174.6) | .07 |
| Follow-up assessment | 96.5 (70.5 - 132.3) | 130.3 (96.3 - 176.3) | .18 |
| Position no6 | | | |
| Baseline | 384.9 (291.5 - 508.5) | 550.0 (420.4 - 718.9) | .07 |
| 2-week assessment | 364.3 (275.7 - 481.0) | 488.8 (372.9 - 641.3) | .13 |
| Follow-up assessment | 332.0 (251.4 - 438.7) | 524.8 (400.3 - 688.4) | .02* |
| Position no9 | | | |
| Baseline | 327.7 (246.4 - 435.5) | 425.8 (322.5 - 562.0) | .19 |
| 2-week assessment | 344.8 (258.5 - 460.0) | 450.3 (340.1 - 596.4) | .19 |
| Follow-up assessment | 357.1 (267.7 - 476.5) | 433.1 (328.1 - 571.8) | .34 |

**Table 4 – Blinding effectiveness by treatment group**

| | | Treatment group | | |
|---|---|---|---|---|
| | | **Active tDCS**[a] | **Sham tDCS**[a] | |
| | | **n = 19** | **n = 20** | ***P* value**[b] |
| **Participants' believes** | **Active** | 8 (42) | 11 (55) | 0.5 |
| | **Sham** | 11 (58) | 9 (45) | |
| **Operator's believes** | **Active** | 16 (84) | 8 (40) | 0.008** |
| | **Sham** | 3 (16) | 12 (60) | |

**Table 5 – Adverse events by treatment group**

| | Treatment group | | |
|---|---|---|---|
| | **Active tDCS**[a] | **Sham tDCS**[a] | |
| **Adverse events** | **n = 19** | **n = 20** | ***P* value**[b] |
| Anodal tingling sensation | 15 (79) | 16 (80) | .6 |
| Cathodal tingling sensation | 9 (47) | 17 (85) | .02* |
| Cathodal pinching sensation | 0 | 1 (5) | .5 |
| Anodal burning sensation | 5 (26) | 2 (10) | .2 |
| Cathodal burning sensation | 12 (63) | 6 (30) | .04* |
| Anodal redness | 6 (32) | 2 (10) | .1 |
| Cathodal redness | 12 (63) | 6 (30) | .04* |
| Anodal heating sensation | 3 (16) | 2 (10) | .5 |
| Anodal itching sensation | 4 (21) | 0 | .05 |
| Fatigue | 5 (26) | 3 (15) | .3 |
| Headache | 12 (63) | 12 (60) | .6 |
| Scalp tenderness | 2 (11) | 0 | .2 |
| Dizziness | 1 (5) | 2 (10) | .5 |
| Nausea | 4 (21) | 1 (5) | .2 |
| Stomach aches | 2 (11) | 1 (5) | .5 |
| Eye flash | 0 | 1 (5) | .5 |
| Gastric reflux | 1 (5) | 1 (5) | .8 |
| Hot face | 1 (5) | 0 | .5 |

## Figures

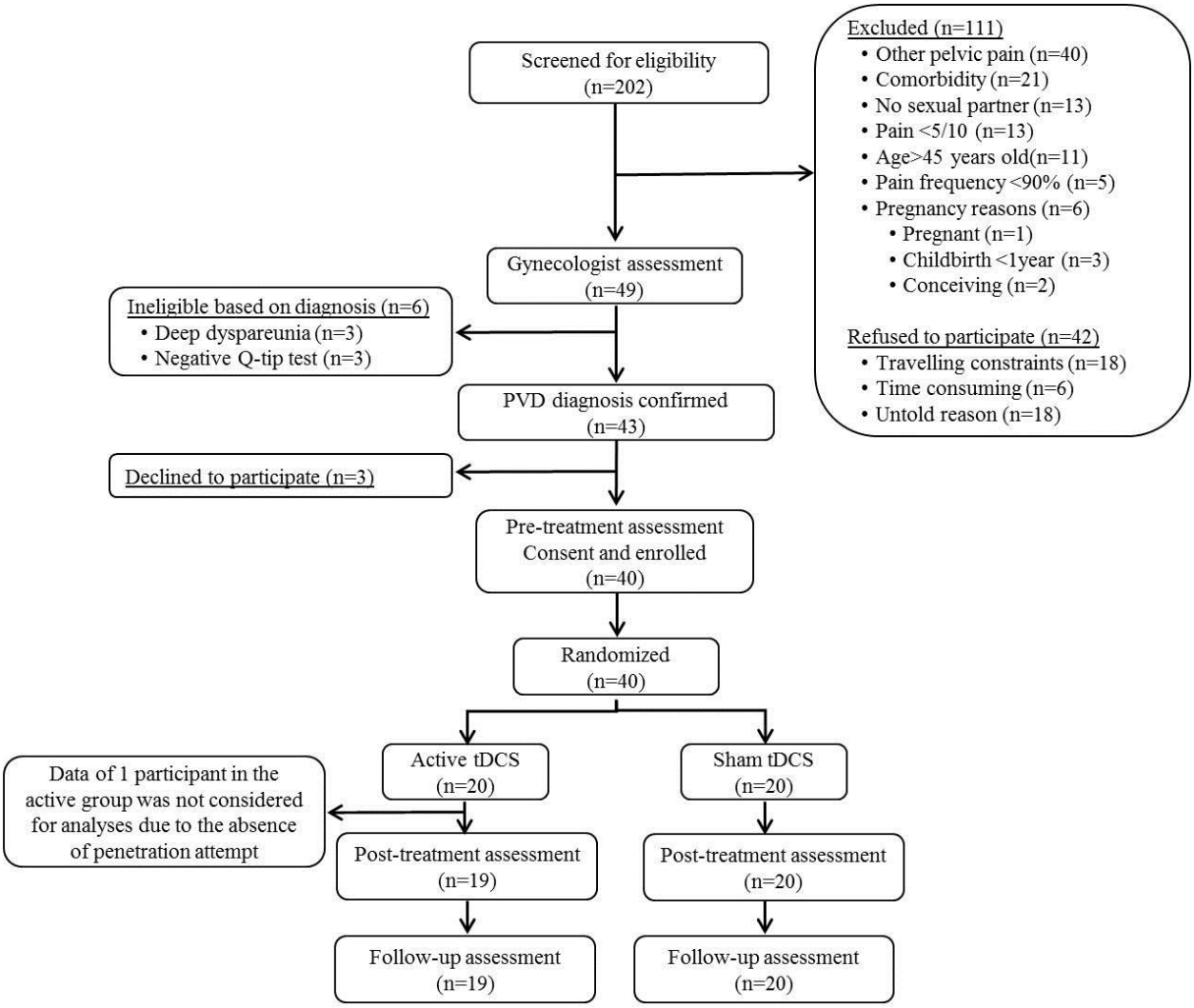


Figure 1 – Participants' selection and assessments

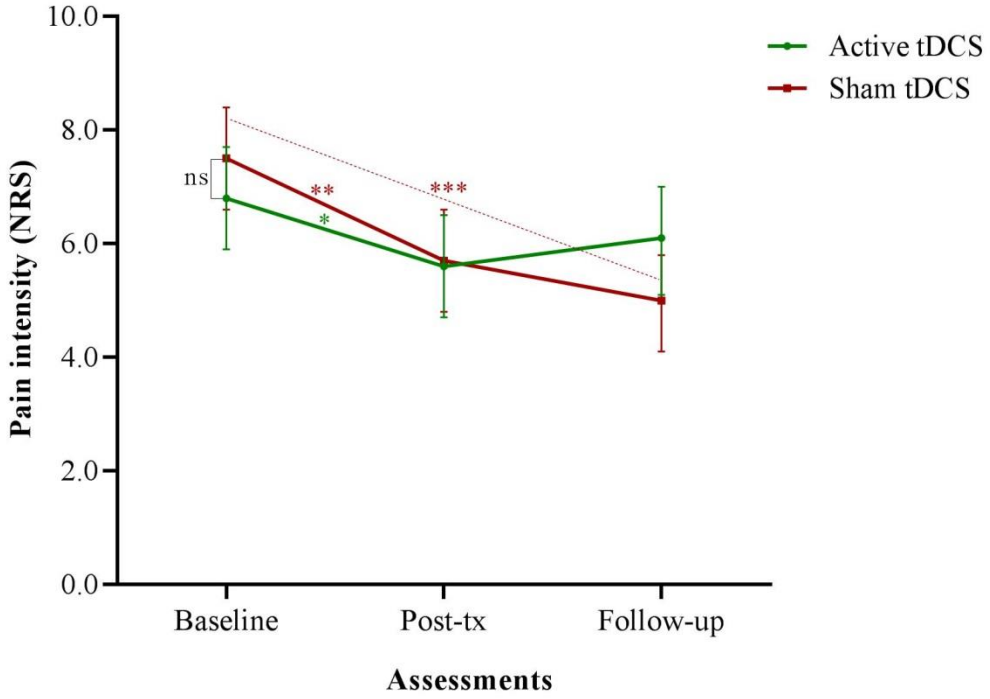


Figure 2 – Mean pain intensity during intercourse ($NRS_{0-10}$) at baseline, post-treatment and follow-up assessments

**Tables and figures legends**

Figure 1
There is no legend for Figure 1.

Figure 2
Asterisk indicates significant difference from baseline.
* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, and ns= non-significant difference; significant difference from baseline.

Table 1
[a]Results are reported as median (interquartile range) or frequency (percentage).

Table 2
[a]Results are reported as mean (95% confidence interval) or frequency (percentage); [b]Mixed linear model for repeated measures; [c]MPQ (range, 0-74); [d]FSFI (range, 19-110); [e]FSDS (range, 0-52); [f]GMSS (range, 19-110); [g]VPCQ (range, 0-6); [h]PCS (range, 0-52); [i]STAI of Spielberger (range, 20-80); [j](range, 0-100); [k]BDI (range, 0-63); [l]PGIC (range, 1-7) and [m]PGIC-Satisfaction (range, 0-10).

* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$; significant difference from baseline.
† $P \leq 0.05$, †† $P \leq 0.01$; significant difference between groups.

Table 3
PPT, Pressure pain thresholds; PPTol, Pressure pain tolerance.
[a]Results are reported as mean (95% confidence interval); [b]Mixed linear model for repeated measures; [c]PPT and PPTol measured by algometer (range, 0-1000).
* $P \leq 0.05$; significant difference between groups.

Table 4
[a]Results are reported as frequency (percentage); [b]Chi-squared test.
** $P \leq 0.01$; significant difference between groups.

Table 5
[a]Results are reported as frequency (percentage); [b]Chi-squared test.
* $P \leq 0.05$; significant difference between groups.