

# Is Transcranial Direct Current Stimulation an Effective Predictor for Invasive Occipital Nerve Stimulation Treatment Success in Fibromyalgia Patients?

Mark Plazier, MD\*<sup>1</sup>; Stephanie Tchen, BS<sup>†1</sup>; Jan Ost, BA<sup>‡</sup>; Kathleen Joos, MD, PhD\*<sup>‡</sup>; Dirk De Ridder, MD, PhD<sup>§5</sup>; Sven Vanneste, PhD<sup>†</sup>

**Background:** Fibromyalgia is a disorder distinguished by pervasive musculoskeletal pain that has pervasive effects on affected individuals magnifying the importance of finding a safe and viable treatment option.

**Objective:** The goal of this study is to investigate if transcranial direct current stimulation (tDCS) treatment can predict the outcome of occipital nerve field stimulation (ONFS) via a subcutaneous electrode.

**Methods:** Nine patients with fibromyalgia were selected fulfilling the American College of Rheumatology-90 criteria. The patients were implanted with a subcutaneous trial-lead in the C2 dermatome innervated by the occipital nerve. After the treatment phase of ONFS using a C2 implant, each patient participated in three sessions of tDCS. Stimulation outcomes for pain suppression were examined between the two methods to determine possible correlations.

**Results:** Positive correlation of stimulation effect was noted between the numeric rating scale changes for pain obtained by tDCS treatments and short-term measures of ONFS, but no correlation was noted between tDCS and long-term ONFS outcomes. A correlation also was noted between short-term ONFS C2 implant pain suppression and long-term ONFS C2 implant treatment success.

**Conclusions:** This pilot study suggests that tDCS is a predictive measure for success of ONFS in short-term but cannot be used as a predictive measure for success of long-term ONFS. Our data confirm previous findings that ONFS via an implanted electrode can improve fibromyalgia pain in a placebo-controlled way and exert a long-term pain suppression effect for ONFS via an implanted electrode.

**Keywords:** Fibromyalgia, greater occipital nerve stimulation, tDCS

**Conflict of Interest:** Mark Plazier and Dirk De Ridder are involved in paid educational tasks for St. Jude Medical Neuromodulation (Plano, TX, USA); none of the other authors have competing interests.

## INTRODUCTION

Fibromyalgia is a disorder distinguished by pervasive musculoskeletal pain. The disease affects every nine women to one man and has a prevalence of 2.9–4.0%. On average, fibromyalgia is acquired between the ages of 20 and 55 years (1–3). According to the American College of Rheumatology, diagnostic criteria include a history of extensive pain in all four quadrants of the body and pain present for at least three months (4). Other common symptoms include fatigue, psychological issues (anxiety, depression), sleep disorders, cognitive impairments, and headaches (5–7). Most of the fibromyalgia-related symptoms can be described as hypersensitivity symptoms: somatosensory hypersensitivity (headaches, jaw tightness, morning stiffness, paresthesia), hypersensitivity to other senses (sound, odor, chemical), hypersensitivity in the autonomic nervous system (irritable bowel, urinary urgency, dryness of mouth and eyes, cold swollen hands), and emotional hypersensitivity (anxiety, depression). Due to its painful and agitating symptoms, fibromyalgia has a significant socioeconomic impact on the affected individuals.

Address correspondence to: Sven Vanneste, PhD, Lab for Clinical & Integrative Neuroscience, School of Behavioral and Brain Sciences, The University of Texas at Dallas, W 1966 Inwood Road, Dallas, TX 75235, USA. Email: sven.vanneste@utdallas.edu

\* Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium;

† School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, TX, USA;

‡ Brai2n. St-Augustinus Hospital, Antwerp, Belgium; and

§ Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to <http://www.wiley.com/WileyCDA/Section/id-301854.html>.

<sup>1</sup> Equally contributed.

Sources of financial support: This work was supported by an educational grant from St. Jude Medical Neuromodulation (Plano, TX, USA).

Medical bills accumulated through patient care/treatment paired with occupational handicap often cause significant financial problems. Medical costs are estimated to be about \$9573/year in the United States and €7814/year in Europe (3,8,9).

The pervasive effects of fibromyalgia on affected individuals magnify the importance of finding a safe and viable treatment option. Most therapeutic interventions have either only a small effect size or benefit only a small number of symptom dimensions (10,11). A network meta-analysis concluded that benefits of pharmacological treatments in fibromyalgia (antidepressants, anticonvulsants, antipsychotics) are of questionable clinical relevance, and evidence for benefits of nonpharmacological interventions is limited (exercise therapy, massage therapy, balneotherapy, acupuncture, etc.) (11). Thus, it was proposed that either a combination therapy was most promising (11), or a fundamentally new therapy might be required to improve treatment outcomes.

A first study of occipital nerve field stimulation (ONFS) as a treatment for fibromyalgia was a serendipitous finding. Thimineur and De Ridder implanted patients who suffered from headache as a comorbidity of fibromyalgia (12). As a surprise, in addition to a decrease in headache, the treatment decreased widespread body pain and improved fatigue and mood (12). In light of those findings, a more recent double blind placebo-controlled crossover study, conducted by Plazier and colleagues, using a modified surgical technique demonstrated long-term effects with a decrease in pain intensity, pain catastrophizing, overall fatigue, number of trigger points, and overall morbidity of the disease (13). Even though it is unknown how ONFS exerts its beneficial effect on fibromyalgia, some working mechanisms have been hypothesized (14). 1) Direct modulation of spinothalamic pathways at the level of C2 in the spinal cord can suppress bodily pain; 2) C2 stimulation can modulate autonomic nervous system involvement in fibromyalgia; 3) C2 modulation acts indirectly via the mesolimbic dopaminergic system as suggested by the first fMRI study performed during C2 stimulation; 4) a combination of the three abovementioned mechanisms (14).

Although ONFS is a promising treatment option for patients with fibromyalgia, not all implanted patients respond to the treatment. In the previous ONFS study mentioned, on average, a decrease of 40% was reported on the pain intensity; however, not all patients had clinically relevant benefit. That is, a closer look at the individual outcome scores show variable reactions to stimulation (13). Therefore, it might be beneficial to be able to select high responders and low responders to treatment prior to implantation. One possible way to help distinguish these groups would be to modulate the occipital nerve noninvasively by using transcranial direct current stimulation (tDCS). tDCS is a noninvasive and painless neuromodulation technique in which weak direct current (DC) is applied transcutaneously to nervous tissue (15). Using this rationale, treatment of tDCS, noninvasive modulation of the C2 nerve, could be conducted to determine whether or not to anticipate successful treatment of ONFS using a subcutaneous C2 electrode implantation. This study investigates the relationship between success rates on pain suppression of tDCS, targeting the C2 nerve, in comparison with C2 ONFS implantation/stimulation, both at short and long term.

## METHODS

### Participants

Patients suffering from fibromyalgia were selected by the Department of Physical Medicine and Rehabilitation at the University Hos-

pital Antwerp, Belgium, according to the criteria of the ACR-90 (4). Patients harboring pathologies mimicking the symptoms of fibromyalgia, as well as patients suffering from severe organic or psychiatric co-morbidity (except minor depressive disorder), were excluded from participation. None of the patients were suffering from cervicotrigenal tract radicular symptoms or types of hemicrania.

Nine patients were included. All patients were of the female gender with a mean age of 42 years ( $\pm 4.23$  S.D.). All patients were intractable to tricyclic antidepressants (amitriptyline), pain medication, magnesium supplements, physical therapy, and psychological support. All patients agreed to make no changes in their current medication intake, which primarily included the aforementioned medication.

All patients gave written informed consent, and the ethical committee of the University Hospital Antwerp, Belgium, approved the study.

### Surgical Intervention

All patients were implanted on the same day with a subcutaneous occipital nerve stimulator under local anesthesia in prone position. A single eight-contact trial wire-lead Octrode (St. Jude Medical, Plano, TX, USA), which has a 5.2-cm contact span, was inserted 2.6 cm from the midline, crossing the midline of the occipital skin area just below the inion, covering both main branches of the greater occipital nerve. This technique was chosen because it was safer compared with high cervical spinal cord stimulation of C2, as it is less invasive. The distal part of the lead was tunneled subcutaneously in a sharp angle to prevent lead migration and externalized just below the hairline. Patients were provided with an external Multi Trial Stimulator (St. Jude Medical) preprogrammed with five different stimulation frequencies (6, 10, 12, 18, and 40 Hz). Pulse widths and polarities were fixed (300  $\mu$ s; alternating positive and negative poles). During a one-week period, patients were able to test the five frequencies as a treatment to fibromyalgia pain. The frequency that decreased pain the most was then selected for the crossover trial period.

After the externalized trial period, the percutaneous leads were removed. All participating patients had the opportunity to be implanted with a permanent Internal Pulse Generator (IPG). Patients, who chose to do so, underwent permanent implantation under general anesthesia, according to the procedure described above. A new eight-contact trial wire Octrode lead was connected to a 60-cm extension lead (St. Jude Medical), tunneled subcutaneously to a pocket at the lower back (side determined according to preference of the patient). Subsequently, the distal part of the extension lead was connected to an IPG (EON, St. Jude Medical), which was placed in the subcutaneous pocket at the lower back. At least ten days were provided between the removal of the old eight-contact trial wire Octrode lead and the placement of a new lead.

### tDCS

DC was transmitted by a saline-soaked pair of surface sponges (35 cm<sup>2</sup>) and delivered by specially developed, battery-driven, constant current stimulator with a maximum output of 10 mA (Eldith<sup>®</sup>; <http://www.eldith.de>). For each patient receiving tDCS, one electrode was placed over left and right C2 nerves dermatomes. A constant current of 1.5-mA intensity was applied for 20 min. For sham tDCS, placement of the electrodes was identical to real tDCS. DC was first switched on in a ramp-up fashion over 5 sec. Current intensity

(ramp down) was gradually reduced (over 5 sec) as soon as DC reached a current flow of 1.5 mA. Hence, sham tDCS only lasted 10 seconds in comparison with 20 min. The rationale behind this sham procedure was to mimic the transient skin sensation at the beginning of real tDCS without producing any conditioning effects on the brain. The order of the sham and real tDCS was randomized over the different patients, but ultimately, each patient experienced both the real tDCS and sham tDCS.

### Procedure

Nine patients were implanted with the eight-contact trial lead Octrode device in the C2 dermatoma covering the occipital nerve. After implantation but before programming, a baseline evaluation for perception of pain was taken. In order to determine programming standards (frequency and amplitude) for each individual patient, a nurse-programmer determined the patient's subthreshold stimulation level and helped the patient to determine what frequency of stimulation best alleviated fibromyalgia pain. During subthreshold stimulation, patients were stimulated at subsensory (for paresthesia) threshold stimulation. This threshold was determined by increasing the amplitude till patients experienced paresthesia, and then decreasing the amplitude to 90% of this threshold, with manual pressure overlying the electrode, to ascertain no paresthesia would be felt while lying down with pressure on the back of the head. Once each patient's specific frequency and amplitude was determined, the patients were then programmed and went through two-week treatment using ONFS with the C2 implant and two weeks of sham. For the sham stimulation, patients were stimulated at minimal stimulation (0.1 mA, the lowest possible output of the external pulse generator) which served as a control situation. Stimulation at 0.1 mA is believed to be none to too minimal effect. During minimal stimulation, patients received continuous stimulation of 0.1 mA with a pulse width of 300  $\mu$ s over the implanted electrode. The patient and investigators did not have any knowledge of when the treatment was activated vs. the sham. The nurse-programmer was not part of the investigators of the study. Treatment consisted of constant ONFS of the C2 implant using subthreshold levels and patient-specific frequency for their stimulation. A difference between the treatment and the sham would not have been noticeable by the patient because all treatment stimulation was subthreshold for paresthesia. After two weeks, and after one month, the patients returned to the clinic and were re-evaluated for pain perception (post-treatment and postsham). If there were no adverse events or complaints reported, the patients were asked to continue treatment for the remainder of the six months postimplantation and return for their six-month evaluation. The patients were informed that any adverse effects or questions should be brought to the attention of the investigators immediately during the duration of the treatment. No adverse events were reported during the treatment periods.

Once the patient returned for their six-month follow-up, another pain perception evaluation was taken, and the device was turned off for two weeks. The two-week period of time was to allow for washout so that patient fibromyalgia symptoms could return. After two weeks, the patient was re-evaluated for pain perception. After the pain percept evaluation, tDCS treatment was conducted. Continuing with the double blind procedure, each patient experienced one consecutive week of sham tDCS treatment, and one week of effective tDCS treatment, with a two-week washout between the sham and effective treatment. Patients were randomized between the sham and the effective treatment. For both the sham and the

tDCS treatment, one week consisted of three sessions (one session of 20 min every two days). After the final tDCS treatment and after the final tDCS sham treatment, a pain perception evaluation was completed.

### Safety and Complications

tDCS was well tolerated, and no tDCS-related complications were noted by the patients during the tDCS sessions. No implanted device malfunctioned after the tDCS.

### Evaluation

A numeric rating scale (NRS) for pain ("How much pain do you have? 0 = no pain and 10 = as painful as imaginable") was asked before (pre) and directly after (post) tDCS stimulation. NRS was compared in a functional analysis against other questionnaires that measure levels of pain, depression, overall mood, health, etc. and had good correlations with all tests, indicating that the NRS for pain is a good tool to evaluate the overall impact of fibromyalgia (16).

Baselines for pain were acquired before the study, immediately after each ONFS treatment session (placebo or actual trial stimulus) during the study, during a six-month follow-up, and after each tDCS treatment session (placebo or actual).

### Statistical Analysis

A repeated measures ANOVA was applied with NRS pain for baseline, real ONFS and sham ONFS as dependent variables. In addition, a repeated ANOVA was conducted for baseline, real ONFS and follow-up ONFS as dependent variables. A similar analysis was conducted to compare NRS pain, pretreatment tDCS, post-treatment tDCS, and sham tDCS.

The Pearson's correlation and Spearman correlation were calculated between the outcome of tDCS (pre-tDCS–post-tDCS) and the outcome of C2 electrode (baseline–immediate effect). In addition, a Pearson's correlation and Spearman correlation was computed between the outcome of tDCS (pre-tDCS–post-tDCS) and the follow-up outcome of C2 electrode (baseline–follow-up). Lastly, the Pearson's correlation and Spearman correlation was calculated between outcome of C2 electrode (baseline–immediate effect) and the follow-up outcome of C2 electrode (baseline–follow-up).

In addition, a ROC analysis was calculated to predict the outcome of the of C2 electrode on tDCS.

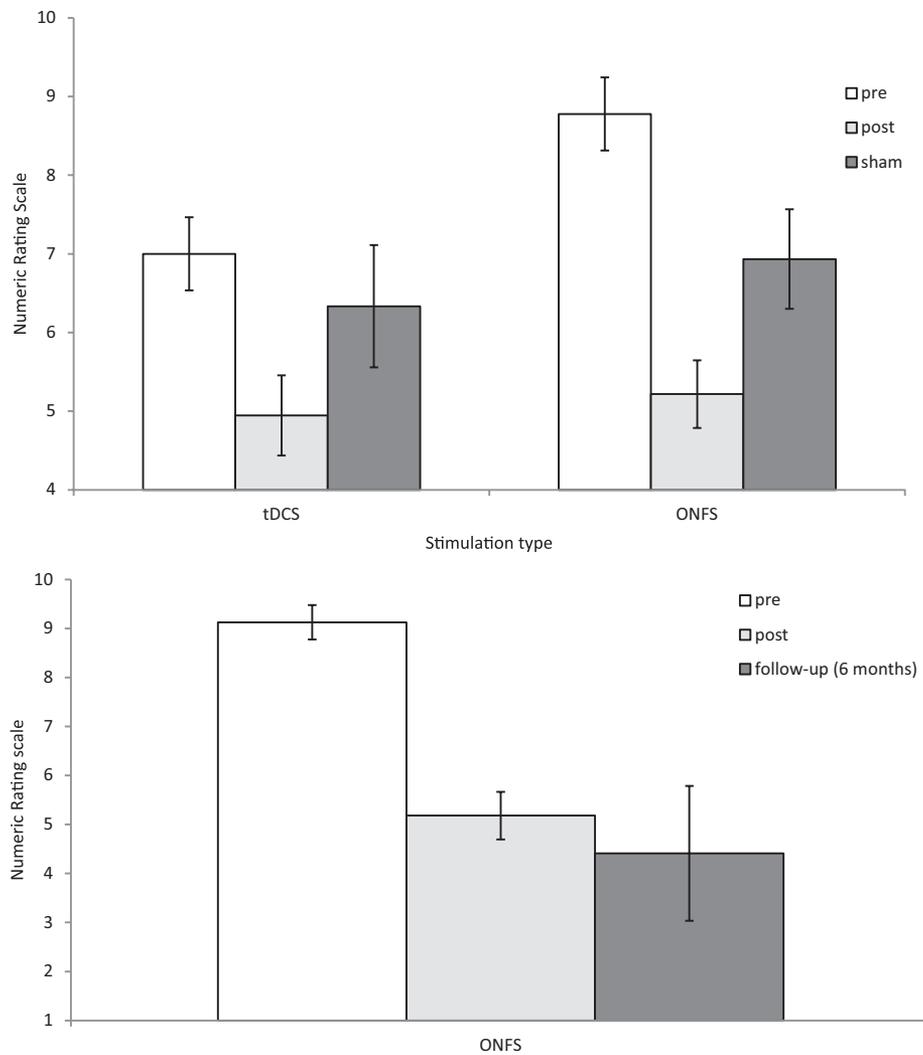
## RESULTS

### Occipital tDCS

A repeated measures ANOVA revealed a significant effect for tDCS ( $F = 10.81$ ,  $p = 0.007$ ; Fig. 1). A pairwise comparison revealed a significant effect ( $p = 0.004$ ) between pretreatment and post-treatment, demonstrated a significant decrease after real occipital tDCS ( $M = 4.94$ ,  $SD = 1.53$ ) in comparison with pretreatment ( $M = 7.00$ ,  $SD = 1.39$ ). This is a reduction of 29.43%. A pairwise comparison between pretreatment tDCS ( $M = 7.00$ ,  $SD = 1.39$ ) and sham tDCS ( $M = 6.33$ ,  $SD = 0.78$ ) revealed no significant effect ( $p = 0.49$ ). In addition, a comparison between sham tDCS ( $M = 6.33$ ,  $SD = 0.78$ ) and real occipital tDCS ( $M = 4.94$ ,  $SD = 1.53$ ) revealed a significant effect ( $p = 0.04$ ) and demonstrated a suppression effect of 21.96%.

### C2 Electrode

A repeated measures ANOVA for ONFS also demonstrated significant effect ( $F = 19.99$ ,  $p = 0.001$ ). A pairwise comparison yielded



**Figure 1.** Top: a comparison between pre, post, and sham tDCS and a comparison between pre, post, and sham ONFS using C2 implant. Bottom: a comparison between pre, post, and follow-up ONFS using C2 implant.

significance between the baseline and real ONFS ( $p = 0.0005$ ), demonstrating a decrease during real ONFS ( $M = 5.22$ ,  $SD = 1.29$ ) in comparison with baseline ( $M = 8.78$ ,  $SD = 1.39$ ). That is a suppression effect of 40.55%. A comparison between real ONFS ( $M = 5.22$ ,  $SD = 1.29$ ) and sham ONFS ( $M = 6.93$ ,  $SD = 1.89$ ) furthermore revealed a significant difference ( $p = 0.009$ ), revealing a suppression of 24.68%. A comparison between baseline ( $M = 8.78$ ,  $SD = 1.39$ ) and sham ONFS ( $M = 6.93$ ,  $SD = 1.89$ ) also revealed a significant effect ( $p = 0.026$ ), demonstrating a decrease of 21.07%.

Furthermore, an additional repeated measures ANOVA yielded a significant effect for the term effect of ONFS ( $F = 41.22$ ,  $p = 0.0003$ ). That is, long-term follow-up ( $M = 4.41$ ,  $SD = 1.18$ ) revealed a significant decrease in comparison with baseline ( $M = 8.78$ ,  $SD = 1.39$ ) ( $p = 0.0001$ ), with a suppression of 49.77%. However no significant effect could be obtained between long-term follow-up ( $M = 4.41$ ,  $SD = 1.18$ ) and the immediate effect after stimulation ( $M = 5.22$ ,  $SD = 1.29$ ) ( $p = 0.78$ ).

### Correlations Analyses

Correlation analysis between the outcome of tDCS (pre-tDCS–post-tDCS) and the outcome of C2 electrode (baseline–immediate

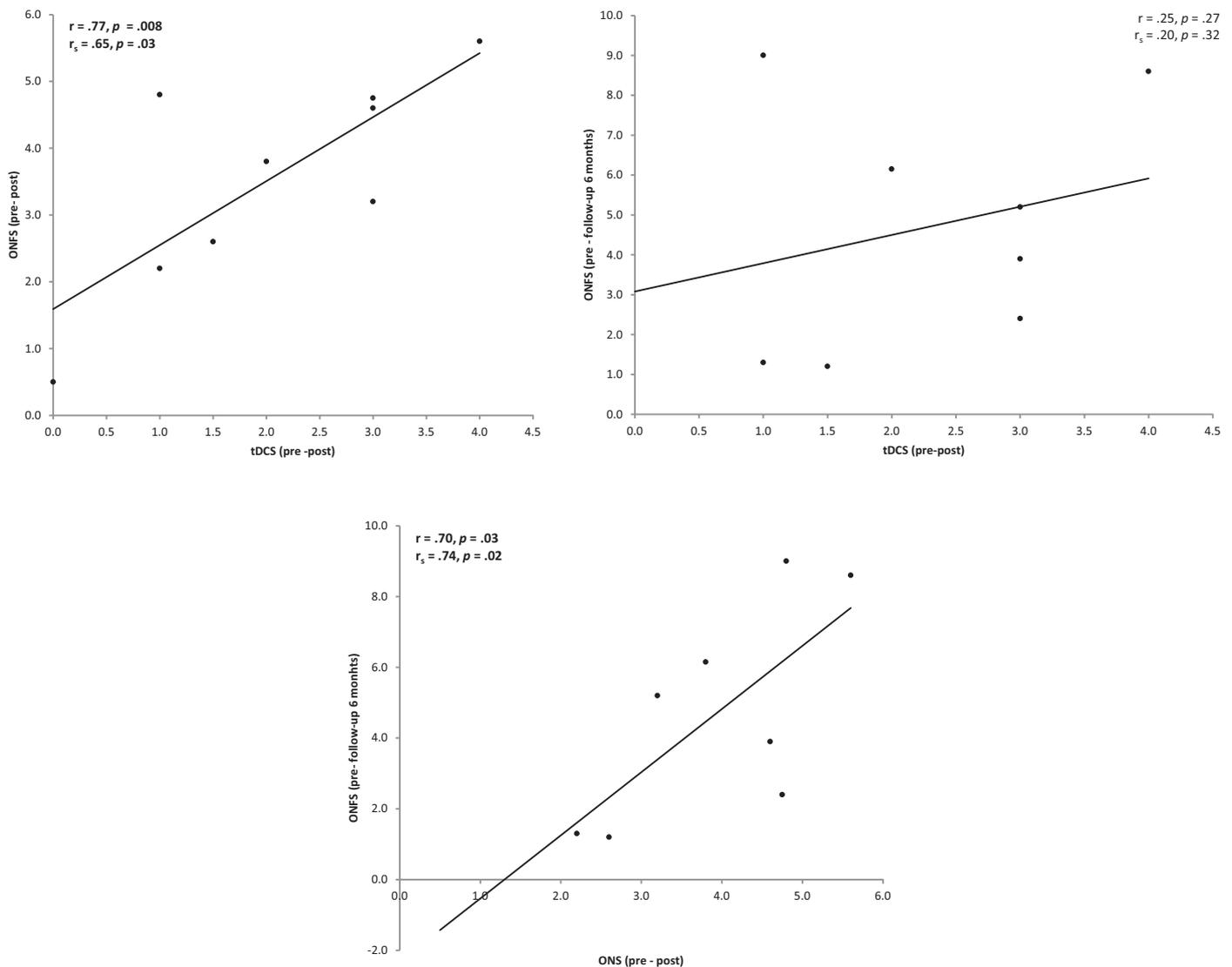
effect) revealed a significant positive association ( $r = 0.77$ ,  $p = 0.008$ ;  $r_s = 0.65$ ,  $p = 0.03$ ). This correlation indicates the larger the suppression effect on tDCS was, the larger the suppression effect was for the C2 electrode (Fig. 2).

A second correlation between the outcome of tDCS (pre-tDCS–post-tDCS) and the follow-up outcome of C2 electrode (baseline–follow-up) yielded no significant effect ( $r = 0.25$ ,  $p = 0.27$ ;  $r_s = 0.20$ ,  $p = 0.32$ ) (Fig. 2).

A correlation between the immediate outcome of C2 electrode (baseline–immediate effect) and the follow-up outcome of C2 electrode (baseline–follow-up) showed a significant positive correlation ( $r = 0.70$ ,  $p = 0.03$ ;  $r_s = 0.74$ ,  $p = 0.02$ ). This effect suggests a direct relationship indicating the larger the immediate effect was on the C2 electrode, the larger the effect was for the follow-up (Fig. 2).

### ROC Analysis

A ROC curve analysis using a cutoff of 40% pain reducing by a C2 electrode revealed a significant test result under area of 0.92 ( $SE = 0.099$ ),  $p = 0.05$ .



**Figure 2.** Left: correlation analysis between the outcome of tDCS (pre-tDCS–post-tDCS) and the outcome of C2 electrode (baseline–immediate effect). Middle: correlation between the outcome of tDCS (pre-tDCS–post-tDCS) and the follow-up outcome of C2 electrode (baseline–follow-up). Right: correlation between outcome of C2 electrode (baseline–immediate effect) and the follow-up outcome of C2 electrode (baseline–follow-up).

## DISCUSSION

The objective of this study is primarily to answer the following questions: Can tDCS predict the outcome of subcutaneous ONFS via an implanted electrode? The secondary research question asks if we were able to replicate previous results as published by the Plazier et al.’s study (13), that is, 1) Is subthreshold ONFS effective in reducing the fibromyalgia symptoms? 2) Are there long-term effects of ONFS, or are these effects limited to short-term outcomes?

Our data provide evidence that occipital nerve stimulation using tDCS could potentially predict the short-term outcome of the ONFS using an implantable electrode. This implies that in a clinical setting, tDCS could become a prognostic tool to decide whether or not a fibromyalgia patient should receive an implanted electrode for ONFS. Although tDCS is a good predictive measure for success of ONFS in short term, tDCS cannot be used as a predictive measure for success of long-term ONFS as no correlation between pain percept measurements were found. However, it seems that the short-term

outcome potentially predicts long-term ONFS success, as our data yielded a significant correlation between ONFS in short and long term. Interestingly, both tDCS and ONFS via an implanted electrode can improve fibromyalgia pain in a placebo-controlled way and exert a long-term pain suppression effect for ONFS via an implanted electrode. These latter results confirm our previous study by Plazier et al. (13) and Thimineur and De Ridder (12). Thimineur and De Ridder reported a mean decrease in VAS over six months of approximately 60% and Plazier et al. of almost 45%. In our study, we found a reduction over six months of almost 50%.

This is the first study that demonstrates that tDCS targeting the occipital nerve can be used to transiently improve fibromyalgia pain. However, it is not clear what the long-term effects are of tDCS and if repeated tDCS (rTDCS) could be potentially used as an alternative noninvasive treatment for fibromyalgia.

Although the exact working mechanism is not known, hypotheses about its beneficial effect have been theorized. The greater occipital nerve afferents enter the C2 segment of the spinal cord at

the level of the nucleus caudalis of the trigeminal nerve forming the trigeminocervical complex (17). The nucleus caudalis projects to the thalamus, which relays sensory input to the cortex. Furthermore, animal studies have shown connections between neurons of the C2 spinal cord and the hypothalamus (18), the thalamus (19), the periaqueductal grey (19), the amygdala (18), anterior cingulate cortex (20), and posterior insula (20). Thus, the C2 neurons in the spinal cord are directly connected to most areas of the pain matrix, and to both the medial and lateral spinothalamic pain pathways. C2 stimulation can thus theoretically modulate both the discriminatory (pain intensity, localization, etc.) and affective (attention to pain, unpleasantness, distress, etc.) components of the pain. C2 stimulation in the MRI scanner induces a BOLD activation of the dorsal anterior cingulate cortex (21), activity that is related to unpleasantness of the pain (22). However, it also influences the thalamus, somatosensory cortex, and periaqueductal grey in a different way depending on the stimulation design (21). PET scans performed during C2 stimulation in patients with headache revealed significant changes in the regional cerebral blood flow in the dorsal rostral pons, anterior cingulate cortex, and the cuneus, correlated to pain scores. Changes in the anterior cingulate cortex and the left pulvinar correlated to paresthesia scores (23). As these structures are well known to be involved in the brain pain matrix, the data might suggest that stimulation of the greater occipital nerve results in a modulation of brain activity in pain-related cortical and subcortical structures.

A consideration must be made to explain why ONFS stimulation treatments work on some patients but not others. One hypothesis that has arisen is based on multiple studies investigating pain characteristics in fibromyalgia. This theory believes that fibromyalgia patients can be further categorized based on their symptoms into different subgroups. In a study conducted by Plazier and co-workers (16), participants were grouped into three different groups based on similarities in questionnaire results. The three fibromyalgia subgroups were "1) A group of patients with mainly mood and catastrophizing-related symptoms; 2) A group of patients with fatigue as most important component; and 3) a mixture of both of these groups" (16). A different study by de Souza et al. (24) defined two different subgroups. The first subgroup consisted of patients with the following subjective measures: low level anxiety, depressive feelings, and morning tiredness. The second subgroup is characterized by fatigue, depression, and anxiety. These differences were measured by comparing results from a number of different questionnaires (in both studies). Differences in symptoms suggest that their outcome to treatment may vary considerably. This could potentially also explain why not all patients respond to ONFS, as it is possible that they belong to a subgroup that is less responsive to C2 treatment. For these specific subgroups, other treatments might be more helpful, or a different stimulation design might need to be selected analogous to what has been demonstrated for spinal cord stimulation (25). Future research needs to look at these different subtypes and their treatment susceptibility.

It should be noted that a difference exists between the NRS tDCS baseline and the NRS OFNS baselines. This difference can likely be attributed to the fact that the two-week washout period between inactivation of the C2 electrode at the six-month mark and the NRS evaluation two weeks after that inactivation was not long enough time for the patient's fibromyalgia pain symptoms to return to their prior levels. However, even though the pain had not returned to their previous magnitude prior to the tDCS trial, a significant change between tDCS baseline evaluation and post-tDCS evaluation was present.

## CONCLUSION

Data from this pilot study support the use of a three-tDCS session as a noninvasive predictor for short-term success but not the long-term success of ONFS with a subcutaneous C2 implant. Our data confirm previous findings that ONFS via an implanted electrode can improve fibromyalgia pain in a placebo-controlled way and exert a long-term pain suppression effect for ONFS via an implanted electrode. Furthermore, our results demonstrated and confirmed previously that short-term ONS with the C2 implant (two-week treatment) success correlates with long-term ONS with C2 implant (six-month) treatment success (13). Findings from this study should be replicated with a larger sample size in order to reaffirm results.

## Authorship Statements

Dr. Ost was responsible for collecting the data. Dr. Plazier designed the study and collected data. Drs. Tchen, De Ridder, and Joos were responsible for drafting the manuscript. Dr. Vanneste assisted in writing the manuscript and performed the data analysis.

## How to Cite this Article:

Plazier M., Tchen S., Ost J., Joos K., De Ridder D., Vanneste S. 2015. Is Transcranial Direct Current Stimulation an Effective Predictor for Invasive Occipital Nerve Stimulation Treatment Success in Fibromyalgia Patients? *Neuromodulation*. 2015; 18: 623–629

## REFERENCES

1. Branco JC, Bannwarth B, Failde I et al. Prevalence of fibromyalgia: a survey in five European countries. *Semin Arthritis Rheum* 2010;39:448–453.
2. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19–28.
3. Berger A, Sadosky A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and patterns of healthcare utilization of patients with fibromyalgia in general practitioner settings in Germany. *Curr Med Res Opin* 2008;24:2489–2499.
4. Wolfe F, Smythe HA, Yunus MB et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum* 1990;33:160–172.
5. Theadom A, Cropley M. Dysfunctional beliefs, stress and sleep disturbance in fibromyalgia. *Sleep Med* 2008;9:376–381.
6. Arnold LM. Management of fibromyalgia and comorbid psychiatric disorders. *J Clin Psychiatry* 2008;69 (Suppl. 2):14–19.
7. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskelet Disord* 2007;8:1–11.
8. Penrod JR, Bernatsky S, Adam V, Baron M, Dayan N, Dobkin PL. Health services costs and their determinants in women with fibromyalgia. *J Rheumatol* 2004;31:1391–1398.
9. Boonen A, van den Heuvel R, van Tubergen A et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann Rheum Dis* 2005;64:396–402.
10. Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. *Eur J Pain* 2014;18:1067–1080.
11. Nuesch E, Hauser W, Bernardy K, Barth J, Juni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. *Ann Rheum Dis* 2013;72:955–962.
12. Thimineur M, De Ridder D. C2 area neurostimulation: a surgical treatment for fibromyalgia. *Pain Med* 2007;8:639–646.
13. Plazier M, Dekelver I, Vanneste S et al. Occipital nerve stimulation in fibromyalgia: a double-blind placebo-controlled pilot study with a six-month follow-up. *Neuromodulation* 2014;17:256–263, discussion 263–254.
14. Plazier M, Vanneste S, Dekelver I, Thimineur M, De Ridder D. Peripheral nerve stimulation for fibromyalgia. *Prog Neurol Surg* 2011;24:133–146.
15. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. *Clin Neurophysiol* 2006;117:1623–1629.

16. Plazier M, Ost J, Stassijns G, De Ridder D, Vanneste S. Pain characteristics in fibromyalgia: understanding the multiple dimensions of pain. *Clin Rheumatol* 2015;34:775–783.
17. Pfaller K, Arvidsson J. Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. *J Comp Neurol* 1988;268:91–108.
18. Newman HM, Stevens RT, Apkarian AV. Direct spinal projections to limbic and striatal areas: anterograde transport studies from the upper cervical spinal cord and the cervical enlargement in squirrel monkey and rat. *J Comp Neurol* 1996;365:640–658.
19. Edvinsson L. Tracing neural connections to pain pathways with relevance to primary headaches. *Cephalalgia* 2011;31:737–747.
20. Keizer K, Kuypers HG. Distribution of corticospinal neurons with collaterals to the lower brain stem reticular formation in monkey (*Macaca fascicularis*). *Exp Brain Res* 1989;74:311–318.
21. Kovacs S, Peeters R, De Ridder D, Plazier M, Menovsky T, Snaert S. Central effects of occipital nerve electrical stimulation studied by functional magnetic resonance imaging. *Neuromodulation* 2011;14:46–55, discussion 56–47.
22. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277:968–971.
23. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. *Brain* 2004;127 (Pt 1):220–230.
24. de Souza JB, Goffaux P, Julien N, Potvin S, Charest J, Marchand S. Fibromyalgia subgroups: profiling distinct subgroups using the Fibromyalgia Impact Questionnaire. A preliminary study. *Rheumatol Int* 2009;29:509–515.
25. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg* 2013;80:642–649.

## COMMENTS

We thank the authors for this interesting manuscript. The results of this pilot study will hopefully create further interest into the study of correlations between transcranial direct current stimulation and peripheral neuromodulation.

Ioannis Skaribas, MD  
Houston, TX, USA

\*\*\*

"It's tough to make predictions, especially about the future."

Yogi Berra, American baseball Hall of Fame player, coach and manager.

Predicting the long-term success of neuromodulation therapy, particularly for chronic pain syndromes, remains a frustrating endeavor. The authors have attempted to use a noninvasive technique, transcranial direct current stimulation, to predict the outcome of an invasive occipital nerve stimulator implant in the fibromyalgia cohort. Fibromyalgia remains a condition viewed skeptically by many physicians specializing in the treatment of chronic pain, due to the lack of objective diagnostic criteria, as well as the significant psychosocial overlay seen in many of these patients. Evidence from placebo-controlled randomized studies of ONS suggests effectiveness in a subset of fibromyalgia patients, although it remains unclear how to separate the wheat from the chaff in this population. Given the significant cost of an implantable neurostimulation system, a low-cost, reliable screening tool would be a welcome addition to the armamentarium of the neuromodulator.

The authors present their clinical case series of patients who underwent tDCS as a screening tool prior to implantation of an occipital stimulator. They demonstrated significant pain relief using subthreshold (90% sensory threshold), non-paresthesia producing ONS, as compared with a sham stimulation arm (0.1 mA). This, in and of itself, is a worthwhile addition to the literature, confirming the results of previous studies. On the other hand, their findings demonstrate the potential value of tDCS as a screening tool only for the short-term success of ONS, but not for success in the long-term. Moreover, as "long-term" is defined as only 6 months of follow-up, there remains ample room to question the true long-term efficacy of ONS in this cohort. I would hope that the authors continue to follow these patients for a longer period of time, both to confirm the duration of efficacy in the fibromyalgia population, and to further elucidate what factors best portend a favorable outcome in this difficult patient population.

Alon Y. Mogilner, MD, PhD  
New York, NY, USA

\*\*\*

Occipital nerve stimulation (ONS) is a promising neuromodulation technique for the treatment of headache and craniofacial pain disorders. There has been some interest in investigating the role of ONS in other chronic pain conditions, such as fibromyalgia. Fibromyalgia is a prevalent, but poorly understood condition. Treatment options are typically non-surgical, though the evidence is weak for most therapies. There have been some studies performed looking at ONS for fibromyalgia, with promising results, though no clear conclusions can be made regarding its efficacy. At our center, we do not offer ONS as a therapy for fibromyalgia. That being said, a non-invasive trial that might help determine candidacy for a trial of ONS, which in turn predicts efficacy of ONS implant, might make the therapy more appealing. Plazier, et al. present a study of transcranial direct current stimulation (tDCS) as a predictor for invasive ONS in fibromyalgia patients. In this study, patients with fibromyalgia were trialed with ONS, implanted with ONS, and underwent true and sham sessions of tDCS. Correlations were found between success of tDCS and success of short-term ONS, and between short-term ONS success and long-term ONS success. This suggests that tDCS might be a predictor of ONS trial success, and that ONS trial success might be a predictor of ONS implant success in fibromyalgia. This small study sets the stage for potential larger scale evaluations of these correlations, before any more definitive statements may be made.

Antonios Mammis, MD  
Newark, NJ, USA

Comments not included in the Early View version of this paper.