J Neural Transm (2017) 124:799–808
DOI 10.1007/s00702-017-1714-y

Differential effects of bifrontal and occipital nerve stimulation on pain and fatigue using transcranial direct current stimulation in fibromyalgia patients

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Received: 14 November 2016 / Accepted: 16 March 2017 / Published online: 20 March 2017

Abstract Fibromyalgia is a disorder characterized by widespread musculoskeletal pain frequently accompanied by other symptoms such as fatigue. Moderate improvement from pharmacological and non-pharmacological treatments have proposed non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) to the occipital nerve (more specifically the C2 area) or to the dorsolateral prefrontal cortex (DLPFC) as potential treatments. We aimed to explore the effectiveness of repeated sessions of tDCS (eight sessions) targeting the C2 area and DLPFC in reducing fibromyalgia symptoms, more specifically pain and fatigue. Forty-two fibromyalgia patients received either C2 tDCS, DLPFC tDCS or sham procedure (15 C2 tDCS–11 DLPFC tDCS–16 sham). All groups were treated with eight sessions (two times a week for 4 weeks). Our results show that repeated sessions of C2 tDCS significantly improved pain, but not fatigue, in fibromyalgia patients, whereas repeated sessions of DLPFC tDCS significantly improved pain as well as fatigue. This study shows that eight sessions of tDCS targeting the DLPFC have a more general relief in fibromyalgia patients than when targeting the C2 area, suggesting that stimulating different targets with eight sessions of tDCS can lead to benefits on different symptom dimensions of fibromyalgia.

Keywords Transcranial direct current stimulation · Fibromyalgia · Occipital nerve stimulation · DLFPC stimulation · Non-invasive

Introduction

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain frequently accompanied by other symptoms including fatigue, headaches, cognitive dysfunction, and disturbances in sleep and mood (e.g. depression, anxiety, etc) (Wolfe et al. 1990; Bennett et al. 2007; Arnold 2008; Theadom and Cropley 2008; Ghavidel-Parsa et al. 2015; Chinn et al. 2016). Due to its physical and psychological impairment, fibromyalgia has a significant impact on the affected individuals and on society (Ghavidel-Parsa et al. 2015; Plazier et al. 2015c). Depending on the diagnostic criteria used, the prevalence of fibromyalgia in the general population ranges from 1.2 to 5.4% (Jones et al. 2015) with fatigue reported to be a debilitating symptom in up to 70% of fibromyalgia patients (Chinn et al. 2016).

Since fibromyalgia lacks a generally accepted pathophysiology, a myriad of treatments has been proposed (Plazier et al. 2014). Current treatment methods consist of pharmacological (e.g. antidepressants, anti-seizure medication, etc.) and non-pharmacological approaches (e.g. exercise therapy, massage therapy, etc.) (Sauer et al. 2011; Chinn et al. 2016). A recent meta-analysis, however, suggested that pharmacological treatment of fibromyalgia results in limited benefits and that there is also insufficient

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evidence with regards to non-pharmacological treatments (Nuesch et al. 2013). Therefore, it has been proposed that a combination of therapies (Nuesch et al. 2013) or a fundamentally new approach can be used to improve treatment outcomes (Plazier et al. 2015c).

In the past decade, non-invasive neuromodulation techniques, such as transcranial direct current stimulation (tDCS), have increasingly been introduced as a potential therapeutic intervention for a wide array of disorders such as aphasia, stroke, tinnitus, depression, schizophrenia, craving, migraine, and Parkinson's disease amongst others (e.g. Boggio et al. 2006; Fregni et al. 2006a, 2008; Chadaide et al. 2007; Vanneste et al. 2010; Brunelin et al. 2012; Stagg et al. 2012; Marangolo et al. 2013). tDCS is a non-invasive technique that uses a low amplitude direct current applied transcutaneously to the scalp to modify underlying neural activity (Nitsche and Paulus 2000; Nitsche et al. 2003; Miranda et al. 2006; Plazier et al. 2015c). Since fibromyalgia is suggested to be a condition associated with functional brain changes (Napadow et al. 2012), tDCS could be a potential approach for the treatment of fibromyalgia symptoms (Montoya et al. 2006; Cook et al. 2007b; Diers et al. 2008; Marlow et al. 2013).

Although the exact mechanism underlying fibromyalgia is unknown, neuroimaging studies have shown brain activity and connectivity changes resulting in enhanced pain facilitation in combination with defective inhibition of nociceptive signals augmenting pain perception (Jensen et al. 2013). These activity changes have been found in the insula, prefrontal cortex, and the anterior cingulate cortex (Pujol et al. 2014; Dehghan et al. 2016). In addition, functional connectivity changes were shown in the self-referential default mode network and the executive control network in fibromyalgia patients (Pujol et al. 2014). These network changes in fibromyalgia are similar to what was found in chronic back pain patients, which was interpreted as a lasting effect of pain on brain function (Baliki et al. 2008). More recently, deficient descending pain inhibitory mechanism originating from the pregenual anterior cingulate cortex has been described in fibromyalgia patients as well (Jensen et al. 2013).

Interestingly, these brain activity and connectivity changes have also been related to fatigue in patients with multiple sclerosis, patients with mild traumatic brain injury and patients with a myalgic encephalomyelitis/chronic fatigue syndrome (Roelcke et al. 1997; Filippi et al. 2002; DeLuca et al. 2008; Saiote et al. 2014; Boissoneault et al. 2016; Gay et al. 2016; Nordin et al. 2016). Indeed, fMRI studies on chronic fatigue syndrome have shown changes in brain activations in, for example, the superior frontal cortex and the default mode network, while performing fatiguing cognitive tasks (Cook et al. 2007a, b). Another study looking at structural changes also showed bilateral decrease in gray matter volume in the prefrontal area among chronic fatigue syndrome patients as a region that regulates sensations of fatigue (Okada et al. 2004).

TDCS studies in fibromyalgia patients have suggested both the left dorsolateral prefrontal cortex (DLPFC) and primary motor cortex (M1) as potential targets for tDCS treatments (e.g. Fregni et al. 2006b; Roizenblatt et al. 2007; Valle et al. 2009; Riberto et al. 2011; Villamar et al. 2013; Fagerlund et al. 2015; Foerster et al. 2015; Castillo-Saavedra et al. 2016; Cummiford et al. 2016; Mendonca et al. 2016; for review see Lefaucheur et al. 2017; Zhu et al. 2017). Although positive results were in favor of tDCS targeting M1 instead of tDCS targeting the DLPFC (20 min tDCS sessions of 2 mA on 5 consecutive days) (Fregni et al. 2006b; Roizenblatt et al. 2007; Zhu et al. 2017), increasing the treatment duration to ten tDCS sessions targeting the DLPFC did lead to improvement in pain scores (Valle et al. 2009; DallAgnol et al. 2015) and quality of life (Valle et al. 2009). In general, pain relief was associated with improvement in quality of life in most tDCS studies in patients with fibromyalgia (Lefaucheur et al. 2017). Based on previous findings that the frontal lobes seem to play a crucial role in both fatigue and pain and based on previous tDCS studies demonstrating pain and quality of life improvements after DLPFC tDCS in fibromyalgia patients, we hypothesized that using tDCS targeting the prefrontal cortex might reduce both symptoms in fibromyalgia patients.

Furthermore, previous implant studies have also demonstrated that stimulating the greater occipital nerve area is beneficial against pain and fatigue complaints in fibromyalgia patients (Thimineur and De Ridder 2007; Plazier et al. 2014, 2015a). A recent tDCS study targeting the same area has further shown improvements in pain symptoms (Plazier et al. 2015c). The exact mechanism of action of occipital nerve field stimulation is still unknown, but studies using fMRI and PET techniques have shown modulated brain activity in several important brain areas involved in pain perception after stimulation (e.g. Matharu et al. 2004; Kovacs et al. 2011).

Hence, in this study, we aim to explore the effectiveness of repeated sessions of tDCS (eight sessions) targeting the dorsal lateral prefrontal cortex and the greater occipital nerve in reducing fibromyalgia symptoms, specifically pain and fatigue. We further investigate whether stimulating different targets for eight sessions will lead to benefits against different symptom dimensions of fibromyalgia. We hypothesize that repeated sessions of tDCS targeting the DLPFC or the C2 would improve pain and fatigue in fibromyalgia patients.

Materials and methods

Participants

Patients suffering from fibromyalgia were selected by the Department of Physical Medicine and Rehabilitation at the University Hospital Antwerp, Belgium according to the criteria of the ACR-90 (Wolfe et al. 1990). To obtain a homogeneous sample and exclude potential variables that would interfere with the response to tDCS we excluded subjects based on the following criteria: patients harboring pathologies mimicking the symptoms of fibromyalgia, having a history of epileptic insults, severe organic co-morbidity, a pacemaker or defibrillator, current pregnancy, neurological disorders such as brain tumors, and patients suffering from severe organic or psychiatric co-morbidity (except minor depressive disorder). None of the patients were suffering from cervicotrigeminal tract radicular symptoms or types of hemicrania.

Forty-two patients (36 females and 6 males) with fibromyalgia participated in the study with a mean age of 46.95 years (±10.07 SD). See descriptions of the sample characteristics in Table 1. 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.

Experimental design

The study was in accordance with the ethical standards of the Helsinki Declaration (1964) and was approved by the Ethical Committee of the University Hospital Antwerp Belgium. Written informed consents were obtained from all patients before participating in the study.

The study is designed as a prospective, single-blinded, placebo controlled, randomized, parallel-group study. Patients were blinded and randomly assigned to one of three groups, namely sham tDCS, bifrontal tDCS or occipital tDCS, after baseline measurements using a computer-generated randomization sequence that is revealed to the investigator conducting the treatments immediately before the first session. Both the bifrontal tDCS and occipital tDCS group received eight sessions (two times a week for 4 weeks) of treatment, while the sham tDCS group received sham treatment for 4 weeks. See Fig. 1 for study design.

Evaluation

Before and immediately after (i.e. after the last session of tDCS) the tDCS procedures, the participants completed a set of validated self-report inventories. The primary outcome measure for the efficacy of treatment was evaluated by changes in the Numeric Rating Scale (NRS).

NRS

A Numeric Rating Scale for pain intensity was used. The scale asks patients to rate their pain intensity on a scale from 1 (i.e. no pain) to 10 (i.e. worst pain imaginable).

Secondary outcome of treatment was measured using the Pain Catastrophizing Scale (PCS) and the Modified Fatigue Impact Scale (MFIS).

PCS

The Pain Catastrophizing Scale indicates the catastrophizing impact of pain experienced by the patient. It consists of 13 statements concerning pain experiences. Each question is rated on a 5-point scale ranging from 1 (i.e. not at all) to 4 (i.e. all the time) (Osman et al. 1997).

MFIS

The Modified Fatigue Impact Scale is 21-item instrument designed to rate the extent to which fatigue affects

Table 1 Characteristics for each group separately and the grand total

	tDCS target			Total ($n = 42$)	
	Occipital ($n = 15$)	Frontal ($n = 11$)	Sham ($n = 16$)		
Gender	M: 3/F: 12	M: 1/F: 10	M: 2/F: 14	M: 6/F: 36	NS
Age	47.13 (10.01)	47.81 (10.17)	46.19 (49)	46.95 (10.07)	NS
Medication	None	None	None	None	
NRS baseline	7.07 (1.33)	6.81 (1.08)	6.00 (1.41)	6.59 (1.36)	NS
PCS baseline	24.73 (10.75)	23.09 (8.43)	23.81 (11.05)	23.95 (10.30)	NS
MFCS baseline	61.27 (9.49)	56.73 (16.96)	51.44 (16.87)	51.44 (14.94)	NS

Information between parentheses is the standard deviation

M male, *F* female, *NS* not significant

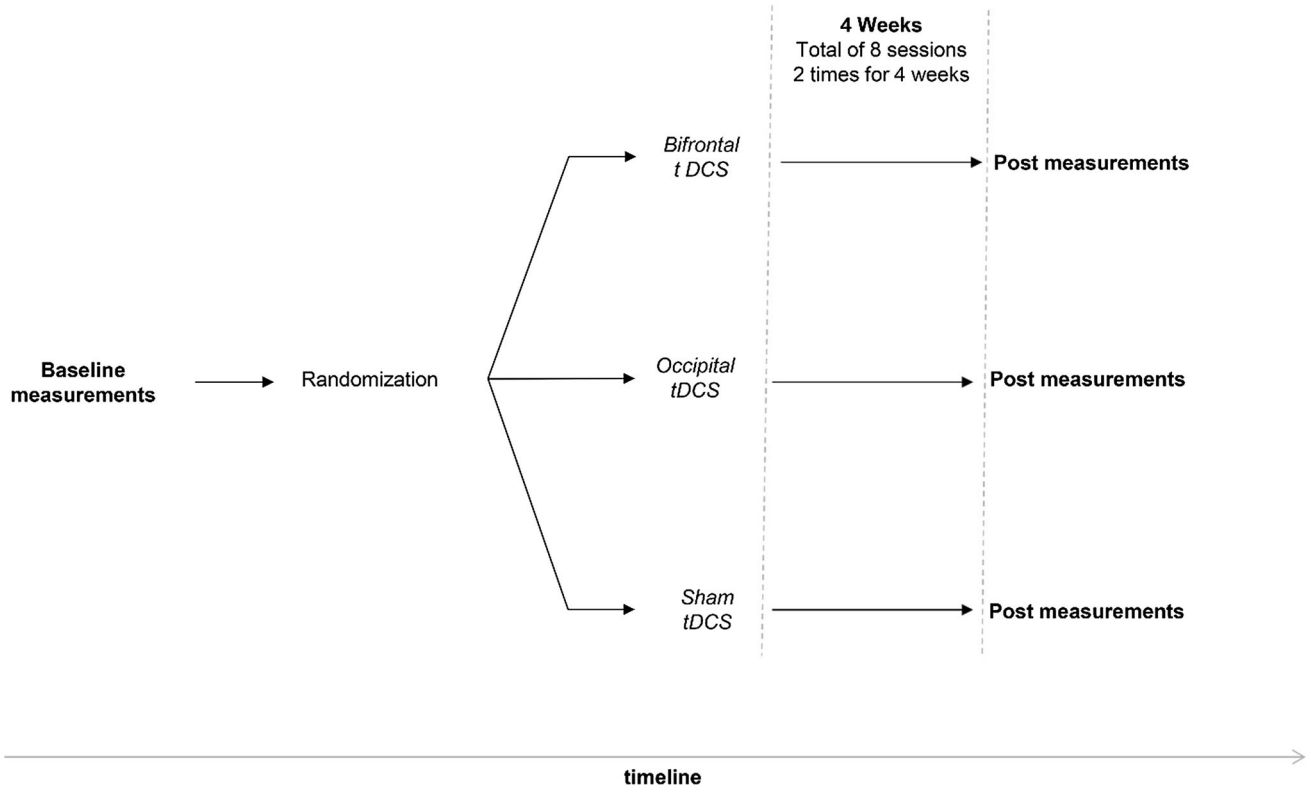

Fig. 1 Study design

perceived function. Each item is rated on a scale from 0 (i.e. never) to 4 (i.e. almost always) (Fisk et al. 1994).

Transcranial direct current stimulation

Direct current (DC) was transmitted by a saline-soaked pair of surface sponges (35 cm^2) and delivered by specially developed, battery-driven, constant current stimulator with a maximum output of 10 mA (Neuroconn©; http://www.neuroconn.de).

Fifteen patients received occipital tDCS in which the electrodes were placed over left and right C2 nerves dermatomes (i.e. left anode, right cathode). Eleven patients received bifrontal stimulation with the anodal electrode placed over left dorsolateral prefrontal cortex and the cathodal electrode over the right dorsal lateral prefrontal cortex. The site for stimulation was determined by the International 10/20 Electroencephalogram System corresponding to F3 and F4, respectively. The DC current was initially increased in a ramp-like fashion over 5 s until it reached 1.5 mA. TDCS stimulation was maintained for a total of 20 min and then ramped down over 5 s. Sixteen patients received sham tDCS, in which the placement of the electrodes was identical to real tDCS (eight patients received C2 and eight received frontal tDCS). The DC in the sham procedure was first switched on in a ramp-up fashion over 5 s until it reached 1.5 mA. Then, the current intensity was gradually reduced (ramp down) over 5 s until it is switched off. This was followed by 20 min of no active stimulation. Thus, the active part in the sham procedure only lasted maximum 10 s (ramping up and ramping down) in comparison to 20 min and 10 s in the real procedure, but the sham session lasted as long as the real tDCS treatment session to appropriately blind the procedure. 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.

Safety and complications

TDCS was well tolerated and no tDCS related complications were noted by the patients during the tDCS sessions.

Statistical analysis

We calculated our sample by assuming an α level of 0.05 (two-sided), power of 80%, and an effect size f of 0.25 of the NRS. This resulted in a sample size of 42.

We used SPSS version 22.0 for all statistical analyses. Kolmogorov–Smirnov test revealed that our data were normally distributed ($KS = 0.123$, $p = 0.123$), i.e. no significant difference was obtained from normal

distribution. A Machly's test of Sphericity revealed no significant effect indicating that the sphericity assumption has been met. A repeated measure ANOVA was applied with as dependent variables time point (pre versus post) and between subjects the condition (frontal stimulation, occipital stimulation and sham stimulation) for NRS, PCS and MFIS. The η^2 was used to indicate the effect size/as simple contrast analysis was used to compare between the three conditions separately. To compare the amount of reduction between the conditions an independent t test was applied. We used the Cohen's d to report the effect size.

Results

A repeated measure ANOVA for the NRS yielded in a significant main effect when comparing pre versus post treatment with post results ($F(1, 39) = 58.27$, $p < 0.001$, $\eta^2 = 0.60$) indicating that, after eight sessions of tDCS ($M = 5.10$, SD = 1.91), a lower score was obtained on the NRS in comparison to pre-stimulation ($M = 6.59$, SD = 1.36). No significant main effect was obtained for condition (frontal, occipital or sham) ($F(2, 39) = 0.25$, $p = 0.78$, $\eta^2 = 0.01$), but a significant interaction effect was demonstrated between conditions and time point ($F(2, 39) = 7.37$, $p = 0.002$, $\eta^2 = 0.27$). A simple contrast analysis revealed that frontal stimulation ($F(1, 39) = 31.18$, $p < 0.001$, $\eta^2 = 0.43$) as well as occipital stimulation ($F(1, 39) = 38.14$, $p < 0.001$, $\eta^2 = 0.48$) had a significant reduction of respectively, 33.50 (SD = 22.79) and 31.05 (SD = 21.39). See Fig. 2 for an overview. Sham stimulation ($F(1, 39) = 2.28$, $p = 0.14$ $\eta^2 = 0.06$; $M = 8.41\%$, SD = 18.07) did not obtain a significant effect. A further analysis showed that frontal stimulation did not significantly differ from occipital stimulation in the amount of pain reduction ($t(24) = 0.28$, $p = 0.78$, $d = 0.11$). However, there were significant effects between frontal stimulation and sham stimulation ($t(25) = 3.19$, $p = 0.004$, $d = 1.28$) as well as between occipital stimulation and sham stimulation ($t(29) = 3.19$, $p = 0.003$, $d = 1.18$).

A repeated measures ANOVA for the PCS showed a significant main effect for pre versus post ($F(1, 39) = 22.74$, $p < 0.001$, $\eta^2 = 0.37$) indicating that after eight sessions of tDCS ($M = 19.90$, SD = 10.09) a lower score was obtained on the PCS in comparison to pre-stimulation ($M = 23.95$, SD = 10.30). No significant main effect was obtained for condition (frontal, occipital or sham) ($F(2, 39) = 0.38$, $p = 0.69$, $\eta^2 = 0.02$), but a significant interaction effect ($F(1, 39) = 4.07$, $p = 0.025$, $\eta^2 = 0.17$) between conditions and time point (pre or post) was shown, indicating a significant difference between pre versus post treatment for the occipital stimulation ($F(1, 39) = 16.23$, $p < 0.001$, $\eta^2 = 0.29$) and frontal stimulation ($F(1, 39) = 12.27$, $p = 0.001$, $\eta^2 = 0.24$). See Fig. 2 for an overview. For the sham group, no significant effect ($F(1, 39) = 0.32$, $p = 0.58$, $\eta^2 = 0.01$) was obtained. A suppression effect of 24.46% (SD = 31.66) was obtained for occipital stimulation, and a suppression effect of 30.21% (SD = 32.18) was obtained for frontal stimulation. Suppression effect for sham stimulation was −1.19% (SD = 21.42). A further analysis showed that frontal ($t(25) = 3.05$, $p = 0.005$, $d = 1.22$) and occipital ($t(29) = 2.66$, $p = 0.013$, 0.99) stimulation significantly differed from sham stimulation, but that there was no significant difference between frontal and occipital stimulation ($t(24) = 0.46$, $p = 0.65$, $d = 0.19$).

A repeated measure ANOVA for MFIS showed a main effect for pre versus post ($F(1, 39) = 20.17$, $p < 0.001$, $\eta^2 = 0.34$) revealing that, after eight sessions of tDCS ($M = 48.13$, SD = 15.70), participants had a reduction in their fatigue scores in comparison to before the tDCS treatment ($M = 56.33$, SD = 14.94). No main effect was obtained for condition ($F(2, 39) = 2.26$, $p = 0.12$, $\eta^2 = 0.10$), but a significant interaction effect was obtained between conditions and time point ($F(1, 39) = 4.16$, $p = 0.023$, $\eta^2 = 0.18$). A simple contrast analysis revealed that frontal stimulation ($F = 20.44$, $p < 0.001$, $\eta^2 = 0.34$) had a significant reduction of 29.78% (SD = 18.35), while occipital stimulation ($F(1, 39) = 3.31$, $p = 0.08$, $\eta^2 = 0.08$; $M = 8.64\%$, SD = 19.10) and sham stimulation ($F(1, 39) = 1.21$, $p = 0.28$, $\eta^2 = 0.03$; $M = 3.10\%$, SD = 20.87) did not obtain a significant effect. See Fig. 2 for an overview. A further analysis showed that frontal stimulation significantly differed from occipital ($t(24) = 2.83$, $p = 0.009$, $d = 1.16$) and sham stimulation ($t(25) = 3.42$, $p = 0.002$, $d = 1.37$), but there was no significant difference between occipital and sham stimulation ($t(29) = 0.77$, $p = 0.45$, $d = 0.29$).

Discussion

This study shows that eight sessions of tDCS targeting the DLPFC resulted in more general relief (reducing pain and fatigue) in fibromyalgia patients when compared to eight sessions of tDCS targeting C2 (only reducing pain). This suggests that using the same stimulation duration for different targets will lead to benefits on different symptom dimensions of fibromyalgia. There were no adverse effects associated with these new treatment protocols of eight sessions.

Findings from related studies can shed some light on why DLPFC tDCS improved pain and fatigue in the fibromyalgia patients in this study. For pain, research has shown that left DLPFC stimulation had an unexpected

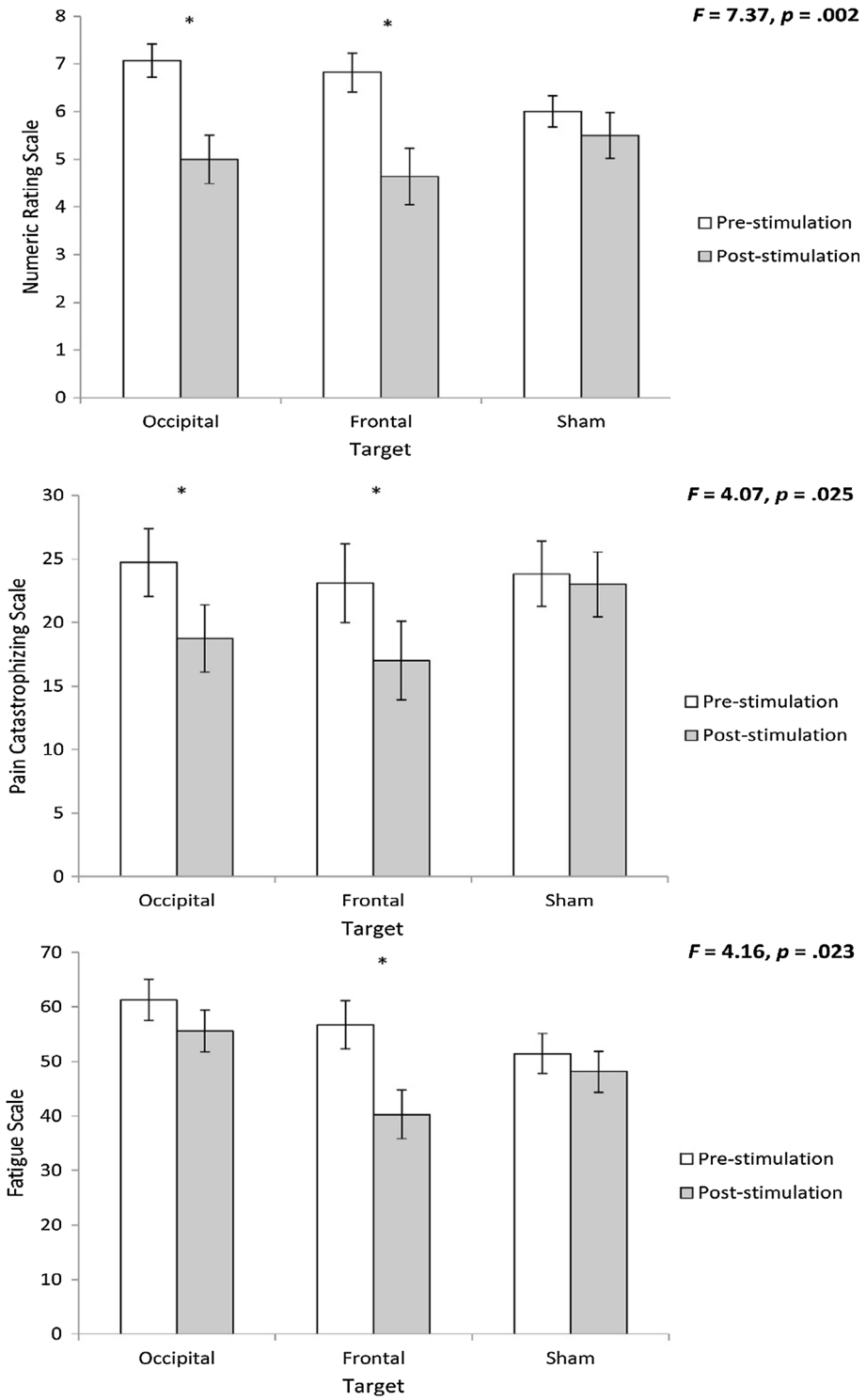

Fig. 2 Both occipital and bifrontal stimulation showed an effect in pain measured by the NRS and PCS compared to sham. Only frontal stimulation demonstrated an effect on the MFAS

effect on pain reduction when treating depression (O'Reardon et al. 2007). Since then, the potential of DLPFC stimulation for chronic pain in general, and pain in fibromyalgia in particular, has been investigated (Lefaucheur et al. 2017), motivated by the proven efficacy of this stimulation target for depression and the well-known relation between depression and chronic pain (Lefaucheur et al. 2014). Studies have shown that DLPFC stimulation can be effective in pain control, decreasing the threshold for pain sensation in healthy subjects (Graff-Guerrero et al. 2005; Borckardt et al. 2007; Boggio et al. 2008; Nahmias et al. 2009; Brighina et al. 2011) as well as reducing

clinical pain symptoms (Borckardt et al. 2006, 2009; Valle et al. 2009; Borckardt et al. 2011; DallAgnol et al. 2015; Ayache et al. 2016). Valle and Colleagues (2009) have previously demonstrated the importance of the duration of the DLPFC tDCS treatment, as five sessions of DLPFC tDCS did not result in pain reduction in the study of Fregni et al. (2006c) and Roizenblatt et al. (2011). This study shows that eight sessions of 1.5 mA DLPFC tDCS spread over 4 weeks (two times a week for 4 weeks) was sufficient to reduce pain symptoms in fibromyalgia and that 10 daily sessions of 2 mA DLPFC tDCS such as the study of Valle et al. (2009) and Dallagnol et al. (2015) was not needed. However, unlike Valle and Colleagues (2009), this study did not measure any potential long-term effects. The key role of the DLPFC in pain modulation has been examined by Lorenz and his colleagues (Lorenz et al. 2002; Lorenz et al. 2003). They suggested that the DLPFC may exert a 'top-down' inhibition on neuronal coupling along the ascending midbrain-thalamic-cingulate pathway through descending fibers from the prefrontal cortex (Lorenz et al. 2003; Brighina et al. 2011).

For fatigue, support can be found in Multiple Sclerosis (MS) research, where fatigue has been associated with functional (Roelcke et al. 1997; Filippi et al. 2002; DeLuca et al. 2008) and structural (Sepulcre et al. 2009; Pardini et al. 2010; Bester et al. 2013) changes in the frontal cortex (Saiote et al. 2014). Saiote and his colleagues (2014) did not find a robust effect after five sessions of 1 mA tDCS targeting the DLPFC in MS patients on fatigue, but suggested that the absence of effect might be due to the chosen stimulation parameters (Saiote et al. 2014). Our study revealed that eight sessions of 1.5 mA tDCS targeting the DLPFC can modulate fatigue.

With regards to the C2 target, occipital nerve field stimulation as a treatment for fibromyalgia patients has been mostly investigated for surgical techniques involving the placements of implanted subcutaneous electrodes on the C2 area (e.g. (Thimineur and De Ridder 2007; Plazier et al. 2014; Plazier et al. 2015b)). In contrast to our study findings using tDCS to non-invasively target C2, the invasive method has demonstrated to treat pain and fatigue in fibromyalgia patients (Thimineur and De Ridder 2007; Plazier et al. 2014; Plazier et al. 2015b). A pilot study investigating the non-invasive technique of C2 tDCS (three sessions) as a predictive measure for invasive occipital nerve stimulation further found a reduction in pain perception compared to the sham group, suggesting that C2 tDCS could potentially become an alternative non-invasive pain treatment for fibromyalgia (Plazier et al. 2015c). Although the exact mechanism of action of C2 nerve field stimulation is still unknown, hypotheses of its beneficial effect have been suggested. Stimulation of the area supplied by the greater occipital nerve modulates brain activity in several important regions involved in pain perception as shown by functional imaging techniques, including fMRI and PET scans (Kovacs et al. 2011; Magis et al. 2011). During occipital nerve field stimulation, PET data demonstrated that activity in the anterior cingulate gyrus, the precuneus, amygdala, ventroposteriolateral nuclei of thalamus, and the frontal cortex are modulated. These structures are involved in attention to pain, pain perception, and emotional interpretation (Garcia-Larrea and Peyron 2013).

Although the DLPFC and C2 stimulation both improved pain, fatigue was only improved with DLPFC stimulation in our study. Previous studies using surgical neuromodulation techniques targeting the C2 area, however, did demonstrate improvement in both pain and fatigue in fibromyalgia patients (Thimineur and De Ridder 2007; Plazier et al. 2014, 2015b). A possible explanation for the absence of significant improvements in fatigue in our study compared to the previous studies might be the duration of the stimulation. In the studies where the electrodes targeting the C2 were implanted, the stimulation was kept on continuously for at least 1–5 weeks, except when patients preferred to turn the unit off on their own initiative (e.g. at night). On the other hand, our non-invasive C2 tDCS stimulation was performed for eight sessions of 20 min spread over 4 weeks. We hypothesize that C2 tDCS might need a longer stimulation duration to evoke significant improvements in fatigue.

This study has some limitations. First, this study did not include other affective dimensions of fibromyalgia, such as depression or anxiety. Adding these aspects can further disentangle the specific benefits of the different stimulation targets. Further, our study did not include M1 stimulation, not being able to compare the results on different symptom dimensions for all possible stimulation targets known for fibromyalgia patients. Also, our study did not include long-term assessments to measure potential long-term effects. Therefore, it remains unknown whether eight sessions of DLPFC tDCS over 4 weeks is sufficient to induce long-term effects compared to the proven ten daily sessions. Lastly, our study sample is relatively small; therefore, the results need to be interpreted with caution. Our findings encourage future research using tDCS in fibromyalgia to elucidate which stimulation targets will lead to benefits on various symptom dimensions to be able to develop more efficient treatments for different subgroups of fibromyalgia patients.

In conclusion, this study shows that repeated sessions of tDCS targeting the DLPFC has a more general relief in fibromyalgia patients than when targeting C2, suggesting that stimulating different targets will lead to benefits on different symptom dimensions of fibromyalgia. The stimulation protocol is feasible for clinical routine and was well

tolerated by all participants. Further studies should take the limitations of this study into account and add more affective aspects of fibromyalgia when investigating the effect of tDCS in fibromyalgia.

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