Adding Prefrontal Transcranial Direct Current Stimulation Before Occipital Nerve Stimulation in Fibromyalgia

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Objectives: Fibromyalgia (FM) is a type of chronic musculoskeletal pain without a clear peripheral origin of nociception, often associated with depression. The underlying pathophysiology involves changes in a functional network that is related to pain and emotional processing in the central nervous system. Transcranial direct current stimulation (tDCS) targeting the dorsolateral prefrontal cortex or the occipital nerve (ON) is a noninvasive neuromodulation technique capable of improving fibromyalgia symptoms. This study aims to test the effect of combining 2 targets of stimulation using tDCS.

Materials and Methods: We applied ON-tDCS in isolation or coupled with pre-ONS right-anode bifrontal tDCS and assessed its effect on fibromyalgia using the Fibromyalgia Impact Questionnaire, the Beck Depression Inventory, and Numeric Rating Scale for pain scores. These measures were compared with a sham control group using repeated measures analysis of variance.

Results: The interaction effect of stimulation trials and the protocols of sham versus ON-tDCS were significant for the impact, distress, and pain caused by fibromyalgia ($P < 0.05$). The interaction effect of trials and protocols of sham versus ON-tDCS with bifrontal tDCS was significant for distress ($P < 0.01$), and it showed a trend of improvement for impact and pain ($P < 0.1$). On the basis of the nonsignificant interaction effect of ON-tDCS versus ON-tDCS with bifrontal tDCS ($P > 0.1$), adding bifrontal tDCS was found not to improve the treatment effect of ON-tDCS in any of the tested clinical outcome measures.

Discussion: This study suggests that adding right-anode bifrontal tDCS to ONS has no added benefit in improving fibromyalgia-related symptoms.

Key Words: transcranial direct current stimulation, occipital nerve stimulation, fibromyalgia, pain

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Fibromyalgia (FM) is characterized by widespread chronic musculoskeletal pain accompanied by sleep problems, mood changes, cognitive dysfunction, autonomic nervous system disturbances impacting the patients' quality of life, and fatigue that is not relieved by rest.[1] An increasing number of studies suggest that FM is associated with disturbances in the central nervous system,[2] including areas involved in pain[3] and mood processing.[4]

Drug therapies have been widely recommended for treating FM.[5] Some of them include the following tramadol[6]; benzodiazepines, zolpidem, and zopiclone (gamma-aminobutyric acid A agonists); duloxetine, venlafaxine, and milnacipran (serotonin-norepinephrine reuptake inhibitors); fluoxetine, citalopram, and paroxetine (selective serotonin reuptake inhibitors).[7–10] These drugs have shown significant benefits, but medications do not treat the entire spectrum of FM symptoms and are frequently associated with significant adverse effects that require switching between drugs.[11] Cognitive-behavioral therapy has also shown significant pain reduction effects and mood improvements,[12] but it requires an extensive amount of sessions, thus lowering its accessibility. In contrast, invasive and noninvasive neuromodulation therapies that apply electrical stimulation on the brain or peripheral nerves appear to be promising techniques in alleviating FM symptoms without major significant adverse effects.[13–15] In addition, studies in tinnitus, which is thought to have overlapping pathophysiological mechanisms,[16,17] have shown that multitarget neuromodulation might exhibit a stronger effect than single-target stimulation.[18,19] Furthermore, it may be beneficial to modulate brain regions related to pain and its comorbid components, such as emotion, to better alleviate these symptoms.

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that can create plastic changes in the brain by delivering a low-amplitude direct current ranging from 0.5 to 2 mA near a region of interest. It has been a useful technique in modulating brain activity by being capable of targeting regions that are pathologic centers or others functionally connected to those regions.[20] Its high accessibility can be especially helpful for treating long-term disorders such as chronic pain, including FM. However, there is no consensus on which method of stimulation is most effective.

Among various possibilities, occipital nerve stimulation (ONS) is an emerging technique that applies weak electrical stimulation using a subcutaneous implant, a transcutaneous electrical nerve stimulation, or a tDCS device.[15,21,22] tDCS applies current on the occipital part of the head or the C2 dermatome. The C2 nerve is functionally and anatomically connected to various regions in the central pain network, including the pregenual anterior cingulate cortex, dorsal anterior cingulate cortex, periaqueductal gray, the thalamus,[23] and the amygdala.[24] Recently, it has been shown that ON-tDCS exerts its efficacy by rebalancing the interacting descending and ascending pain pathways

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that are involved in pain sensation.[13] Another possible treatment is to stimulate the dorsolateral prefrontal cortex (DLPFC) to influence the emotional network to modulate the negative emotions associated with FM.[14,25] The top-down inhibitory control of DLPFC over emotion and the associated pain matrix may alter the subjective experience of pain.[26] DLPFC stimulation seems to modulate subjective pain perception via descending pain pathways involving the pregenual anterior cingulate cortex.[13]

The stimulated regions in ON-tDCS are anatomically distant from DLPFC, and the additional treatment effect of DLPFC tDCS before the consequent ON-tDCS is yet to be verified. It is also unclear whether applying tDCS on DLPFC will exert its main effect on the emotional component independently or additionally to other subcomponents of FM. The objective of this study was to evaluate whether this additional stimulation results in better pain suppression and/or a differential effect on mood and the general severity of FM that influences everyday life.

MATERIALS AND METHODS

Participants

A total of 58 FM individuals were recruited for the study. They were all outpatients who had had FM for at least 3 months and were constantly visiting St. Augustinus Hospital, Belgium, for consultation. Specialized anesthesiologists in the department of physical health and rehabilitation in St. Augustinus Hospital diagnosed the FM on the basis of the American College of Rheumatology (ACR)-90 criteria[27] and recruited potential participants on the basis of our inclusion and exclusion criteria (Table 1). Professionally trained psychiatrists further examined the patients for exclusion criteria such as major depressive disorders and other psychiatric disorders that are associated with FM symptoms. Postmenopausal women were excluded, as previous studies note that changes in female hormones are associated with the pathogenesis and symptoms of FM.[28,29] Informed consent was obtained from all individual participants included in the study. The ethical review board of the St. Augustinus Hospital, Belgium, approved this study, in accordance with the ethical standards of the Helsinki declaration (1964).

Study Design

The graphical representation of the study design is illustrated in Figure 1. We included prestimulation and poststimulation conditions within subjects and 3 different stimulation designs between subjects. All participants were randomly assigned to one of the 3 stimulation groups: (1) control with sham occipital stimulation (sham), (2) tDCS on the occipital nerve (ON) only (occipital only), and (3) tDCS on bilateral DLPFC before occipital stimulation (prefrontal added). Participants had 8 consecutive sessions of stimulation for 4 weeks (tDCS twice weekly), and the sessions were 3 days apart from each other to exclude the washout effect, which lasts for at least 48 hours.[30] For the sham-stimulated and occipital-stimulated groups, the sessions were 20 minutes long. The prefrontal-added group had a net 40-minute session consecutively, 20 minutes for both DLPFC tDCS and ON-tDCS on the same day. Behavioral outcome measures were assessed right before the first session and after the last one finished. All the evaluations on the outcome measures were provided and completed by an evaluator blinded to the stimulation conditions.

Power Analysis

The sample size was calculated with the power analysis provided by G*Power 3.1.[31] The statistical effect of interest was the interaction effect between the stimulation (prestimulation vs. poststimulation) and the protocol (occipital only vs. prefrontal added). This study evaluated the treatment effect using the repeated measures analysis of variance (ANOVA) with simple contrast (K matrix). For this design, the sample size was calculated for the medium effect size of 0.25, assuming an α level of 0.05 and power of 80%. The number of groups was set at 2 with prestimulation and poststimulation measurements. The results yielded the sample size of 17 for each group (total 34), and we attempted to recruit as many as 20 participants for each group considering a dropout rate of 20%. Among the originally recruited, 58 participants remained valid for the statistical tests.

Behavioral Assessments

The primary outcome measure for FM severity was the FM Impact Questionnaire (FIQ), one of the most widely

TABLE 1. Inclusion and Exclusion Criteria for Fibromyalgia Patients

Inclusion Criteria	Exclusion Criteria
Patients able to provide informed consent to participate in the study	The patient has current evidence of any psychiatric disorder, as documented by the DSM-IV-TR criteria with psychotic characteristics (eg, bipolar disorder, major depressive disorder)
The patient has had chronic widespread pain for at least 3 months in all 4 body quadrants	The patient has been diagnosed with any disease mimicking the symptoms of the fibromyalgia (eg, Epstein Barr, autoimmune diseases) that is not currently being treated or has not been stable for at least 6 mo
The patient has at least 11 of 18 tender points on the basis of the tender points' examination	Patient is currently in active menopause
The patient has attempted "best" medical therapy and has tried and failed at least 3 documented medically supervised treatments (including but not limited to drugs, physical therapy, acupuncture, etc.)	Patient has been diagnosed with sleep apnea and is not currently involved in a treatment regimen
The patient's medication has remained stable for at least 4 wk before baseline data collection	The patient has a history of substance abuse or substance dependency in the past 6 mo before baseline data collection
Psychological screening has been completed and the patient has been cleared by a psychologist as a suitable study candidate	The patient is currently participating in another clinical study
The patient agrees not to add or increase medication throughout the randomization trial period of the study	Patient with demand-type cardiac pacemakers, an infusion pump, or any implantable nerve-stimulating device
The patient is willing to cooperate with the study requirements including compliance with the treatment regimen and completion of all office visits	

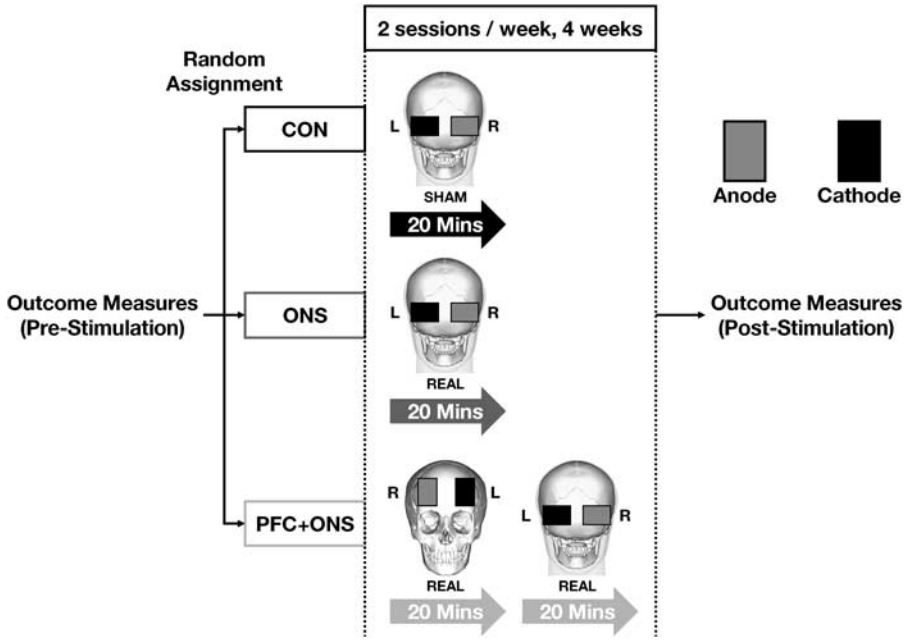

FIGURE 1. Graphical representation of study protocol. CON indicates sham stimulated; L, left; ONS, occipital nerve stimulation only; PFC +ONS, PFC stimulated by transcranial direct current stimulation and then the occipital nerve was stimulated; R, right.

used scales for the clinical state of FM.[32] It measures general disabilities caused by FM in everyday life.[33] It ranges from 0 (least impacting the quality of life) to 100 (maximally impacting). FIQ items were significantly correlated with the corresponding items in Arthritis Impact Measurement Scale ($r = 0.28$ to 0.83).[34] The Dutch version of FIQ that has been validated for reliability[35] was used.

The secondary outcome measures were the Beck Depression Inventory (BDI)[36] and the pain Numeric Rating Scale (NRS).[37] The validated Dutch translation of BDI was used.[38] These are recommended by the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials for emotional and pain components of chronic pain disorders.[39] BDI includes 21 items that evaluate the degree of depression on a 3-point scale (0 = FM does not impact mood; 3 = maximally depressing). The total score of BDI ranges from 0 to 63. In contrast, NRS assesses the subjective severity of pain in a discrete 10-point scale ("How much pain do you feel?" 0 = not at all; 10 = unbearable).

tDCS Stimulation on DLPFC

A battery-driven direct current stimulator (NeuroConn; www.neuroconn.de) was applied on bilateral sides of the forehead that overlie the DLPFC via a pair of saline-soaked surface sponges (7-by-5 cm^2). A constant current of 2 mA was delivered for 20 minutes with a ramp-up time of 10 seconds. The anodal electrode (positive) was placed over the right DLPFC and the cathodal electrode (negative) on the left, with positions determined by the International 10/20 Electroencephalogram System corresponding to F4 and F3 channels, respectively.

ONS Protocol

Using the same device (NeuroConn), a constant current of 1.5 mA was applied for 20 minutes via saline-soaked sponges (7-by-5 cm^2) on the occipital part of the head corresponding to the left and right side of the C2 dermatome. The direct current was ramped up to 1.5 mA in 5 seconds. The anode was placed on the right occipital region and the cathode on the left. Sham stimulation was set up in the same manner. However, the current delivery lasted for 10 seconds instead of 20 minutes.

Statistical Analysis

Age and prestimulation outcome measures were compared between the groups using ANOVA to verify whether their pathologic conditions were equivalent. A repeated measures ANOVA was used to assess the treatment effect on the primary and secondary outcome measures, and the differences between subjects induced by the main effect of stimulation strategies. Prestimulation and poststimulation measures of FIQ, BDI, and NRS have been compared among sham, occipital-only, and prefrontal-added groups. In addition, the likelihood of a treatment effect larger than an improvement of 10% was predicted by the stimulation types using logistic regression, with an improvement of minimum 10% in chronic pain intensity suggesting clinically important changes.[40] The improvement in percentage between prestimulation and poststimulation was defined as (pre−post)/pre×100 (%).

RESULTS

Demographics

ANOVA compared each stimulation group for age and prestimulation measures of FIQ, BDI, and NRS. No significant differences among groups were identified (Table 2). Age showed a score of $F_{2,55} = 0.270$ ($P = 0.76$) and prestimulation FIQ a score of $F_{2,55} = 1.285$ ($P = 0.35$), prestimulation BDI a score of $F_{2,55} = 0.199$ ($P = 0.82$), and prestimulation NRS a score of $F_{2,55} = 0.496$ ($P = 0.61$). Post hoc tests using the Bonferroni method also showed no significant differences of these measures between group pairs.

TABLE 2. Demographic and Clinical Characteristics of the Participants (Mean ± SD)

Variables (Total n = 58)	Maximum	Minimim	CON	ONS	PFC+ONS
Age (y)	69	20	47.19 ± 8.14	47.81 ± 8.23	45.76 ± 10.80
Sex (F/M)	NA	NA	15/1	20/1	20/1
Prestimulation FIQ	94.54	23.04	56.58 ± 13.86	55.80 ± 14.45	50.38 ± 14.85
Prestimulation BDI	42	0	21.75 ± 11.20	21.67 ± 11.57	19.90 ± 8.44
Prestimulation NRS	10	4	6.75 ± 1.39	6.86 ± 1.24	7.19 ± 1.63

BDI indicates Beck Depression Inventory; CON, Sham stimulated; F, female; FIQ, Fibromyalgia Impact Questionnaire; M, male; NA, not available; NRS, Numeric Rating Scale; ONS, Occipital nerve stimulation only; PFC+ONS, PFC stimulated by tDCS and then the occipital nerve was stimulated.

Behavioral Outcome

Repeated measures ANOVA compared the changes in pain scales between prestimulation and poststimulation depending on the stimulation protocols. Dependent variables were prestimulation and poststimulation scores in FIQ, BDI, and NRS, and the independent variables were stimulation protocols.

There was a significant main effect of the stimulation within subjects. The between-subject effect of the stimulation type was only significant for FIQ (Fig. 2, $P = 0.02$) but not for BDI ($P = 0.19$) and NRS ($P = 0.49$). The interaction effect between the stimulation trial and the type of stimulation protocols was significant for all outcome measures, except NRS (Fig. 2, $P = 0.096$). This indicates that "occipital-only" stimulation and "prefrontal-added" stimulation together influence the severity of FM compared with sham. To further contrast the effect size of "occipital-only" and "prefrontal-added" groups against the sham group, the interaction effect between either of the groups and sham was calculated. Table 3 shows that the interaction of stimulation trial and the protocol is significant between the sham and "occipital only" groups for FIQ, BDI, and NRS. For the "prefrontal-added" group, the interaction was significant for BDI with the largest effect size, but trending for FIQ and NRS.

When the contrast matrix of comparing "occipital-only" versus "prefrontal-added" and prestimulation versus poststimulation was used, the prefrontal-added group was found to have no additional effect on improving any of the tested measures. Comparison of FIQ resulted in $F_{1,55} = 0.403$ giving $P = 0.528$, comparison of BDI resulted in $F_{1,55} = 0.629$ giving $P = 0.431$, and comparison of NRS resulted in $F_{1,55} = 0.093$ giving $P = 0.762$.

Responder Rates

Pain score improvement of $> 10\%$ was predicted using logistic regression with the stimulation types (categorical value). For the response of FIQ, an omnibus test for the model showed that the stimulation type tends to distinguish between responders and nonresponders ($\chi^2_2 = 5.818$, $P = 0.055$), with a prediction success rate of 63.8%. The occipital-only group significantly contributed to the improvement ($P = 0.030$), and the prefrontal-added group showed a marginal tendency ($P = 0.056$) in comparison with the sham stimulation group.

In secondary outcome measures, a model for BDI showed that the stimulation significantly distinguishes responders ($\chi^2_2 = 10.891$, $P = 0.004$), with a prediction success rate of 72.4%. Both the occipital-only ($P = 0.015$) and the prefrontal-added groups ($P = 0.003$) significantly contributed to the improvement compared with the sham group. A model for NRS tends to distinguish responders ($\chi^2_2 = 5.265$, $P = 0.072$), with a prediction success rate of 65.5%. Occipital-only stimulation significantly contributed to the improvement ($P = 0.037$), whereas the prefrontal-added group showed a marginal tendency ($P = 0.070$) in comparison with controls.

DISCUSSION

This study used noninvasive direct current stimulation to stimulate the ON, or both prefrontal regions and the ON sequentially to evaluate the difference in the treatment's effect. In general, the tDCS sessions were well tolerated and there were no adverse effects reported, except the reports of tingling and itching sensations. It is demonstrated that electrical direct current stimulation of the ON only or adding prefrontal tDCS beforehand results in significant improvements in the general

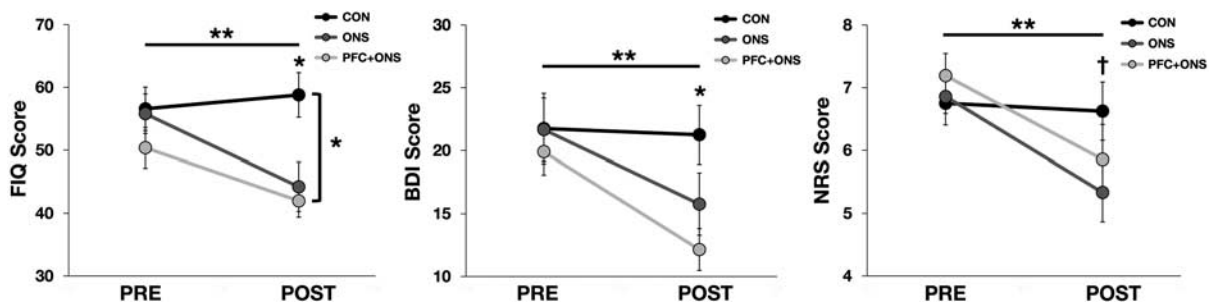

FIGURE 2. Mean scores in pain measured before and after the stimulation. Higher scores indicate higher severity of symptoms. Error bars represent SE. Horizontal bars show statistical significance of the main effect of applying stimulation and vertical bars the between-subject effect of the stimulation type, and the marks on the poststimulation data point the interaction effect of stimulation trials and protocols in repeated measures analysis of variance. BDI indicates Beck Depression Inventory; CON, sham stimulated; FIQ, Fibromyalgia Impact Questionnaire; NRS, Numeric Rating Scale; ONS, occipital nerve stimulation only; PFC+ONS, PFC stimulated by transcranial direct current stimulation and then the occipital nerve was stimulated. †$P < 0.1$, *$P < 0.05$; **$P < 0.01$.

TABLE 3. Primary and Secondary Outcomes at Prestimulation and Poststimulation Periods

	ONS				PFC+ONS			
Outcome Measures (Mean ± SD)	**Pre**	**Post**	$F_{1,55}$	**Effect Size**	**Pre**	**Post**	$F_{1,55}$	**Effect Size**
FIQ	55.80 ± 14.45	44.22 ± 18.02	6.547*	0.344	50.38 ± 14.85	41.98 ± 11.88	3.875†	0.266
BDI	21.67 ± 11.57	15.76 ± 9.90	4.606*	0.289	19.90 ± 8.44	12.14 ± 7.64	8.315**	0.388
NRS	6.86 ± 1.24	5.33 ± 2.15	4.331*	0.281	7.19 ± 1.63	5.86 ± 2.54	3.232†	0.241

The treatment effect is compared between each group and sham by the interaction effect and its effect size in Cohen *f*.

BDI indicates Beck Depression Inventory; FIQ, Fibromyalgia Impact Questionnaire; NRS, Numeric Rating Scale; ONS, Occipital nerve stimulation only; PFC+ONS, PFC stimulated by tDCS and then the occipital nerve was stimulated; Post, poststimulation; Pre, prestimulation.

†$P < 0.1$.

*$P < 0.05$.

**$P < 0.01$.

severity (FIQ), mood state (BDI), and pain degree (NRS) in FM compared with sham stimulation. However, the 2 stimulation protocols do not demonstrate differences in the degree of the treatment's effect. In other words, adding bifrontal tDCS does not improve the effect obtained with isolated ON-tDCS. In short, the addition of tDCS on DLPFC did not benefit FM patients in any of the outcome measures more than ON-tDCS did. However, it seems to work on subcomponents of FM differently compared with ONS.

FM is a pain syndrome with central sensitization characterized by an imbalance between pain-suppressing and pain-provoking pain pathways.[13,41] To target these pathways, ON-tDCS very likely transmits the current via the C2 spinal nerve, which is functionally connected to the ascending[42] and opioidergic descending pain pathway.[23,24] Indeed, the C2 area in the spinal cord is in a unique position, processing both ascending external sensory information and information via the descending periaqueductal gray-rostral ventromedial medulla-spinal opioidergic pathway, which selectively gates sensory information.[43] One of the important neural correlates in FM is the pregenual anterior cingulate cortex, which is active during pain relief (analgesia) and is also activated by ONS.[44] However, the functional connectivity between the pregenual and dorsal anterior cingulate cortex suggests that rather than a mere deficiency of the pain-inhibitory pathway, FM is related to an imbalance between pain-inhibitory and pain-provoking pathways.[13] Indeed, the dorsal anterior cingulate cortex is known to encode salience,[45] which is also correlated to the salience for pain,[46] permitting near-threshold nociceptive stimuli to become detected.[47] Together, this suggests that ON-tDCS alleviates pain by the integration of multiple circuits.[48] In other words, top-down prediction of pain may be maintained by the prevention of resolving the mismatch with the real sensory information by bottom-up modulation, which presents itself as salience of pain.

The treatment effect of ON-tDCS in the present study reflects its generality. Sole ON-tDCS appears to be sufficient to induce the treatment effect in not only the general index of FM severity but also in subcomponents of pain and emotion. This result is consistent with previous studies that showed the reduction of various pain-related symptoms,[15,22] as well as the pain component itself.[49] ON-tDCS was implied in enhancing the pain inhibition and reducing the affective component of pain,[13] and this interaction is known to improve the emotional valence.[50] In other words, ON-tDCS may improve emotional aspects of pain via alleviating the pain sensation.[51]

The DLPFC is another stimulation target in pain treatment,[25,52] and its active modulation of opioidergic pathways is known to induce changes in pain perception without effective external medications.[53] In support of this, its structural connectivity to periaqueductal gray is found to be a distinct indicator of descending pain modulation.[54] However, there was no additional effect of stimulating the DLPFC before ON-tDCS. One possibility is that the mechanisms of action in stimulating the DLPFC interferes with those of ON-tDCS, instead of being beneficial. DLPFC has been implicated in both the affective-cognitive pain modulation via connectivity to the anterior cingulate cortex and insula,[53] and subcortical structures such as periaqueductal gray and the thalamus.[26,55] In line with this mechanism, a functional imaging study found that anodal stimulation on left DLPFC induces a decrease in connectivity between left DLPFC and the thalamus.[56] Stimulating DLPFC may have reduced the pain by disconnecting the pain sensory information from being realized,[57] whereas the subsequent ON-tDCS tried to restore the balance between the inhibition and the realization of the pain.[13] Therefore, we surmise that stimulating DLPFC may only reduce the degree of pain information so that retrieving the balance of its remainder is not additionally effective.

The DLPFC also appears to be an effective target of neuromodulation techniques for enhancing emotion regulation.[58] One suggested mechanism of action of tDCS on DLPFC relates to its capacity to increase working memory,[59] which is demanded by the reappraisal of negative states such as pain.[60,61] However, such reappraisal is an active process that constantly refers to the current situation.[62] The anterior insula is a central neural correlate in the salience network that provides pain information,[46,63,64] and it appears to have a negative correlation in activity level to the reappraisal that is driven in DLPFC.[65] In addition, the perception of pain via the salience network is downregulated after ON-tDCS,[13] and such an effect will also update the state of reappraisal, depending on the input of external information. It suggests that the enhancement of reappraisal by tDCS on DLPFC and the normalization of salience network by ONS overlap in the mechanism of action make the addition of DLPFC stimulation obsolete.

This study has some limitations with regard to the study design and model. It is important that our results should be tested after applying minor changes to the stimulation protocol, especially the polarity of stimulation on the prefrontal cortex, which shows variable results.[66] Utilizing the transcranial random noise stimulation instead of tDCS is another possibility, as it can provide polarity-neutral stimulations on DLPFC, as well as on the C2 nerve. Another limitation is that we have not tested the temporal

dependence of stimulating multiple targets by applying the stimulation on DLPFC and the ON simultaneously instead of using the sequential protocol. It is also noted that the tDCS operator was not blinded while stimulating the participant. Further studies with randomized double-blind designs will be useful in confirming our results. Finally, using tDCS also has methodological limitations in terms of spatially locating the position of the electrodes. This may be improved by performing an a priori computational simulation or with the aid of functional imaging studies that are coupled with tDCS. Finally, a conventional tDCS has the possibility of skin-shunting effects.[67] A future study using high-definition tDCS that resolves such technical problems[68] is suggested.

In summary, the application of tDCS on DLPFC in addition to ON-tDCS was found to have no advantages over isolated ON-tDCS for treating FM. Both primary and secondary outcome measures were improved by either ON-tDCS or DLPFC+ON-tDCS protocols, but the difference between 2 protocols was insignificant. Current results suggest that applying ON-tDCS by itself is sufficient to treat FM symptoms including its emotional subcomponents, showing its clinical benefits. Our study is the first to evaluate the clinical benefits of applying tDCS on DLPFC in addition to ON-tDCS in FM. Further studies are needed to investigate long-term effects on pain and mood induced by tDCS on DLPFC, and the order effect of adding it to ONS.

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