Effects of transcranial direct current stimulation on physical and mental health in older adults with chronic musculoskeletal pain: a randomized controlled trial

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Key summary points
Aim of the study Investigated the effects of transcranial direct current stimulation combined with physical therapy on pain levels, physical activity levels, quality of life, and depression in older adults with chronic musculoskeletal pain.
Findings Our results showed that the active group yielded greater improvements in all the measured scores compared to the sham group.
Message These results suggest a positive effect of transcranial direct current stimulation combined with physical therapy in the reduction of chronic pain in older adults.

Abstract
Purpose We investigated the effects of transcranial direct current stimulation (tDCS) combined with physical therapy (PT) on pain levels, physical activity levels, quality of life, and depression in older adults with chronic musculoskeletal pain.
Methods Twenty-five older adults (9 males and 16 females), aged between 66 and 86 years (active group 77.2 ± 3.9; sham group 76.6 ± 6.2), volunteers were randomly allocated in the active (active tDCS + PT) and sham groups (sham tDCS + PT), and received the intervention three times per week for 8 weeks. Pain level, physical activity level, depression state, and quality of life were assessed based on the Visual Analog Scale (VAS), Physical Activity Scale for the Elderly (PASE), Beck Depression Inventory (BDI) scale, and Short-Form 36 Health Survey Questionnaire (SF-36), respectively. Measurements were conducted four times: at baseline, mid-intervention, post-intervention, and 1-month follow-up.
Results As a result, at 8 weeks, the active group yielded greater improvements in VAS, BDI, and SF-36 scores than the sham tDCS group. At follow-up, the tDCS group led to a greater improvement in VAS, PASE, and SF-36 scores compared to sham tDCS group (p < 0.05).
Conclusion Our results suggest a beneficial effect of tDCS combined with PT in older adults with chronic musculoskeletal pain in the reduction of pain sensation, increment of physical activity level, increment of the quality of life, and reduction of depression incidents. This opens the possibility the possibility of using tDCS as a regular treatment for this population’s physical and mental health.


**Introduction**

One of the most common forms of pain is chronic musculoskeletal pain (CMP). Chronic musculoskeletal pain is defined using the proposed International Classification of Diseases 11th Revision (ICD-11) classification system as “persistent or recurrent pain that arises as part of a disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s)” [1]. It is a highly prevalent, disabling, and costly condition, with a substantial socioeconomic burden to individuals, employers, health care systems, and society [2–5]. The prevalence of CMP is strongly age related [6], and it is commonly accompanied by the reduction of physical activity, owing to pain and body function limitations. Specifically, the older adults can feel the burdens of this condition, which are even more limiting, affecting their quality of lives, and often lead to depression [7].

Medication is the most used method for the treatment of CMP, as well as depression. Among the type of medications used are anti-inflammatory, antidepressants, and musculoskeletal laxatives. However, excessive drug treatment is risky as it can cause several side effects, including lack of tolerance, physical dependence, addiction, gastrointestinal or central nervous system-related adverse events, constipation, nausea, somnolence, and, in some cases, death [8]. As an alternative to drugs, physical therapy (PT) has been extensively used for the treatment of pain control. PT treatments include methods that utilize physical agents such as heating pads, ultrasound, and electrotherapy. In addition, neurostimulation techniques have also been considered as a treatment: electroconvulsive therapy [9], vagal nerve [10], deep brain [11], repetitive transcranial magnetic (rTMS) [12], and magnetic seizure therapy and transcranial direct current stimulation (tDCS) [13]. These forms of brain stimulation appear to be effective not only in the treatment of chronic pain but also for depression and for the improvement of quality of life.

Among the previously mentioned neurostimulation techniques, tDCS is still considered to be a new but promising novel technique. It is a noninvasive brain stimulation technique based on the application of a weak electrical current over the scalp through the use of two electrodes. It is highly considered to be an appealing intervention as part of electrotherapy, with distinct characteristics such as noninvasiveness, low cost, ease of use, and its capacity to exert powerful effects on cortical excitability [13].

According to previous studies, tDCS treatment has been found to be more effective when tDCS and other interventions were used in combination [13–16]. Training programs combined with tDCS exist, but conventional PT programs have rarely been combined with tDCS. Furthermore, previous studies were limiting in that the intervention was only applied to a few sessions of tDCS, thus suggesting the necessity of longer term interventions to achieve greater results in future research.

Taking this into consideration, this study attempts to combine tDCS with conventional PT and assesses the combined long-term effect of both treatments in pain levels, physical activity levels, quality of life, and depression in the older adult population with CMP. Furthermore, the implementation of this experimental study during the coronavirus disease (COVID-19) pandemic is important, because these levels of physical activity in the older adults fell during this time and thus resulted in increased pain, depression, and a decrease in their overall quality of life.

**Methods**

**Participants**

This study was approved by the institutional review board of Korea University (KUIRB-2020-0087-01) and it was conducted in compliance with the 1964 Declaration of Helsinki. The trial was performed at the Korea University of Seoul, Korea. Participants agreed to participate by signing an informed consent after they received a general explanation of the purpose and processes of the study, and they were briefed on any possible discomfort they would possibly experience during the intervention. They were allowed to leave the study at any time without negative repercussions.

Participants that met the following criteria were included in the study: (1) CMP that lasted more than 3 months and (2) older adults who did not have difficulty moving in daily life (> 65 years old). Participants with the following criteria were excluded from the study: (1) bipolar disorder; (2) drug or alcohol dependence or abuse; (3) neurological disorders, such as epilepsy, Alzheimer disease and other dementias, stroke, multiple sclerosis, Parkinson’s disease, neuroinfections, brain tumours or traumatic disorders of the nervous system; and (4) medical conditions, such as rheumatological diseases (Osteoarthritis, Rheumatoid arthritis, Lupus, Sjogren’s syndrome, Gout, Scleroderma, Infectious arthritis, Juvenile idiopathic arthritis, Polymyalgia rheumatica) (5) Consumption of antidepressants or analgesics at the time of recruitment.
Experimental design

This study was a randomized, single-blinded, sham-controlled trial that was designed to evaluate the effectiveness of 8-week sessions (three times per week) tDCS and PT in combination and the lasting effects 4 weeks after the conclusion of the intervention (follow-up test) in the older adults with CMP. A computer-generated list was used to distribute the participants randomly in one of the two possible groups at a ratio of 1:1, namely, in the active (active tDCS + PT) or sham (sham tDCS + PT) groups (Fig. 1). The participants were completely blinded regarding the group identity they belonged to until the completion of the study and data processing.

Intervention

Participants who met the inclusion criteria received a total of 24 interventions during an 8-week period (3 times per week). The participants received active tDCS or sham tDCS combined with PT. Wireless rechargeable tDCS device (Y-brain Inc., Seoul, Korea) with anode and cathode electrodes (diameters: 6 cm) covered by saline solution-soaked sponges was used. The stimulation intensity was set to 2 mA for 30 min. In both groups, anode electrodes were placed over the left dorsolateral prefrontal cortex (DLPFC), and cathode electrodes were placed over the right DLPFC [17]. Both electrodes were fixed using rubber bandages. In the sham group, the electrode montage was equal to that of the active group. However, the tDCS was turned off after 30 s of stimulation. The participants were instructed to stop the experiment at any time if they experienced any discomfort (headache, itching, tingling, or burning sensations) while they received tDCS. PT on the pain site was conducted by two physical therapists right after the tDCS application was concluded. The personalized PT intervention included: manual therapy, exercises, and the used of physical agents, such as hot-packs, ultrasound, and interferential current therapy [18–20].

Outcome measures

The participants took part in four evaluation sessions: (1) baseline (right before any intervention was conducted), (2) mid-term test (at 4 weeks during the intervention period), (3) post-test (immediately after the last session was concluded), and (4) follow-up test (1 month after the last intervention). The tests were performed by two physical therapists who had more than 3 years of experience.

Pain intensity was assessed with the use of the visual analog scale (VAS). This is a method that grasps the degree of pain, and the pain felt at the time of evaluation was written on the ship. It consisted of bidirectional 10-cm straight lines with two labels, that is, “no pain” and “worst possible pain,” located at either end of the line. Patients were instructed to draw a vertical mark on the line, which indicated their pain levels [21].

Physical activity was analyzed as a second indicator of pain based on the use of the Physical Activity Scale for the Elderly (PASE). This was weighted according to the type of physical activity and consisted of a total of ten questions (leisure hour activities, six questions; domestic household activities, three questions; and work-related activities, one question) [22, 23]. The total scores ranged from 0 to 360, and higher scores indicated greater physical activities. A validated Korean version of the PASE test was used [22].

Health-related quality of life was assessed by the 36-item Short-Form Health Survey Questionnaire (SF-36). The participants were given a validated Korean version of the test [24]. This consisted of 36 items and 9 subscales, including general health (5 items), health transition (1 item), physical functioning (10 items), role-physical (4 items), role-emotional (3 items), social functioning (2 items), bodily pain (2 items), vitality (4 items), and mental health (5 items). Higher
scores on all SF-36 subscales indicate more favorable levels of functioning [25].

Depression was evaluated through a validated Korean version of the Beck Depression Inventory-II (BDI-II)[26]. This is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed. There is a 4-point scale for each item, which ranges from 0 to 3. Higher total scores indicate more severe depressive symptoms [27].

Statistical analysis

All the statistical analyses were executed using the statistical software package SPSS (version 25, IBM, NY, ISA). The Shapiro–Wilk test was used to examine whether the data were normally distributed. Additionally, Mauchly’s test was used to check for sphericity violations. If the Mauchly’s test result was violated ($p < 0.05$), the Greenshouse–Geisser corrected $p$ values were applied. A 2 × 2 (Group × Time) two-way repeated-measures analysis of variance (ANOVA) was used to assess differences in dependent variables (VAS, BDI, PASE, and SF-36).

Results

Twenty-five older adults (active group: male = 4/female = 9; sham group: male = 5/female = 7), aged between 66 and 86 years (active group 77.2 ± 3.9; sham group 76.6 ± 6.2) participated in the study. The demographic characteristics at baseline are listed in Table 1. CMP in participants was identified in the following body parts: wrists ($n = 1$), neck ($n = 1$), shoulders ($n = 7$), lumbar spine ($n = 11$), and knees ($n = 5$). No significant differences were observed between active group and sham group regarding their mean age, weight, height, and body mass index (BMI).

Comparisons of the changes in the outcome measurements from the baseline to follow-up between the active and sham groups are presented in Tables 2 and 3.

VAS

The two-way repeated-measures ANOVA results for VAS showed a significant effect of time of $p < 0.05$ and also between time and group ($p < 0.05$). Even though the sham group showed a tendency to decrease the VAS scores, it was not statistically significant after analyzing each period. Conversely, the active group showed significant changes between baseline and post-test scores ($p < 0.01$) and between baseline and follow-up scores ($p < 0.01$).

PASE

The two-way repeated-measures ANOVA yielded a significant main effect of time ($p < 0.05$) and a significant interaction effect of time and group ($p < 0.05$). Considering each evaluation period, PASE scores in the sham group tended to increase, but the changes were not significant in comparison with the baseline. In the case of the active group, only the comparison between baseline and follow-up scores yielded a significant difference ($p < 0.03$).

SF-36

For SF-36 periods, the two-way repeated-measures ANOVA yielded a significant main time effect with $p < 0.05$ and also a significant interaction effect of time and group ($p < 0.05$). Differences between each period of time were found in the active group with significant changes between baseline and post-test ($p < 0.02$) and baseline and follow-up ($p = 0.02$). Even though the sham group scores yielded a tendency to increase, they were not statistically significant.
BDI

For BDI periods, the two-way repeated-measures ANOVA yielded a significant main time effect ($p < 0.05$) and also a significant interaction time and group effect ($p < 0.05$). After each period was analyzed, the active group exhibited significant improvements only between baseline and post-test scores with $p < 0.01$. The sham group did not show any significant changes between periods.

Discussion

The current study tested the efficacy of tDCS in conjunction with PT in older adults with CMP during the COVID-19 pandemic period based on a randomized, sham-controlled design. The outcome measures showed significantly greater results in the active group than in the sham group for the reduction of pain, improvement of physical activity, quality of life, and depression.

The findings of the study indicate the superior feasibility and clinical efficacy of tDCS combined with PT for the treatment of CMP compared with sole PT intervention. Based on the increment of the sham group scores, and the significant changes found in the VAS scores for the active group, it can be observed that even though PT influenced pain, it was combined with tDCS more effectively.

These results can be explained by the neuromodulator effect of the tDCS over the DLPFC. It is known that the DLPFC contributes to the cognitive process of experiencing pain, especially that related to pain prediction, evaluation, and reinterpretation, and that painful stimulus can activate patterns on the DLPFC, suggesting that this zone has an essential role in the interpretation of pain. Studies of neuroimaging have proven that the reduction in pain levels could be attributed to the connection between this area and other pain perception areas (the cingulate cortex, insula, amygdala, and thalamus) [28]. One theory related to the fact that the application of tDCS over the DLPFC can produce an indirect inhibitory modulation of the thalamic activity, which alleviates pain after the stimulation [29]. Another theory is that chronic pain can produce maladaptive neuroplasticity, thus leading to an imbalance in attentional and cognitive resource allocation. This creates pain misperception. The effect of tDCS over the DLPFC could induce an inhibition of this maladaptive problem leading to pain reduction [30, 31]. Clinical trials have used tDCS for the reduction of pain in patients with fibromyalgia, thus yielding similar results to the ones found in this study. A study found that after 12 weeks of home-based tDCS, there was a 62.05% reduction in the accumulative pain scores [32]. Another study showed how one session of tDCS combined with a go/no-go task was effective in reducing pain and how it affected positively other aspects related to the existed pain [29].

Physical activity, quality of life, and depression are all parameters that are directly influenced by pain and its consequent limitations [33–35]. The increment found in the PASE scores for the active group correlated with the reduction of the VAS scores. Physical activity was found to be avoided for people with chronic pain, because it was often associated with pain-related fear. This means that patients with chronic pain tend to avoid physical activity for fear of feeling more pain or causing re-injury [33]. The reduction of pain achieved after the tDCS + PT intervention is the principal factor that influences the PASE scores’ growth. Moreover, depression and quality of life scores also yielded positive improvements, which correlated not only with pain reduction but also with physical activity improvements. This can be supported by a study conducted in patients with fibromyalgia, wherein after increasing

| Group | Baseline | Mid-test | Post-test | Follow-up |
|-------|----------|----------|-----------|-----------|
|       | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|       | $p$       | $p$       | $p$       | $p$       |
| PASE  |          |          |           |           |
| Active| 146.84 ± 21.05 | 136.58 ± 17.10 | 161.60 ± 29.94 | 167.80 ± 25.11 |
|       | 0.630     | 0.576     | 0.258     | 0.030*    |
| Sham  | 132.00 ± 21.91 | 127.86 ± 17.81 | 156.96 ± 31.16 | 141.69 ± 26.14 |
| SF-36 |          |          |           |           |
| Active| 54.21 ± 5.68 | 59.95 ± 5.67 | 64.25 ± 5.71 | 62.04 ± 5.65 |
|       | 0.994     | 0.163     | 0.022*    | 0.015*    |
| Sham  | 54.15 ± 5.90 | 58.70 ± 5.90 | 58.36 ± 5.94 | 58.02 ± 5.88 |
| BDI   |          |          |           |           |
| Active| 13.39 ± 2.74 | 11.23 ± 2.47 | 9.08 ± 2.03 | 10.92 ± 2.33 |
|       | 0.617     | 0.176     | 0.014*    | 0.073     |
| Sham  | 14.17 ± 2.85 | 15.08 ± 2.57 | 15.42 ± 2.11 | 15.58 ± 2.43 |

Table 3: Mean ± SD of the Physical Activity Scale for the Elderly, Short-Form 36, and Beck Depression Inventory for the active and sham groups

There were no significant differences at baseline between the groups.
their levels of physical activity, their depression scores were reduced in comparison with baseline scores [35]. In addition, another study that assessed changes in quality of life after the application of active tDCS found a correlation between pain reduction and improvements in the quality of life [36].

Following the results obtained in this study, the use of tDCS over the DLPFC combined with PT showed the effectiveness of this treatment for pain reduction and the enhancement of its associated problems, such as depression, low-physical activity levels, and the degradation of the quality of life, in older adult participants with CMP. Furthermore, the advantages of tDCS as a possible common technique in PT include the facts that it is inexpensive, is easy to prescribe, and has fewer side effects. However, it is necessary to consider that after or during the use of tDCS, the participant may perceive itching and tingling sensations (not all the participants reported these sensations). After taking the right considerations and precautions before its use, tDCS can be considered an excellent treatment tool for this type of population. Nevertheless, to commercialize tDCS, more studies with a larger number of participants and a prolonged period of intervention are needed in the future.

In addition, since 2019, the world population has faced the outbreak of the coronavirus disease (COVID-19). During the pandemic, social isolation has been enforced in an attempt to stop the spread of the virus. Nevertheless, this measure has limited the ability of individuals to perform their normal daily activities and has, therefore, restricted people from exercising outdoors or in gyms. This has led to an increased CMP, a characteristic of a sedentary lifestyle. Additionally, it has been proven that in this period, the likelihood of developing depression has increased and quality of life has reduced considerably in the older adult population [37, 38]. Therefore, the results of this study can impulse a more completed treatment for reduction of pain and depression; and influent the increase of physical activity and quality of life during these new times.

The study’s main limitation was the local government’s requirement for a quarantine period during the first weeks of the intervention. The COVID-19 pandemic situation in Seoul, South Korea (the city in which the study was conducted), worsened during the recruitment of participants and implementation of this study. The country’s population was asked to stay at home to prevent the virus from spreading further, and the participants were only allowed to leave their homes for short time periods, including periods during which they received the intervention. Therefore, there was a brief reduction in the PASE scores associated with the two groups as a result of these environmental changes, regardless of the intervention.

Conclusions

During the COVID-19 pandemic, the population around the globe was affected by the isolation periods. The most affected subgroup of the population is the older adults. Based on the findings, the tDCS + PT intervention was shown to be more effective in the reduction of pain in older adults with CMP than was the PT intervention alone. In addition, the PASE, BDI, and SF-36 scores, which are directly correlated with the variances of pain, exhibited improvements in the active group. It can be concluded that tDCS over the DLPFC combined with PT is effective in achieving reduced pain sensation, can generate an associated positive impact in the increment of physical activity, can increase the quality of life, and can thus reduce the number of depression incidents.

Authors contribution All authors contributed to the study in the following roles: Seungmin Kim: conceptualization, methodology, writing—original draft. Jhoseydn Carolym Salazar Fajardo: data curation, writing—review and editing, visualization. Eunyoung Seo: investigation. Chang Gao: investigation. Rockhyun Kim: project administration. BumChul Yoon: conceptualization, supervision

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest

Ethical approval This study was approved by the institutional review board of Korea University (KUIRB-2020-0087-01) and it was conducted in compliance with the 1964 Declaration of Helsinki. The trial was performed at the Korea University of Seoul, Korea.

Consent to participate Participants agreed to participate by signing an informed consent after they received a general explanation of the purpose and processes of the study, and they were briefed on any possible discomfort they would possibly experience during the intervention. They were allowed to leave the study at any time without negative repercussions.

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