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# Noninvasive brain stimulation over dorsolateral prefrontal cortex for pain perception and executive function in aging

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ABSTRACT

*Objectives:* Based on the evidence that the dorsolateral prefrontal cortex (DLPFC) is the main region affected by the aging process, and that tDCS modulates cortical excitability, the aim of the study is to prove the feasibility of tDCS for pain perception and executive function of community-dwelling elderly individuals.
*Methods:* We performed a double-blind, single-arm trial, including a sham period. 5 consecutive anodal tDCS was applied over DLPFC of twenty-four elderly for 20 min during each intervention periods (in order of Sham-1 mA–2 mA). First, we classified chronic non-inflammatory pain sites into three domain (Neck and upper extremity, low back, lower extremity). Then, we used visual analogue scale, pain self-efficacy scale, Tampa scale for kinesiophobia, and Global perceived Effect scale to observe the change in pain perception, as well as Trailing Making Test and Timed Up and Go (dual) to observe the change in executive function. The changes in maximal grip strength and 12-item Short Form survey were measured secondarily.
*Results:* In the results, we observed significant improvement in pain perception and quality of life, while executive function and grip strength did not change significantly.
*Conclusion:* Our findings demonstrated the feasibility of tDCS for aging-related pain perception and suggest that further randomized controlled trials with longer duration are necessary to examine the effects on executive function.

## 1. Introduction

Chronic pain is one of the major issues affecting the health of elderly individuals, with a prevalence of more than 50% in the aging population (Patel, Guralnik, Dansie, & Turk, 2013). Among the types of chronic pain, Korea centers for Disease Control and Prevention (KCDC) reported that musculoskeletal pain accounted for 90% of the cases of chronic pain in elderly individuals in South Korea (Jung, Park, Kim, & Park, 2015) as compared to others countries (Donald, 2004; Mailis-Gagnon, Nicholson, Yegneswaran, & Zurowski, 2008). In the elderly population, pain is characterized by multiple trigger sites (Patel et al., 2013). and an association with the level of cognition (Whitlock et al., 2017); it is reported as the most common risk factor of disability (Covinsky, Lindquist, Dunlop, & Yelin, 2009; Melzer, Gardener, & Guralnik, 2005), which results in loss of physical health in terms of activities of daily living, psychosocial problems owing to fear of movement (Meier et al., 2016), depression, (Casten, Parmelee, Kleban, Lawton, & Katz, 1995) and reduced quality of life (Hopman-Rock, Kraaimaat, & Bijlsma, 1997).

In studies of brain imaging, the prefrontal cortex (PFC) has been documented as the main structure vulnerable to aging, with effects such as functional decline in pain processing (Farrell, 2012; Raz, Rodrigue, & Haacke, 2007) as well as the executive system, which utilizes attention and memory (Holtzer et al., 2011; Mandrick et al., 2013). Recently, the decline in the pain control has been reported to be associated with cognitive processes in older adults, and these findings indicate the effects of aging on the structure and function of the PFC (Marouf et al., 2014). In addition, other review article documented the considerable similarities in the loss of neurocognitive integrity through neuroanatomical changes in aging and those in chronic pain (Oosterman & Veldhuijzen, 2016). In other words, the decrease in gray matter of the PFC and anterior cingulate cortices was pronounced in the both conditions and, naturally, the subsequent loss in pain control and cognitive function were also similar in both conditions. Overall, despite the functional connectivity of the PFC and the clinical similarities, the problems with regard to chronic pain and cognitive function associated

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**Table 1**
Intervention periods for transcranial direct current stimulation (tDCS).

| **T0** | D1 | D2 | D3 | D4 | D5 | D6 | **T1** | D1 | D2 | D3 | D4 | D5 | D6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| · Consent Reception · Precaution Explanation | | | | | Pre tDCS evaluation | | | ⟵ Sham → | | | | | Post tDCS evaluation |
| **T2** | D1 | D2 | D3 | D4 | D5 | D6 | **T3** | D1 | D2 | D3 | D4 | D5 | D6 |
| | ⟵ 1ma → | | | | Post tDCS evaluation | | | ⟵ 2mA → | | | | | Post tDCS evaluation |

D: day; T0: Pre-tDCS; T1: Post-sham current; T2: Post-1 mA; T3: Post-2 mA.

with the aging process are treated individually using bottom-up approaches.

Based on the changes in the activation pattern in the brain during aging (Mirelman et al., 2017), transcranial direct current stimulation (tDCS) is a promising tool as a non-invasive and top-down approach to directly stimulate the brain with a low-intensity current and to modulate cortical excitability. In the studies on tDCS for reducing pain, primary motor cortex (M1) was usually targeted in various types of pain (Antal, Terney, Kuhnl, & Paulus, 2010; Fregni et al., 2006; Volz, Farmer, & Siegmund, 2016) by regulating the cortical excitability (Hoogendam, Ramakers, & Di Lazzaro, 2010) and the concentration of gamma-Aminobutyric acid (GABA) neurotransmitter at the synaptic level (Stagg et al., 2009).

On the basis of the above-mentioned evidence and a recent article reviewing the role of PFC and the relevance as a target location for age-related chronic pain (Seminowicz & Moayedi, 2017) and executive function, we applied anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) in elderly individuals.

In this study, we observed variables related to pain perception such as pain intensity, fear of movement, and self-efficacy, and those related to executive function, such as working memory and dual-tasking. Secondarily, grip strength and quality of life, which are likely to be affected by chronic pain and aging, were also evaluated.

## 2. Methods

### 2.1. Participants

Twenty-four volunteers (6 men, 18 women, 71.25 ± 4.54 yr) participated in the study. Inclusion criteria were as follows: 1) non-inflammatory musculoskeletal pain related to the aging process as defined in a previous study (Zis et al., 2017), 2) pain duration more than three months, 3) a single area or at more than two sites among 18 musculoskeletal locations on the body (Haukka et al., 2013; Pensola, Haukka, Kaila-Kangas, Neupane, & Leino-Arjas, 2016). Exclusion criteria were as follows: 1) past experience of tDCS, 3) a history of surgical operation or injection in the past six months, 4) pain due to acute traumatic injury or ongoing inflammation (Mallen et al., 2013), 5) less than 3 scores on the visual analogue scale 6) difficulty in communication owing to cognitive problems, and 7) illiteracy. All participants provided written informed consent before enrolling in the study. The experimental protocol was approved by the Institutional Review Board of the Korea University (KU-IRB-17-126-A-2).

### 2.2. Classification of pain sites

Participants were asked two questions: First, “For how long have you experienced the current pain?” and second, “Did you have pain in a specific area or at more than two sites among the 18 body locations that you can see?” (Zis et al., 2017; Haukka et al., 2013). Then, they described the pain sites on an evaluation sheet. All pain sites of the participants were classified into three subgroups: 1) neck and upper extremity, 2) low back, and 3) lower extremity. In the case of a participant who had more than two pain sites, the participant belonged to more than one subgroup.

### 2.3. tDCS

A transcranial direct current stimulator transmitting a current via two $5 \times 5\ cm^2$ electrodes with a saline-soaked synthetic sponge was used for applying sham or anode current to the left PFC over a period of two weeks. Before turning on the stimulator, according to the international 10–20 EEG system montage, anode electrodes were placed on the left DLPFC, applicable F3 in the system, and cathode electrodes were placed on the contralateral supraorbital area, applicable Fp2 in the system. We scheduled each participant to receive tDCS at the same time from 09:00 AM to 12:00 PM.

### 2.4. Experimental protocol (Table 1)

All participants received the same experimental protocol. We evaluated participants a total of 4 times, including one pre-tDCS evaluation and three post-tDCS evaluations. Pre-tDCS evaluation (T0) was performed 2 days before the intervention period. During the first week of the intervention period (T1), all participants received sham current for five consecutive days, with one intervention period comprising 20 min over one week, to identify the placebo effects in the variables. During the second week (T2), we applied a 1-mA current in the same way. During the third week (T3), a 2-mA current was used in the same manner. Both participants and assessors were blinded to the current polarity types.

In all experiments, any adverse effects that the participants experienced were recorded using a self-reported questionnaire.

### 2.5. Primary outcomes

#### 2.5.1. Pain perception

*2.5.1.1. Visual analogue scale (VAS) and pain self-efficacy questionnaire (PSEQ).* VAS was measured for evaluating pain intensity. Participants marked their level of pain for each pain site during last 5 days on a line from 0 cm (no pain) to 10 cm (unbearable pain) at baseline and in each intervention period (sham-1 mA-2 mA). PSEQ was used at baseline and in each intervention period for evaluating self-confidence for 10 items indicating daily activities. Each item was rated on a 7-point Likert scale from score 0 meaning “completely no confidence” to score 6 meaning “completely confidence.”

*2.5.1.2. Tampa scale for Kinesiophobia (TSK).* The TSK was used for evaluating the patient’s behavioral characteristics in terms of fear of pain. Each question was rated on a 4-point Likert scale from score 1 indicating “strongly disagree” to score 4 indicating “strongly agree”. The TSK was subdivided into three components, TSK-total scores, TSK-

**Table 2**
Participants' demographic characteristics.

| Characteristics | Values |
|---|---|
| Male/female | 6/18 |
| Age (y) | 71.25 (4.54) |
| Multisite pain /single-site pain (n) | 18/6 |
| Category of pain sites | |
| Neck and upper extremity (n) | 9 (19.4) |
| Low back (n) | 22 (38.9) |
| Lower extremity (n) | 16 (41.7) |
| Pain duration (month) | 94.04 (99.08) |
| Time spent during activities of daily living per week (min) | 211.25 (126.78) |

Values are Mean (SD).

AA (activity avoidance), and TSK-SF (somatic focus), as proposed in previous studies (Roelofs et al., 2007).

*2.5.1.3. Global perceived effect scale (GPES).* After all experiments, the participants indicated their satisfaction with regard to tDCS by using scores, with score 1 meaning "very satisfied" and score 5 meaning "very dissatisfied". GPES was also measured at baseline and in each intervention period for evaluating the participant's perception regarding pain improvement, by asking "how much has the pain improved compared to the pain at onset?" For GPES, participants marked a score on an 11-point Likert scale. Score 0 indicated "no effect", a score ranging from +1 to +5 indicated the magnitude of positive effect, and a score ranging from −1 to −5 indicated the magnitude of negative effect.

*2.5.2. Executive function*

*2.5.2.1. Trail making test (TMT) and timed Up and Go dual (TUG dual).* TMT and TUG dual test were used to observe the change in working memory and dual-tasking in the elderly individuals. For TMT, the participants were asked to answer two types of questionnaires (Part A for attention, B for working memory). For the TUG dual task, measurements were performed three times, and the values obtained were averaged. Participants were asked to rise from a chair, walk three meters, turn back, and then sit again as fast as possible while they counted backward aloud from an initial number, which was selected randomly from a range of 100 to 50.

### 2.6. Secondary outcomes

*2.6.1. Maximal grip strength (MGS)*

MGS was the representative measurement used to evaluate general health status. For MGS, a grip strength dynamometer (DW-781, Daewoo sport industry Inc., Korea) was used; measurements were performed three times and averaged. All participants performed maximal voluntary gripping with the dominant hand for 3 s in sitting position with the elbow at 90-degree flexion. If participants had pain in the upper extremity, which could negatively influence the grip strength, we performed measurements with the opposite pain-free hand instead.

*2.6.2. The 12-item short form survey (SF-12)*

SF-12 is a brief version of SF-36 used to evaluate quality of life and perception of health status. (Jakobsson, 2013) It consists of 12 items, with questions on difficult experiences with regard to physical and mental health during a month.

### 2.7. Intervention satisfaction

A 5-point Likert scale from score 1 meaning "very satisfied" to score 5 meaning "very dissatisfied" was used. We calculated the sum of the scores for satisfaction from all participants, including dropped-out participants, for whom we assumed score 3, meaning "neither satisfied nor dissatisfied."

### 2.8. Data analysis

We performed the intention-to-treat (ITT) analysis by assuming that four drop-out participants had no changes in all variables. Shapiro-Wilk test was used for evaluating normality. The normality of data was identified. One-way repeated measures ANCOVA was performed for evaluating the changes in the variables, except for GPES scores, which were analyzed using one-way ANOVA. Age, pain duration, and time taken for activities of daily living for maintaining health were set as covariates. Post-hoc analysis was performed using Bonferroni correction. SPSS (version 20, IBM, USA) was used for the analysis, and *P*-value was set as .05.

## 3. Results

### 3.1. Participants demographic characteristics (Table 2)

Twenty-four elderly individuals were recruited and evaluated at baseline. Four participants dropped out of the study: one due to complaint of the dizziness and sleep disturbance at night, one due to the distance between the participant's home and the intervention place, and two because they were visiting their hometowns. No adverse effects were reported by the participants except for one participant who dropped out because of dizziness and sleep disturbance during the sham period (T1).

### 3.2. Primary outcomes (Table 3)

*3.2.1. Pain perception*

*3.2.1.1. VAS for each pain site.* Nine participants belonged to the subgroup of neck and upper extremity (one neck pain, five shoulder pain, one wrist pain, and two thumb finger pain). Further, 16 participants belonged to the subgroup of low back. Additionally, 21 participants belonged to the subgroup of lower extremity (17 knee pain, one calf pain, and three ankle pain).

- Neck and upper extremity

There were significant decreases in the scores in the period of stimulation using 2 mA (T3, $P = .008$) when compared to baseline (T0). No significant differences in the scores for the neck and upper extremity site were observed in the sham (T1) and 1 mA (T2) periods.

- Low back

When compared to baseline (T0), there were significant decreases in the scores in periods of stimulation using 1 mA [T2, $P = .011$], and 2 mA [T3, $P = .024$]).

- Lower extremity

When compared to baseline (T0), there were no significant decreases in all periods.

*3.2.1.2. PSEQ.* PSEQ was increased significantly only after the period of stimulation using 2 mA (T3, $P = .012$) when compared with baseline (T0). There were no significant changes in the period of sham (T1) and stimulation using 1 mA (T2).

*3.2.1.3. TSK.* For TSK-total, there were significant changes only after the period of stimulation using 2 mA (T3, $P = .013$). In TSK, while TSK-AA subcomponent showed significant changes in 1 mA (T2, $P = .002$) and 2 mA (T3, $P = .004$), TSK-SA subcomponent did not show any significant change in all post-tDCS periods.

**Table 3**
Results of independent variables at each intervention period.

| Variables | T0 | T1 | T2 | T3 |
|---|---|---|---|---|
| ***Primary outcomes*** | | | | |
| *Pain perception* | | | | |
| VAS (analyzed sample size) | | | | |
| · Neck & upper extremity (9) | 5.89 (1.62) | 5.60 (1.54) | 4.67 (1.53) | 3.96 (1.20)* |
| · Low back (22) | 7.18 (1.47) | 6.15 (1.29) | 4.89 (0.85)* | 5.06 (1.68)* |
| · Lower extremity (16) | 6.09 (1.72) | 5.32 (1.38) | 4.39 (1.27) | 3.40 (1.57) |
| PSEQ | 41.42 (11.90) | 42.88 (9.17) | 43.58 (9.44) | 47.17 (9.09)* |
| Fear of movement on (re)injury | | | | |
| · TSK-total | 23.20 (7.10) | 23.88 (5.32) | 21.33 (7.11) | 18.70 (7.80)* |
| · TSK-AA | 20.21 (5.24) | 20.54 (4.35) | 17.87 (5.11)* | 16.38 (5.21)* |
| · TSK-SA | 14.92 (2.55) | 15.45 (1.89) | 15.41 (3.73) | 13.46 (2.81) |
| GPES | N/a | 1.42 (1.77) | 1.96 (1.88) | 2.54 (1.64) |
| *Executive function* | | | | |
| TMT B-A (second) | 93.59 (12.01) | 94.54 (12.17) | 87.92 (12.52) | 84.85 (11.31) |
| TUG dual (second) | 10.01 (0.75) | 8.98 (0.51) | 8.28 (0.39) | 8.44 (0.66) |
| ***Secondary outcomes*** | | | | |
| *General physical state* | | | | |
| MGS *(Newton)* | 24.49 (1.52) | 22.91 (1.43) | 23.70 (1.45) | 23.98 (1.51) |
| *Quality of life* | | | | |
| Physical health subscore | 11.13 (0.59) | N/a | N/a | 13.20 (0.72) ** |
| Mental health subscore | 19.41 (0.81) | N/a | N/a | 21.50 (0.78) * |

Values are Mean (SD); GPES: Global perceived effect scales; PSEQ: Pain self-efficacy questionnaire; MGS: Maximal Grip Strength; TMT: Trail Making Test; TSK: Tampa Scale for Kinesiophobia; TUG dual: Timed Up and Go test dual; T0: Pre-tDCS; T1: Post-sham current; T2: Post-1 mA; T3: Post-2 mA. Statistical analysis was performed by repeated measures ANCOVA, except for GPES scores, which were analyzed by ANOVA; post-hoc analysis was performed using Bonferroni correction. * $P < .05$; ** $P < .001$.

*3.2.1.4. GPES.* When we compared the scores of GPES after each post-tDCS period, the scores between the post-sham period (T1) and the post-2 mA (T3) and those between the post-1 mA (T2) and post-2 mA (T3) period showed significant differences (respectively, $P = .011$ and $P = .030$)

### 3.2.2. Executive function

*3.2.2.1. TMT.* The normalized TMT (B-A) showed no significant changes compared to baseline (T0) during all post-tDCS periods.

*3.2.2.2. TUG dual.* The TUG dual test showed that there was no significant decrease after all periods when compared to baseline (T0)

### 3.3. Secondary outcomes (Table 3)

#### 3.3.1. MGS

During all post-tDCS periods, there were no significant changes in maximal grip strength compared to the values at baseline (T0).

#### 3.3.2. SF-12

During all periods, the SF-12 showed significant increase in both physical health subscore ($P < .001$) and mental health subscore ($P = .003$).

#### 3.3.3. Intervention satisfaction

After all periods, with regard to the level of satisfaction, 7 participants chose score 1, 8 participants chose score 2, 8 participants chose score 3 (including the drop-out participants), and 1 participant chose score 4.

## 4. Discussion

PFC is the major structure in the brain affected by aging and plays a key role in pain processing and executive function. The current study examined the feasibility of anodal tDCS applied over the DLPFC for pain perception and executive function in elderly individuals.

### 4.1. Effects of tDCS on chronic pain perception in elderly individuals

For pain perception, first, we classified types of pain according to three body regions (neck and upper extremity, low back, lower extremity) and evaluated VAS scores for each region during the intervention periods. In each body region, despite diversity in the causes of pain, the elderly individuals generally experienced statistically significant pain relief, except for lower extremity. Decrease in the VAS score of neck and upper extremity, and low back reached its minimal clinically important difference (Lee, Hobden, Stiell, & Wells, 2003) approximately at the end of all intervention periods.

Typically, in patients with chronic pain, decrease in chemistry such as N-acetyl aspartate and glucose in DLPFC was reported (Apkarian, Bushnell, Treede, & Zubieta, 2005) and our findings supported the results of some studies that demonstrated the effectiveness of brain stimulation with anodal current over the DLPFC on the improvement in pain levels in patients (Choi, Jung, Lee, & Lee, 2014; Vaseghi, Zoghi, & Jaberzadeh, 2014). Furthermore, we also demonstrated the importance of DLPFC stimulation to facilitate the ability to process pain for the elderly population in whom show the noticeable volume loss of the brain (Farrell, 2012).

Second, we observed changes in self-efficacy and fear of movement, which are reportedly strongly related to chronic pain. (Turner, Ersek, & Kemp, 2005) Tuner J.A. (2005) reported that self-efficacy, which is psychological confidence to perform specific activities, was not only negatively associated with pain and disability but also positively associated with effective self-pain coping strategy. For self-efficacy, significant change in PSEQ was found after all intervention periods in the current study. We identified fear of movement arising from (re)injury in terms of three categories (TSK-total, TSK-AA, TSK-SA) (Mallen et al., 2013). TSK-AA indicates belief that some activity may cause (re)injury, and TSK-SA indicates belief that severe medical problems are present. Interestingly, in the elderly individuals in our study, TSK-AA showed significant changes while TSK-SA did not. Overall, anodal tDCS over the left DLPFC in the elderly individuals induced pain-related psychological changes, although improvement was not observed in grip strength, which is an indicator of the elderly individual's physical and cognitive functional states (Fritz, McCarthy, & Adamo, 2017). These results could not be explained separately from the positive effects of tDCS on the

depression, which several studies have already demonstrated (Mondino et al., 2014).

### 4.2. Global perceived effect of tDCS on chronic pain

We evaluated GPES after each intervention period, asking "how much has the pain improved compared to the pain at onset?" Although increasing trends were observed after each intervention period, a significant change was observed compared to the baseline (T0) in only the post-2 mA (T3) period. This indicates that using anodal tDCS over the DLPFC is a feasible approach for management of chronic pain. However, we could not determine which type of current was the most effective due to the study design. Therefore, future studies to determine the most appropriate type of current for using tDCS are needed.

### 4.3. Effects of tDCS on executive functions

For working memory, which is the ability to temporarily hold information needed to simultaneously perform more than two specific tasks, we observed that TMT results did not show significant changes during the intervention periods; only a decreasing trend was observed. This finding supports recent findings in previous studies that application of anodal tDCS over the DLPFC had a small effect on working memory or global cognition. (Hill, Rogasch, Fitzgerald, & Hoy, 2017; Nilsson, Lebedev, & Lovden, 2015; Nilsson, Lebedev, Rydstrom, & Lovden, 2017; Summers, Kang, & Cauraugh, 2016) However, some studies have reported acute positive effects of anodal tDCS over the DLPFC in patients with loss of cognitive function on working memory. (Eddy, Shapiro, Clouter, Hansen, & Rickards, 2017; Oliveira et al., 2013) The differential effects across studies might stem from the task methods used because aging-related deficit can be observed more clearly in tasks requiring divided attention (Verhaeghen, 2011). For dual-tasking, although our findings showed no significant changes in all periods, the results were close to significance, which indicated partial agreement with the results from previous studies that there was a significant improvement in dual-tasking after tDCS (Concerto et al., 2017). Unlike task-switching, counting backward while walking was likely to be affected even with a single session of tDCS in healthy elders. (Manor et al., 2016) Since difficulty in gait performance with concurrent cognitive challenges is associated with risks of fall in elderly individuals (Beurskens & Bock, 2012; Hausdorff et al., 2006), our findings provide meaningful evidence for the usage of tDCS in elderly fallers with chronic pain. To identify authentically the effects of tDCS on executive function, further studies of tDCS with a longer time of application or intervention duration for working memory in aging population are needed.

### 4.4. Feasibility of tDCS for elderly individuals

After all intervention periods, we evaluated changes in QoL and satisfaction with regard to tDCS in the participants who completed the experiments. Both physical and mental health states were significantly improved, and the level of satisfaction was favorable, with a low rate of drop-out due to adverse effects (one participant complained of dizziness and sleep disturbance). Thus, we demonstrated the feasibility of using tDCS for decline in pain processing and executive function associated with aging.

### 4.5. Conclusion

The current study examined the feasibility of application of anodal tDCS over the left DLPFC for pain perception and executive function in the aging population. In conclusion, our results showed that applying anodal tDCS over the DLPFC induces positive effects, thus indicating feasibility of this approach for aging-related pain perception, although the feasibility for executive function needs to be evaluated in future studies.

### 4.6. Study limitation

In our study, we did not control for the daily activities of the elderly individuals that might be directly linked to their health problems; therefore, these activities may have affected our findings. Additionally, because of the shadow effects of tDCS, other brain regions, that is, the regions surrounding the DLPFC or inside the DLPFC could have affected our results. Lastly, we applied a progressively increasing intensity of current on the DLPFC across the intervention periods; therefore, future studies should use various types of current intensities and compare different brain areas to determine the region that shows the maximal effects.

## Declarations of interest

None.

## Conflict of interest

There are no conflicts of interest to disclose.

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